IARC MONOGRAPHS
ON THE
EVALUATION OF THE
CARCINOGENIC RISK
OF CHEMICALS TO HUMANS

Some Halogenated Hydrocarbons

VOLUME 20

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of the Carcinogenic Risk of Chemicals to Humans
which met in Lyon,
6-13 June 1978

October 1979

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
In 1971, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for groups of chemicals to which humans are known to be exposed, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

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SOME HALOGENATED HYDROCARBONS

Lyon, 6-13 June 1978

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NOTE TO THE READER

The term 'carcinogenic risk' in the IARC Monograph series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Inclusion of a chemical in the monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of a chemical for humans is encouraged to make that information available to the Unit of Chemical Carcinogenesis, International Agency for Research on Cancer, Lyon, France, in order that the chemical may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Chemical Carcinogenesis, so that corrections can be reported in future volumes.
BACKGROUND

In 1971, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans with the object of producing monographs on individual chemicals*. The criteria established at that time to evaluate carcinogenic risk to humans were adopted by all the working groups whose deliberations resulted in the first 16 volumes of the IARC Monograph series. In October 1977, a joint IARC/WHO ad hoc Working Group met to re-evaluate these guiding criteria; this preamble reflects the results of their deliberations(1) and those of a subsequent IARC ad hoc Working Group which met in April 1978(2).

OBJECTIVE AND SCOPE

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for groups of chemicals to which humans are known to be exposed, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

The monographs summarize the evidence for the carcinogenicity of individual chemicals and other relevant information. The critical analyses of the data are intended to assist national and international authorities in formulating decisions concerning preventive measures. No recommendations are given concerning legislation, since this depends on risk-benefit evaluations, which seem best made by individual governments and/or international agencies. In this connection, WHO recommendations on food additives(3), drugs(4), pesticides and contaminants(5) and occupational carcinogens(6) are particularly informative.

*Since 1972, the programme has undergone considerable expansion, primarily with the scientific collaboration and financial support of the US National Cancer Institute.
The IARC Monographs are recognized as an authoritative source of information on the carcinogenicity of environmental chemicals. The first users' survey, made in 1976, indicates that the monographs are consulted routinely by various agencies in 24 countries.

Since the programme began in 1971, 20 volumes have been published in the IARC Monograph series, and 442 separate chemical substances have been evaluated. Each volume is printed in 4000 copies and distributed via the WHO publications service.

SELECTION OF CHEMICALS FOR MONOGRAPHS

The chemicals (natural and synthetic, including those which occur as mixtures and in manufacturing processes) are selected for evaluation on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some experimental evidence of carcinogenicity and/or there is some evidence or suspicion of a risk to humans. In certain instances, chemical analogues were also considered.

Inclusion of a chemical in a volume does not imply that it is carcinogenic, only that the published data have been examined. The evaluations must be consulted to ascertain the conclusions of the Working Group. Equally, the fact that a chemical has not appeared in a monograph does not mean that it is without carcinogenic hazard.

The scientific literature is surveyed for published data relevant to the monograph programme. In addition, the IARC Survey of Chemicals Being Tested for Carcinogenicity often indicates those chemicals that are to be scheduled for future meetings. The major aims of the survey are to prevent unnecessary duplication of research, to increase communication among scientists, and to make a census of chemicals that are being tested and of available research facilities.

As new data on chemicals for which monographs have already been prepared and new principles for evaluating carcinogenic risk receive acceptance, re-evaluations will be made at subsequent meetings, and revised monographs will be published as necessary.

WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, a list of the substances to be considered is prepared by IARC staff in consultation with other experts. Subsequently, all relevant biological data are collected by IARC; in addition to the published literature, US Public Health Service Publication No. 149 has been particularly
PREAMBLE

valuable and has been used in conjunction with other recognized sources of information on chemical carcinogenesis and systems such as CANCERLINE, MEDLINE and TOXLINE. The major collection of data and the preparation of first drafts for the sections on chemical and physical properties, on production, use, occurrence and on analysis are carried out by SRI International under a separate contract with the US National Cancer Institute. Most of the data so obtained on production, use and occurrence refer to the United States and Japan; SRI International and IARC supplement this information with that from other sources in Europe. Bibliographical sources for data on mutagenicity and teratogenicity are the Environmental Mutagen Information Center and the Environmental Teratology Information Center, both located at the Oak Ridge National Laboratory, USA.

Six to nine months before the meeting, reprints of articles containing relevant biological data are sent to an expert(s), or are used by the IARC staff, for the preparation of first drafts of the monographs. These drafts are edited by IARC staff and are sent prior to the meeting to all participants of the Working Group for their comments. The Working Group then meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, then edited and prepared for reproduction. The monographs are usually published within six months after the Working Group meeting.

DATA FOR EVALUATIONS

With regard to biological data, only reports that have been published or accepted for publication are reviewed by the working groups, although a few exceptions have been made. The monographs do not cite all of the literature on a particular chemical: only those data considered by the Working Group to be relevant to the evaluation of the carcinogenic risk of the chemical to humans are included.

Anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals for which monographs have appeared is urged to make them available to the Unit of Chemical Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

THE WORKING GROUP

The tasks of the Working Group are five-fold: (a) to ascertain that all data have been collected; (b) to select the data relevant for the evaluation; (c) to ensure that the summaries of the data enable the reader to follow the reasoning of the committee; (d) to judge the significance of the results of experimental and epidemiological studies; and (e) to
make an evaluation of the carcinogenic risk of the chemical.

Working Group participants who contributed to the consideration and evaluation of chemicals within a particular volume are listed, with their addresses, at the beginning of each publication (see p. 1). Each member serves as an individual scientist and not as a representative of any organization or government. In addition, observers are often invited from national and international agencies, organizations and industries.

GENERAL PRINCIPLES FOR EVALUATING THE CARCINOGENIC RISK OF CHEMICALS

The widely accepted meaning of the term 'chemical carcinogenesis', and that used in these monographs, is the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are usually observed, and/or the induction by chemicals of more neoplasms than are usually found — although fundamentally different mechanisms may be involved in these three situations. Etymologically, the term 'carcinogenesis' means the induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign tumours. In the monographs, the words 'tumour' and neoplasm' are used interchangeably (In scientific literature the terms 'tumourigen', 'oncogen' and 'blastomogen' have all been used synonymously with 'carcinogen', although occasionally 'tumourigen' has been used specifically to denote the induction of benign tumours).

Experimental Evidence

Qualitative aspects

Both the interpretation and evaluation of a particular study as well as the overall assessment of the carcinogenic activity of a chemical involve several qualitatively important considerations, including:
(a) the experimental parameters under which the chemical was tested, including route of administration and exposure, species, strain, sex, age, etc.;
(b) the consistency with which the chemical has been shown to be carcinogenic, e.g., in how many species and at which target organ(s);
(c) the spectrum of neoplastic response, from benign neoplasia to multiple malignant tumours;
(d) the stage of tumour formation in which a chemical may be involved: some chemicals act as complete carcinogens and have initiating and promoting activity, while others are promoters only; and
(e) the possible role of modifying factors.

There are problems not only of differential survival but of differential toxicity, which may be manifested by unequal growth and weight gain in treated and control animals. These complexities should also be considered in the interpretation of data, or, better, in the experimental design.
Many chemicals induce both benign and malignant tumours; few instances are recorded in which only benign neoplasms are induced by chemicals that have been studied extensively. Benign tumours may represent a stage in the evolution of a malignant neoplasm or they may be 'end-points' that do not readily undergo transition to malignancy. If a substance is found to induce only benign tumours in experimental animals, the chemical should be suspected of being a carcinogen and requires further investigation.

**Hormonal carcinogenesis**

Hormonal carcinogenesis presents certain distinctive features: the chemicals involved occur both endogenously and exogenously; in many instances, long exposure is required; tumours occur in the target tissue in association with a stimulation of non-neoplastic growth, but in some cases, hormones promote the proliferation of tumour cells in a target organ. Hormones that occur in excessive amounts, hormone-mimetic agents and agents that cause hyperactivity or imbalance in the endocrine system may require evaluative methods comparable with those used to identify chemical carcinogens; particular emphasis must be laid on quantitative aspects and duration of exposure. Some chemical carcinogens have significant side effects on the endocrine system, which may also result in hormonal carcinogenesis. Synthetic hormones and anti-hormones can be expected to possess other pharmacological and toxicological actions in addition to those on the endocrine system, and in this respect they must be treated like any other chemical with regard to intrinsic carcinogenic potential.

**Quantitative aspects**

Dose-response studies are important in the evaluation of carcinogenesis: the confidence with which a carcinogenic effect can be established is strengthened by the observation of an increasing incidence of neoplasms with increasing exposure.

The assessment of carcinogenicity in animals is frequently complicated by recognized differences among the test animals (species, strain, sex, age), in route(s) of administration and in dose/duration of exposure; often, target organs at which a cancer occurs and its histological type may vary with these parameters. Nevertheless, indices of carcinogenic potency in particular experimental systems (for instance, the dose-rate required under continuous exposure to halve the probability of the animals remaining tumourless(10)) have been formulated in the hope that, at least among categories of fairly similar agents, such indices may be of some predictive value in other systems, including humans.

Chemical carcinogens differ widely in the dose required to produce a given level of tumour induction, although many of them share common biological properties which include metabolism to reactive (electrophilic (11-13)) intermediates capable of interacting with DNA. The reason for this variation in dose-response is not understood but may be due either to
differences within a common metabolic process or to the operation of qualitatively distinct mechanisms.

Statistical analysis of animal studies

Tumours which would have arisen had an animal lived longer may not be observed because of the death of the animal from unrelated causes, and this possibility must be allowed for. Various analytical techniques have been developed which use the assumption of independence of competing risks to allow for the effects of intercurrent mortality on the final numbers of tumour-bearing animals in particular treatment groups.

For externally visible tumours and for neoplasms that cause death, methods such as Kaplan-Meier (i.e., 'life-table', 'product-limit' or 'actuarial') estimates (10), with associated significance tests (14,15), are recommended.

For internal neoplasms which are discovered 'incidentally' (14) at autopsy but which did not cause the death of the host, different estimates (16) and significance tests (14,15) may be necessary for the unbiased study of the numbers of tumour-bearing animals.

All of these methods (10,14-16) can be used to analyse the numbers of animals bearing particular tumour types, but they do not distinguish between animals with one or many such tumours. In experiments which end at a particular fixed time, with the simultaneous sacrifice of many animals, analysis of the total numbers of internal neoplasms per animal found at autopsy at the end of the experiment is straightforward. However, there are no adequate statistical methods for analysing the numbers of particular neoplasms that kill an animal host.

Evidence of Carcinogenicity in Humans

Evidence of carcinogenicity in humans can be derived from three types of study, the first two of which usually provide only suggestive evidence: (1) reports concerning individual cancer patients (case reports), including a history of exposure to the supposed carcinogenic agent; (2) descriptive epidemiological studies in which the incidence of cancer in human populations is found to vary (spatially or temporally) with exposure to the agent; and (3) analytical epidemiological studies (e.g., case-control or cohort studies) in which individual exposure to the agent is found to be associated with an increased risk of cancer.

An analytical study that shows a positive association between an agent and a cancer may be interpreted as implying causality to a greater or lesser extent, if the following criteria are met: (a) there is no identifiable positive bias (By 'positive bias' is meant the operation of factors in study design or execution which lead erroneously to a more strongly positive association between an agent and disease than in fact
exists. Examples of positive bias include, in case-control studies, better documentation of exposure to the agent for cases than for controls, and, in cohort studies, the use of better means of detecting cancer in individuals exposed to the agent than in individuals not exposed; (b) the possibility of positive confounding has been considered (By 'positive confounding' is meant a situation in which the relationship between an agent and a disease is rendered more strongly positive than it truly is as a result of an association between that agent and another agent which either causes or prevents the disease. An example of positive confounding is the association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking); (c) the association is unlikely to be due to chance alone; (d) the association is strong; and (e) there is a dose-response relationship.

In some instances, a single epidemiological study may be strongly indicative of a cause-effect relationship; however, the most convincing evidence of causality comes when several independent studies done under different circumstances result in 'positive' findings.

Analytical epidemiological studies that show no association between an agent and a cancer ('negative' studies) should be interpreted according to criteria analogous to those listed above: (a) there is no identifiable negative bias; (b) the possibility of negative confounding has been considered; and (c) the possible effects of misclassification of exposure or outcome have been weighed.

In addition, it must be recognized that in any study there are confidence limits around the estimate of association or relative risk. In a study regarded as 'negative', the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above this upper limit. This usually means that a 'negative' study must be large to be convincing. Confidence in a 'negative' result is increased when several independent studies carried out under different circumstances are in agreement.

Finally, a 'negative' study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

Experimental Data Relevant to the Evaluation of Carcinogenic Risk to Humans

No adequate criteria are presently available to interpret experimental carcinogenicity data directly in terms of carcinogenic potential for humans. Nonetheless, utilizing data collected from appropriate tests in animals, positive extrapolations to possible human risk can be approximated.
Information compiled from the first 17 volumes of the IARC Monographs (17-19) shows that of about 26 chemicals or manufacturing processes now generally accepted to cause cancer in humans, all but possibly two (arsenic and benzene) of those which have been tested appropriately produce cancer in at least one animal species. For several (aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan, mustard gas and vinyl chloride), evidence of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports.

In general, the evidence that a chemical produces tumours in experimental animals is of two degrees: (a) sufficient evidence of carcinogenicity is provided by the production of malignant tumours; and (b) limited evidence of carcinogenicity reflects qualitative and/or quantitative limitations of the experimental results.

For many of the chemicals evaluated in the first 20 volumes of the IARC Monographs for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard such chemicals as if they presented a carcinogenic risk to humans.

Sufficient evidence of carcinogenicity is provided by experimental studies that show an increased incidence of malignant tumours: (i) in multiple species or strains, and/or (ii) in multiple experiments (routes and/or doses), and/or (iii) to an unusual degree (with regard to incidence, site, type and/or precocity of onset). Additional evidence may be provided by data concerning dose-response, mutagenicity or structure.

In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw/day) of a particular chemical required to produce cancer in test animals and the dose which would produce a similar incidence of cancer in humans. The available data suggest, however, that such a relationship may exist (20, 21), at least for certain classes of carcinogenic chemicals. Data that provide sufficient evidence of carcinogenicity in test animals may therefore be used in an approximate quantitative evaluation of the human risk at some given exposure level, provided that the nature of the chemical concerned and the physiological, pharmacological and toxicological differences between the test animals and humans are taken into account. However, no acceptable methods are currently available for quantifying the possible errors in such a procedure, whether it is used to generalize between species or to extrapolate from high to low doses. The methodology for such quantitative extrapolation to humans requires further development.

Evidence for the carcinogenicity of some chemicals in experimental animals may be limited for two reasons. Firstly, experimental data may be restricted to such a point that it is not possible to determine a causal relationship between administration of a chemical and the development of a particular lesion in the animals. Secondly, there are certain neoplasms,
including lung tumours and hepatomas in mice, which have been considered of lesser significance than neoplasms occurring at other sites for the purpose of evaluating the carcinogenicity of chemicals. Such tumours occur spontaneously in high incidence in these animals, and their malignancy is often difficult to establish. An evaluation of the significance of these tumours following administration of a chemical is the responsibility of particular Working Groups preparing individual monographs, and it has not been possible to set down rigid guidelines; the relevance of these tumours must be determined by considerations which include experimental design and completeness of reporting.

Some chemicals for which there is limited evidence of carcinogenicity in animals have also been studied in humans with, in general, inconclusive results. While such chemicals may indeed be carcinogenic to humans, more experimental and epidemiological investigation is required.

Hence, 'sufficient evidence' of carcinogenicity and 'limited evidence' of carcinogenicity do not indicate categories of chemicals: the inherent definitions of those terms indicate varying degrees of experimental evidence, which may change if and when new data on the chemicals become available. The main drawback to any rigid classification of chemicals with regard to their carcinogenic capacity is the as yet incomplete knowledge of the mechanism(s) of carcinogenesis.

In recent years, several short-term tests for the detection of potential carcinogens have been developed. When only inadequate experimental data are available, positive results in validated short-term tests (see p. 19) are an indication that the compound is a potential carcinogen and that it should be tested in animals for an assessment of its carcinogenicity. Negative results from short-term tests cannot be considered sufficient evidence to rule out carcinogenicity. Whether short-term tests will eventually be as reliable as long-term tests in predicting carcinogenicity in humans will depend on further demonstrations of consistency with long-term experiments and with data from humans.

EXPLANATORY NOTES ON THE MONOGRAPH CONTENTS

Chemical and Physical Data (Section 1)

The Chemical Abstracts Service Registry Number and the latest Chemical Abstracts Primary Name (9th Collective Index)(22) are recorded in section 1. Other synonyms and trade names are given, but no comprehensive list is provided. Further, some of the trade names are those of mixtures in which the compound being evaluated is only one of the ingredients.

The structural and molecular formulae, molecular weight and chemical and physical properties are given. The properties listed refer to the pure substance, unless otherwise specified, and include, in particular,
data that might be relevant to carcinogenicity (e.g., lipid solubility) and those that concern identification. A separate description of the composition of technical products includes available information on impurities and formulated products.

Production, Use, Occurrence and Analysis (Section 2)

The purpose of section 2 is to provide indications of the extent of past and present human exposure to the chemical.

Synthesis

Since cancer is a delayed toxic effect, the dates of first synthesis and of first commercial production of the chemical are provided. In addition, methods of synthesis used in past and present commercial production are described. This information allows a reasonable estimate to be made of the date before which no human exposure could have occurred.

Production

Since Europe, Japan and the United States are reasonably representative industrialized areas of the world, most data on production, foreign trade and uses are obtained from those countries. It should not, however, be inferred that those nations are the sole or even the major sources or users of any individual chemical.

Production and foreign trade data are obtained from both governmental and trade publications by chemical economists in the three geographical areas. In some cases, separate production data on organic chemicals manufactured in the United States are not available because their publication could disclose confidential information. In such cases, an indication of the minimum quantity produced can be inferred from the number of companies reporting commercial production. Each company is required to report on individual chemicals if the sales value or the weight of the annual production exceeds a specified minimum level. These levels vary for chemicals classified for different uses, e.g., medicinals and plastics; in fact, the minimal annual sales value is between $1000 and $50,000 and the minimal annual weight of production is between 450 and 22,700 kg. Data on production in some European countries are obtained by means of general questionnaires sent to companies thought to produce the compounds being evaluated. Information from the completed questionnaires is compiled by country, and the resulting estimates of production are included in the individual monographs.

Use

Information on uses is meant to serve as a guide only and is not complete. It is usually obtained from published data but is often complemented by direct contact with manufacturers of the chemical. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their clinical efficacy.
Statements concerning regulations and standards (e.g., pesticide registrations, maximum levels permitted in foods, occupational standards and allowable limits) in specific countries are mentioned as examples only. They may not reflect the most recent situation, since such legislation is in a constant state of change; nor should it be taken to imply that other countries do not have similar regulations.

Occurrence

Information on the occurrence of a chemical in the environment is obtained from published data, including that derived from the monitoring and surveillance of levels of the chemical in occupational environments, air, water, soil, foods and tissues of animals and humans. When available, data on the generation, persistence and bioaccumulation of a chemical are also included.

Analysis

The purpose of the section on analysis is to give the reader an indication, rather than a complete review, of methods cited in the literature. No attempt is made to evaluate critically or to recommend any of the methods.

Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans (Section 3)

In general, the data recorded in section 3 are summarized as given by the author; however, comments made by the Working Group on certain shortcomings of reporting, of statistical analysis or of experimental design are given in square brackets. The nature and extent of impurities/contaminants in the chemicals being tested are given when available.

Carcinogenicity studies in animals

The monographs are not intended to cover all reported studies. Some studies are purposely omitted (a) because they are inadequate, as judged from previously described criteria (e.g., too short a duration, too few animals, poor survival); (b) because they only confirm findings that have already been fully described; or (c) because they are judged irrelevant for the purpose of the evaluation. In certain cases, however, such studies are mentioned briefly, particularly when the information is considered to be a useful supplement to other reports or when it is the only data available. Their inclusion does not, however, imply acceptance of the adequacy of their experimental design and/or of the analysis and interpretation of their results.

Mention is made of all routes of administration by which the compound has been adequately tested and of all species in which relevant tests have been done (5, 26). In most cases, animal strains are given (General characteristics of mouse strains have been reviewed (27)). Quantitative data are given to indicate the order of magnitude of the effective carcinogenic
doses. In general, the doses and schedules are indicated as they appear in the original paper; sometimes units have been converted for easier comparison. Experiments on the carcinogenicity of known metabolites, chemical precursors, analogues and derivatives, and experiments on factors that modify the carcinogenic effect are also reported.

Other relevant biological data

Lethality data are given when available, and other data on toxicity are included when considered relevant. The metabolic data are restricted to studies that show the metabolic fate of the chemical in animals and humans, and comparisons of data from animals and humans are made when possible. Information is also given on absorption, distribution, excretion and placental transfer.

Embryotoxicity and teratogenicity

Data on teratogenicity from studies in experimental animals and from observations in humans are also included. There appears to be no causal relationship between teratogenicity(28) and carcinogenicity, but chemicals often have both properties. Evidence of teratogenicity suggests transplacental transfer, which is a prerequisite for transplacental carcinogenesis.

Indirect tests (mutagenicity and other short-term tests)

Data from indirect tests are also included. Since most of these tests have the advantage of taking less time and being less expensive than mammalian carcinogenicity studies, they are generally known as 'short-term' tests. They comprise assay procedures which rely on the induction of biological and biochemical effects in in vivo and/or in vitro systems. The end-point of the majority of these tests is the production not of neoplasms in animals but of changes at the molecular, cellular or multicellular level: these include the induction of DNA damage and repair, mutagenesis in bacteria and other organisms, transformation of mammalian cells in culture, and other systems.

The short-term tests are proposed for use (a) in predicting potential carcinogenicity in the absence of carcinogenicity data in animals, (b) as a contribution in deciding which chemicals should be tested in animals, (c) in identifying active fractions of complex mixtures containing carcinogens, (d) for recognizing active metabolites of known carcinogens in human and/or animal body fluids and (e) to help elucidate mechanisms of carcinogenesis.

Although the theory that cancer is induced as a result of somatic mutation suggests that agents which damage DNA in vivo may be carcinogens, the precise relevance of short-term tests to the mechanism by which cancer is induced is not known. Predictions of potential carcinogenicity are currently based on correlations between responses in short-term tests and
data from animal carcinogenicity and/or human epidemiological studies. This approach is limited because the number of chemicals known to be carcinogenic in humans is insufficient to provide a basis for validation, and most validation studies involve chemicals that have been evaluated for carcinogenicity only in animals. The selection of chemicals is in turn limited to those classes for which data on carcinogenicity are available. The results of validation studies could be strongly influenced by such selection of chemicals and by the proportion of carcinogens in the series of chemicals tested; this should be kept in mind when evaluating the predictivity of a particular test. The usefulness of any test is reflected by its ability to classify carcinogens and noncarcinogens, using the animal data as a standard; however, animal tests may not always provide a perfect standard. The attainable level of correlation between short-term tests and animal bioassays is still under investigation.

Since many chemicals require metabolism to an active form, tests that do not take this into account may fail to detect certain potential carcinogens. The metabolic activation systems used in short-term tests (e.g., the cell-free systems used in bacterial tests) are meant to approximate the metabolic capacity of the whole organism. Each test has its advantages and limitations; thus, more confidence can be placed in the conclusions when negative or positive results for a chemical are confirmed in several such test systems. Deficiencies in metabolic competence may lead to misclassification of chemicals, which means that not all tests are suitable for assessing the potential carcinogenicity of all classes of compounds.

The present state of knowledge does not permit the selection of a specific test(s) as the most appropriate for identifying potential carcinogenicity. Before the results of a particular test can be considered to be fully acceptable for predicting potential carcinogenicity, certain criteria should be met: (a) the test should have been validated with respect to known animal carcinogens and found to have a high capacity for discriminating between carcinogens and noncarcinogens, and (b), when possible, a structurally related carcinogen(s) and noncarcinogen(s) should have been tested simultaneously with the chemical in question. The results should have been reproduced in different laboratories, and a prediction of carcinogenicity should have been confirmed in additional test systems. Confidence in positive results is increased if a mechanism of action can be deduced and if appropriate dose-response data are available. For optimum usefulness, data on purity must be given.

The short-term tests in current use that have been the most extensively validated are the Salmonella typhimurium plate-incorporation assay(29-33), the X-linked recessive lethal test in Drosophila melanogaster(34), unscheduled DNA synthesis(35) and in vitro transformation(33,36). Each is compatible with current concepts of the possible mechanism(s) of carcinogenesis.

An adequate assessment of the genetic activity of a chemical depends on data from a wide range of test systems. The monographs include, therefore, data not only from those already mentioned, but also on the induction
of point mutations in other systems (37-42), on structural (43) and numerical chromosome aberrations, including dominant lethal effects (44), on mitotic recombination in fungi (37) and on sister chromatid exchanges (45-46).

The existence of a correlation between quantitative aspects of mutagenic and carcinogenic activity has been suggested (5, 44-50), but it is not sufficiently well established to allow general use.

Further information about mutagenicity and other short-term tests is given in references 45-53.

**Case reports and epidemiological studies**

Observations in humans are summarized in this section.

**Summary of Data Reported and Evaluation (Section 4)**

Section 4 summarizes the relevant data from animals and humans and gives the critical views of the Working Group on those data.

**Experimental data**

Data relevant to the evaluation of the carcinogenicity of a chemical in animals are summarized in this section. Results from validated mutagenicity and other short-term tests are reported if the Working Group considered the data to be relevant. Dose-response data are given when available. An assessment of the carcinogenicity of the chemical in animals is made on the basis of all of the available data.

The animal species mentioned are those in which the carcinogenicity of the substance was clearly demonstrated. The route of administration used in experimental animals that is similar to the possible human exposure is given particular mention. Tumour sites are also indicated. If the substance has produced tumours after prenatal exposure or in single-dose experiments, this is indicated.

**Human data**

Case reports and epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are described. Human exposure to the chemical is summarized on the basis of data on production, use and occurrence. Other biological data which are considered to be relevant are also mentioned. An assessment of the carcinogenicity of the chemical in humans is made on the basis of all of the available evidence.

**Evaluation**

This section comprises the overall evaluation by the Working Group of the carcinogenic risk of the chemical to humans. All of the data in the monograph, and particularly the summarized information on experimental and human data, are considered in order to make this evaluation.
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Volume 10 (1976)  Some Naturally Occurring Substances (32 monographs), 353 pages

Volume 11 (1976)  Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics (24 monographs), 306 pages

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Volume 18 (1978)  Polychlorinated Biphenyls and Polybrominated Biphenyls (2 monographs), 140 pages

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Volume 20 (1979)  Some Halogenated Hydrocarbons (25 monographs), 609 pages


Number 1 (1973)  52 pages
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Number 6 (1976)  360 pages
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Introduction

This twentieth volume of the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans comprises monographs on 28 halogenated hydrocarbons (mainly organochlorine compounds), which are used as pesticides and microbicides, as industrial solvents and intermediates, or as flame retardants.

Of the chemicals considered in this volume, two are brominated compounds: the flame retardant, tris(2,3-dibromopropyl) phosphate, and the fumigant and nematocide, 1,2-dibromo-3-chloropropane, which is also an impurity in and a metabolite of tris(2,3-dibromopropyl) phosphate.

Polybrominated biphenyls were considered at the same time, but the resulting monograph has been combined with one on polychlorinated biphenyls which resulted from a previous meeting in October 1977; the two monographs have been published together as IARC Monographs Volume 18 (IARC, 1978a). The Working Group also considered a monograph on methyl bromide, but since no carcinogenicity studies on this compound had become available by the time of the meeting, publication of the monograph was postponed.

Several of the pesticides covered in this volume were considered previously: HCH and lindane, heptachlor, methoxychlor and mirex in Volume 5 of the IARC Monographs, (IARC, 1974); carbon tetrachloride and chloroform in Volume 1 (IARC, 1972); trichloroethylene in Volume 11 (IARC, 1976); and 1,2-dibromo-3-chloropropane in Volume 15 (IARC, 1977). Because new, relevant data on these compounds have since become available the monographs have been updated and the compounds re-evaluated.

Halogenated aromatic hydrocarbon pesticides and microbicides

Halogenated aromatic hydrocarbon pesticides and microbicides are or have been produced in vast quantities and have wide application. Their major uses are against insect pests (HCH and lindane, chlordane, chlordecone, 1,2-dibromo-3-chloropropane, dichlorvos, heptachlor, methoxychlor, mirex and toxaphene) and as microbicides (hexachlorobenzene, hexachlorobutadiene, hexachlorophene, pentachlorophenol and trichlorophenols).

Most of these chemicals, except the tri- and pentachlorophenols and dichlorvos (which also has an organophosphate grouping), are degraded slowly; the chlorophenols can, however, contain or form the highly toxic chlorinated aromatic hydrocarbon impurities, chlorinated dibenzo-para-dioxins and chlorinated dibenzofurans (IARC, 1978b), which are also degraded slowly. Such slow degradation and environmental persistence enhances potential chronic exposure. Other common characteristics of these chemicals are their lipid (fat) solubility and slow metabolism or limited excretion in vertebrate species, resulting in long-term persistence in body tissues. Environmental persistence combined with slow excretion strongly favours bioaccumulation in an ecosystem.
Human exposure to certain of the halogenated aromatic hydrocarbon pesticides and microbicides results in a body burden of long duration; preferential storage occurs in fat or in tissues with high lipid content. Blood levels are usually lower than those in fat but are proportional to the fat levels. Residues have also been observed in the skin months or years after dermal exposure (Kazen et al., 1974). Since these chemicals have an extended biological half-life, continuing exposure over a period of time is cumulative. Males typically retain higher levels than females (Burns & Miller, 1975; Wassermann et al., 1974a,b).

Body burdens of these pesticides have been reported in populations throughout the world: in Australia (Siyali, 1972; Siyali & Simson, 1973), the Federal Republic of Germany (Rappl & Waiblinger, 1975), France (Luquet et al., 1975), Israel (Wassermann et al., 1974a), Japan (Curley et al., 1973; Morita et al., 1975), Norway (Lunde & Bjørseth, 1977), Uganda (Wassermann et al., 1974b) and the US (Jonsson et al., 1977; Kutz et al., 1974).

The principal source of general human exposure is thought to be diet, although direct exposure is also likely to occur from the spraying of large geographic areas during insect control campaigns (Mughal & Rahman, 1973). Most of these compounds have also been detected in US drinking-water (US Environmental Protection Agency, 1978). Dietary exposure can result from consumption of contaminated vegetables and seeds, meat, fish, eggs, milk and dairy products. Occupational exposure to many of these chemicals results in body burdens that are higher than those of the general population (Burns et al., 1974; Lunde & Bjørseth, 1977). Populations geographically proximate to industrial chemical plants have also been found to have increased body burdens (Burns & Miller, 1975). Human infants are exposed transplacentally to chemicals stored in maternal tissues and subsequently through consumption of their mothers' milk (Rappl & Waiblinger, 1975; West et al., 1975).

Halogenated hydrocarbon solvents

The most widely used degreasing solvents among the compounds considered are tetrachloroethylene (also used in dry-cleaning textiles), 1,1,1-trichloroethane, trichloroethylene and dichloromethane. Trichloroethylene and dichloromethane have also been used in the extraction of caffeine, fats and hops; dichloromethane is used extensively as a paint remover. Carbon tetrachloride and chloroform have been used as fumigants and for the manufacture of fluorocarbons. 1,2-Dichloroethane is used as a fumigant, as a lead scavenger in petrol and in the manufacture of vinyl chloride. 1,1,1-Trichloroethane and 1,1,2-trichloroethane are used in the manufacture of vinylidene chloride. All of these compounds have been found in US drinking-water (US Environmental Protection Agency, 1978).

Unlike the halogenated aromatic hydrocarbon pesticides, these compounds are readily metabolized in vivo, and their degradation products are rapidly excreted, mainly in the urine. There is little long-term storage in fat tissues.
Flame retardant

The flame retardant, tris(2,3-dibromopropyl) phosphate, has been used widely in textiles, notably in those used to make sleeping apparel for children. It was considered here because the results of a National Cancer Institute Bioassay Report had become available, subsequent to its identification as a mutagen in bacterial systems.

Production volumes

The amounts of these compounds that are manufactured commercially and the year of their introduction into commerce are shown in Table 1. The year of first commercial production is given because it allows a reasonable estimation to be made of the time from which human exposure could have occurred. The total, worldwide annual production of these compounds was estimated on the basis of the latest available figures from three representative areas - Europe, Japan and the US.

Rebuttable presumption against registration of pesticides

The 1972 Federal Environmental Pesticide Control Act (amendments to the 1947 Federal Insecticide, Fungicide and Rodenticide Act) gives the US Environmental Protection Agency (EPA) additional authority for registering new pesticides and provides for re-authorization of currently registered pesticide uses. A pesticide is registered for use only if labelling requirements are satisfied and only if its use according to directions causes no 'unreasonable adverse effects on man or the environment'. The burden of providing evidence of safety is placed on the manufacturer.

In July 1975, the EPA implemented new regulations which further defined 'unreasonable adverse effects' in terms of chronic toxic, mutagenic or carcinogenic effects. Pesticides that produce such effects are subject to a 'rebuttable presumption' of being banned. If the EPA determines that the use of a pesticide meets or exceeds any of several published risk criteria that are designed to identify unreasonable adverse effects in the environment, a notice of a 'rebuttable presumption against registration' (RPAR) is issued. The prospective registrant is given 90 days to challenge this presumption by submitting information that the evidence supporting the RPAR is not valid, in that the risk is not real or that potential benefits exceed potential risks. If the notice is successfully rebutted, re-registration occurs without a hearing; if the new information is insufficient or if none is supplied, the EPA issues a notice of intent to deny, cancel or suspend registration, or to hold a public hearing. So far, the EPA has initiated RPARs against about 45 pesticides.

Experimental data

Evaluations of the carcinogenicity in experimental animals of several compounds considered in this volume are based largely on data obtained from the US National Cancer Institute Bioassay Program. The Working Group
<table>
<thead>
<tr>
<th>CHEMICAL</th>
<th>YEAR OF FIRST COMMERCIAL PRODUCTION</th>
<th>LATEST ESTIMATED ANNUAL WORLD PRODUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides and microbicides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordane</td>
<td>1947</td>
<td>10 million kg</td>
</tr>
<tr>
<td>Chlordecone</td>
<td>1966</td>
<td>~500,000 kg</td>
</tr>
<tr>
<td>1,2-Dibromo-3-chloropropane</td>
<td>1955</td>
<td>30 million kg</td>
</tr>
<tr>
<td>Dichlorvos</td>
<td>1961</td>
<td>12 million kg</td>
</tr>
<tr>
<td>Heptachlor and heptachlor epoxide</td>
<td>1953</td>
<td>3 million kg</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
<td>1933</td>
<td>2 million kg</td>
</tr>
<tr>
<td>Hexachlorobutadiene</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hexachlorocyclohexane Lindane</td>
<td>1945</td>
<td>~100 million kg</td>
</tr>
<tr>
<td>Hexachloroprene</td>
<td>1951</td>
<td>8 million kg</td>
</tr>
<tr>
<td>Methoxychlor</td>
<td>1946</td>
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<tr>
<td>Mirex</td>
<td>1958</td>
<td>2.5 million kg</td>
</tr>
<tr>
<td>Pentachlorophenol</td>
<td>1950</td>
<td>225,000 kg</td>
</tr>
<tr>
<td>Toxaphene</td>
<td>1947</td>
<td>20 million kg</td>
</tr>
<tr>
<td>2,4,5-Trichlorophenol</td>
<td>1950</td>
<td>~20 million kg</td>
</tr>
<tr>
<td>2,4,6-Trichlorophenol</td>
<td>1950</td>
<td>Unknown, but &gt;10 million kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown, but &gt;120,000 kg</td>
</tr>
<tr>
<td>CHEMICAL</td>
<td>YEAR OF FIRST COMMERCIAL PRODUCTION</td>
<td>LATEST ESTIMATED ANNUAL WORLD PRODUCTION</td>
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<td>-------------------------------</td>
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</tr>
<tr>
<td>Solvents</td>
<td></td>
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<tr>
<td>Carbon tetrachloride</td>
<td>1907</td>
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<td>Chloroform</td>
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<td>Dichloromethane</td>
<td>1934</td>
<td>&gt;270 million kg</td>
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<tr>
<td>Hexachloroethane</td>
<td>1921</td>
<td>&gt;730,000 kg</td>
</tr>
<tr>
<td>1,1,2,2-Tetrachloroethane</td>
<td>1921</td>
<td>20 million kg</td>
</tr>
<tr>
<td>Tetrachloroethylene</td>
<td>1925</td>
<td>950 million kg</td>
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<tr>
<td>1,1,1-Trichloroethane</td>
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<td>~600 million kg</td>
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<tr>
<td>1,1,2-Trichloroethane</td>
<td>1941-1943</td>
<td>Unknown, but &gt;40 million kg</td>
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<tr>
<td>Trichloroethylene</td>
<td>1908</td>
<td>500 million kg</td>
</tr>
<tr>
<td>Flame retardant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tris(2,3-dibromopropyl) phosphate</td>
<td>1959</td>
<td>5 million kg</td>
</tr>
</tbody>
</table>

*Also a waste product in the manufacture of tetrachloroethylene, carbon tetrachloride, chlorine and trichloroethylene: ~6 million kg*
recognized that in several instances these data had limitations, most often due to the design of the test and partly to the incomplete reporting of the results; in particular: (1) the limited number of concurrent controls and the varying number of pooled controls do not permit, in certain instances, a statistical analysis of the results; (2) the initial doses used in tests on certain chemicals were in excess of the maximum tolerated dose and caused early mortality among treated animals; the dose levels and dosage schedules therefore had to be altered during the course of the test; and (3) some of the reports were made available in the form of preliminary drafts, and the results appearing on such drafts will have to be compared with those in the final published reports.

With regard to the study involving intraperitoneal injection of several of the compounds into mice (Theiss et al., 1977), the Working Group noted that this test system was designed as a short-term, whole-animal bioassay in which the development of lung tumours was used as an indication of carcinogenicity. Negative results in this system were considered to be insufficient evidence that a compound is not carcinogenic.

When the Working Group carried out statistical analyses of tumour incidences in treated animals compared with those in controls, the $\chi^2$ test (one-tailed) with the introduction of Yates' correction was normally employed. When the incidence of tumours in controls was zero, a Fisher exact analysis was done. The resulting $P$ values have been inserted, in square brackets, in the text of the monographs.

Among the chemicals considered in this volume that were evaluated as having sufficient evidence of carcinogenicity in experimental animals (see preamble, p. 14), the order of magnitude of the total doses of the substances varied widely. On the other hand, adequate dose-response experiments were not available for most substances, thus precluding any indication of the lowest effective doses. For chemicals that caused cancer in animals at relatively high dose levels, the possibility exists that the effects were caused by impurities or additives; known carcinogens that may occur, either as contaminants or additives, in several of the chemicals evaluated (in parentheses) are: heptachlor (in chlordane); 2,3,7,8-tetrachlorodibenzo-para-dioxin, 2,4,5-trichloro- and pentachlorophenol (in hexachlorophene); epichlorohydrin (in trichloroethylene); and 1,2-dibromo-3-chloropropane [in tris(2,3-dibromopropyl) phosphate]. Human populations are exposed more often to such technical-grade products or mixtures than they are to pure compounds. Another concern in evaluating carcinogenic potential is the wide chemical variability and percentage composition of certain commercial products, such as HCH and toxaphene.

For several of the chemicals considered in this volume, the data available to the Working Group were considered inadequate to evaluate carcinogenicity. The Working Group was aware, however, that carcinogenicity studies are in progress on most of them (IARC, 1978c). For some, further experimental studies using multiple doses would be desirable;
however, specific recommendations would necessitate extensive *ad hoc* discussions in each case.

The Working Group strongly supported the concept that negative results should be reported and disseminated with the same thoroughness and accuracy as *are* positive results. To satisfy the need to obtain results that are internationally acceptable and comparable, basic requirements for the conduct of long-term carcinogenicity and related short-term tests should be developed and followed.

In the section on mutagenicity and other related short-term tests, the variable results (or lack of concordance between carcinogenicity in experimental animals and results of short-term tests) for many of the compounds may indicate that these tests are of limited value for screening some halogenated hydrocarbons. Negative results may be attributable to low metabolic rates or to inappropriate pathways in *in vitro* metabolic systems, to limited solubility (which may prevent interaction with genetic targets) or to mutagen specificity (selective induction of genetic changes which are not scored in a particular test system).

**Epidemiological data**¹

Results from epidemiological studies and/or case reports were available for only a limited number of chemicals considered in this volume; the scarcity of epidemiological studies on these compounds was stressed by the Working Group. A longitudinal study on exposed cohorts that were followed up for a reasonable period was available for only one substance, trichloroethylene; this careful, but relatively small study involved 518 individuals observed for a total of 7688 person-years (Axelson *et al.*, 1978).

Barthel (1976) reported a high incidence of lung cancer (10 cases *versus* 0.54 expected) among farm workers exposed to various pesticides (including DDT, HCH, toxaphene, phenoxyacetic acids, organophosphorous compounds and arsenic-containing agents). This study illustrates the difficulties of distinguishing between various concomitant, and therefore confounding, exposures. It would thus probably be difficult to undertake meaningful epidemiological studies for many of the compounds reviewed in this volume, since exposed individuals can be expected to have had contact with other carcinogenic substances; the detection of a carcinogenic risk due specifically to a particular chemical can rarely be assessed. This does not, however, rule out the usefulness of occupational health epidemiology related to work practices.

¹The Working Group was aware of an epidemiological study in progress to evaluate the carcinogenic effects of pollutants in the general environment, including halogenated hydrocarbons in drinking-water (IARC, 1978d).
Reports of cases of cancer following exposure to a single chemical were available for HCH (Jedlicka et al., 1958), carbon tetrachloride (Johnstone, 1948; Simler et al., 1964; Tracey & Sherlock, 1968) and chlordane containing heptachlor (Infante & Newton, 1975).

Reports of medical surveys of workers exposed to particular chemicals were available for chlordane (Alvarez & Hyman, 1953; Fishbein et al., 1964; Morgan & Roan, 1969; Princi & Spurbeck, 1951), chloroform (Bomski et al., 1967) and dichloromethane (Kuzelova & Vlasak, 1966).

An epidemic of cutanea tarda porphyria in Turkey due to consumption of grain treated with hexachlorobenzene as a fungicide has been reported (Peters, 1976).

Other studies reported in the monographs, which do not relate directly to carcinogenicity in humans, include investigation of the concentrations of ß-HCH and heptachlor in fat from terminal patients; there are case reports of aplastic anaemia following exposure to HCH and lindane (over 30 cases) and to pentachlorophenol plus tetrachlorophenol (1 case); lindane has been shown to induce inhibition of cell division in human peripheral blood lymphocytes in vitro and to increase the frequency of chromatid breaks; and a significant excess of chromosome aberrations has been observed in lymphocyte cultures from farm workers exposed to polychlorocamphene. The relevance of this information to evaluations of carcinogenicity for humans is unknown; nonetheless, it must be stressed that, although many of the chemicals considered in this volume are of industrial importance and are produced in considerable amounts in many parts of the world, very few investigations have been carried out on their long-term effects in humans.
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Luquet, F.M., Goursaud, J. & Casalis, J. (1975) Pollution of human milk with organochlorine insecticide residues in France (Fr.). Lait, 55, 207-211


Simler, M., Maurer, M. & Mandard, J.C. (1964) Liver cancer and cirrhosis due to carbon tetrachloride (Fr.). Strasbourg Méd., December, pp. 910-918


THE MONOGRAPHS
PESTICIDES AND MICROBICIDES
A review on chlordane is available (Mercier, 1975).

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methano-1H-indene

Synonyms: Dichlorochlordene; 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene; 1,2,4,5,6,7,8,8-octachloro-4,7-methano-3a,4,7,7a-tetrahydroindane; octachloro-4,7-methanotetrahydroindane; 1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindan

Trade names: 1068; Aspon; Belt; CD 68; Chlordan; Chlorindan; Chlor Kil; Chlorodane; Corodane; Cortilan-neu; Dowchlor; ENT-9932; HCS 3260; Kypchlor; M 140; M 410; Niran; Octachlor; Octa-Klor; Oktaterr; Ortho-Klor; Synklor; Tat Chlor 4; Topichlor 20; Topiclor; Toxiclor; Velsicol 1068

1.2 Structural and molecular formulae and molecular weight

\[
\text{Cl} \quad \text{Cl} \\
\text{Cl} \quad \text{Cl} \\
\text{Cl} \quad \text{Cl} \\
\text{Cl} \quad \text{Cl}
\]

\[\text{C}_{10}\text{H}_6\text{Cl}_8 \quad \text{Mol. wt:} \quad 409.8\]

1.3 Chemical and physical properties

From Spencer (1973), unless otherwise specified

(a) Description: Viscous, amber-coloured liquid
Melting-point: 106-107°C (cis-isomer); 104-105°C (trans-isomer) (Martin & Worthing, 1977)

Density: \( d^{25} \) 1.59-1.63

Refractive index: \( n^{25} \) 1.56-1.57

Spectroscopy data: Infra-red, ultra-violet (Gore et al., 1971) and Raman spectra (Nicholas et al., 1976) have been tabulated.

Solubility: Insoluble in water; soluble in most organic solvents, including petroleum hydrocarbons

Viscosity: 75-120 centistokes at 55°C

Volatility: Vapour pressure is 0.00001 mm at 25°C.

Reactivity: Chlorine is lost in the presence of alkali.

1.4 Technical products and impurities

The approximate composition of technical chlordane is as follows: trans-chlordane (γ-chlordane), 24%; chlordene isomers, 21.5%; cis-chlordane (α-chlordane), 19%; heptachlor, 10%; nonachlor, 7%; Diels-Alder adduct of cyclopentadiene and pentachlorocyclopentadiene, 2%; hexachlorocyclopentadiene, 1%; octachlorocyclopentene, 1%; miscellaneous constituents, 15.5%.

Chlordane has been available in the US as dusts containing 5, 6 and 10% chlordane, as granules containing 5-33.3%, as wettable powders containing 25 and 40%, as oil solutions containing 2 and 20%, and as emulsifiable concentrates containing 4 and 8 lbs/gal (480 and 960 g/l) of the chemical (von Rumker et al., 1975).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Chlordane was first prepared in the 1940s by exhaustive chlorination of the cyclopentadiene-hexachlorocyclopentadiene adduct (Hyman, 1949). For its commercial manufacture, hexachlorocyclopentadiene is condensed with cyclopentadiene to produce chlordene, which is then chlorinated to give chlordane.
Chlordane was first produced commercially in the US in 1947 (US Tariff Commission, 1949); in 1976, only one US company reported production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977). US production in 1974 amounted to 9.5 million kg (US Environmental Protection Agency, 1976a). In 1972, US exports of chlordane were 2.3 million kg; none was imported (von Rumker et al., 1975).

Chlordane is not produced in Europe and has never been manufactured or imported into Japan.

(b) Use

In the past, chlordane was registered in the US for insecticidal use on a wide variety of fruit, vegetable and grain crops, as well as for non-crop uses such as on agricultural premises, ditch banks and roadsides (US Environmental Protection Agency, 1971).

In 1974, 9.5 million kg chlordane were used in the US as follows: pest control (commercial), 34.7%; home, lawn and garden, 29.9%; corn, 20.4%; turf, 5.9%; potatoes, 5.2%; tomatoes, 1.6%; ornamental shrubs, 1.2%; strawberries, 0.8%; and other vegetables, 0.3% (US Environmental Protection Agency, 1976a).

On 6 March, 1978, a cancellation proceeding instituted by the US Environmental Protection Agency on heptachlor/chlordane was terminated, and a settlement was reached for the contested uses (US Environmental Protection Agency, 1978). The settlement allows for limited usage of chlordane by crop, location (in some cases), maximum time interval for permitted use and amount allowed for specific uses (technical chlordane), as follows: citrus, California and Texas, until 31 December 1979, a total of 36.3 thousand kg; grapes, California, until 1 July 1980, 40.9 thousand kg; flax, until 1 October 1978, 6.8 thousand kg; and strawberries, until 1 August 1979, 22.7 thousand kg. In addition, 159 thousand kg of technical chlordane may be used, until 31 December 1980, on fire ants in 9 US states; no more than 227 thousand kg may be used for nursery stock quarantine programs until 31 December 1979 (Anon. 1978a). After 1 July 1983, the only approved use for chlordane will be for underground termite control (Anon. 1978b).

A tolerance of 0.3 mg/kg has been established by the US Environmental Protection Agency for residues of chlordane (containing not more than 1% of the intermediate compound, hexachlorocyclopentadiene, as an impurity) in or on approximately 50 fruit and vegetable crops (US Environmental Protection Agency, 1976b).

The Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues, in November 1972, re-established residue tolerances ranging from 0.02–0.5 ppm (mg/kg)
for the sum of the *cis*- and *trans*-isomers of chlordane and oxychlordane (WHO, 1973). An acceptable daily intake (ADI) for humans of 0-0.001 mg/kg bw was confirmed in December 1977 (FAO/WHO, 1978).

The US Occupational Safety and Health Administration's health standards require that an employee's dermal exposure to chlordane not exceed 0.5 mg/m³ in the workplace in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977).

2.2 Occurrence

Chlordane is not known to occur as a natural product.

Reviews on the occurrence of chlordane in fish and wildlife, air, soil, water, crops and food items have been published (Fairchild *et al.*, 1976; Fitzhugh *et al.*, 1976).

(a) Air

Chlordane was found in 10/13 air samples taken around Bermuda and between Bermuda and Rhode Island during February-June 1973; levels ranged from <0.005-0.90 ng/m³ (Bidleman & Olney, 1974).

(b) Water and sediments

The occurrence of chlorinated cyclopentadiene pesticides, including chlordane, in US drinking-water has been reviewed (Safe Drinking Water Committee, 1977). Tabulations of the occurrence of chlordane in rainwater, river-water, drinking-water, land runoff and chemical plant effluent water in the US have also been published (Eurocop-Cost, 1976; Shackelford & Keith, 1976).

Rain, snow and lake water in Hawaii have been analysed for organochlorine pesticides: chlordane was found in 4 samples of rainwater in parts per trillion (ng/l) amounts (Bevenue, *et al.*, 1972).

Chlordane was found in two streams in Ontario at levels ranging from <1-21 ng/l (*trans*-chlordane) (Miles & Harris, 1973), in drainage ditches, wells, ponds and reservoirs in Nova Scotia at levels ranging from 0-31.3 µg/l (*cis*-chlordane) and 0-17.89 µg/l (*trans*-chlordane) (Burns *et al.*, 1975) and in the lower Mississippi River at concentrations which varied during the year from 0.4-1.2 ng/l (*trans*-chlordane) (Brodtmann, 1976).

*cis*-Chlordane was found in 89.9% of filtered samples and 42.7% of unfiltered samples of sea-water from a marina in Hawaii, and *trans*-chlordane in 67.7% of filtered and 67.7% of unfiltered samples. The authors suspected that organic particulate matter interfered with the determination of *cis*-chlordane in the unfiltered samples. Of samples of sediment from the same marina, 97.2% contained *cis*-chlordane, in a
concentration range of 0.4-5.27 µg/kg (average, 3.0), and 92.7% contained trans-chlordane, in a concentration range of 1.33-5.12 µg/kg (average, 2.3) (Tanita et al., 1976).

Chlordane was found in concentrations ranging from 4.3-8.0 µg/kg in bottom material from 36/39 streams tributary to San Francisco Bay (Law & Goerlitz, 1974), in 32.7% of 214 sediment samples from surface waters in southern Florida (Mattraw, 1975), in bottom mud from 2 streams in Ontario, at levels ranging from <0.1-3.1 µg/kg (trans-chlordane) (Miles & Harris, 1973), and in sediments from streambeds and drainage ditches in Nova Scotia, at levels ranging from 0-664 µg/kg (cis-chlordane) and 0-51 µg/kg (trans-chlordane) (Burns et al., 1975).

(c) Soil

Residues of chlordane were found in 16-64% of 400 soil samples taken from 8 cities, at levels of 0.02-20.48 mg/kg (Wiersma et al., 1972), and in 7.4-42.3% of 356 soil samples taken from 14 cities, at levels of 0.04-13.9 mg/kg (Carey et al., 1976).

In 1970, as part of the National Soils Monitoring Program, data on soil and crop residues were collected from 1506 cropland sites in 35 states; chlordane was detected 165 times, in a range of 0.01-13.34 mg/kg (Crockett et al., 1974).

The half-life of chlordane in soil when used at agricultural rates is approximately 1 year (Anon., 1976).

(d) Food and drink

In a continuing programme involving the monitoring of pesticide residues in food, the US Department of Health, Education, and Welfare found chlordane in a trace amount in one composite sample of garden fruits collected at retail outlets in the period July 1972-July 1973 (US Food & Drug Administration, 1975a), and in one composite sample of grains and cereals collected at retail outlets in the period August 1973-July 1974 (US Food & Drug Administration, 1977).

trans-Chlordane was found in 78% of chicken eggs, at an average concentration of 2 µg/kg, and cis-chlordane was found in 81% of eggs, at an average concentration of 1 µg/kg (Mes et al., 1974).

Of 200 cow's milk samples analysed in the US, 87% were positive for chlordane, with levels ranging from 0.02-0.06 mg/l (Safe Drinking Water Committee, 1977).

Chlordane was found in Canadian meat samples at levels ranging from 0-106 µg/kg in beef, 0-32 µg/kg in pork and 0-70 µg/kg in fowl (Saschenbrecker, 1976).
One-third of small oysters sampled in Hawaii contained cis-chlordane in a concentration range of 2.34-57.64 µg/kg (18.64 average), and 13% contained trans-chlordane in an average concentration of 8.17 µg/kg. All of the large oysters sampled contained cis-chlordane in a concentration range of 1.58-22.99 µg/kg (8.277 average), and 64% contained trans-chlordane in a concentration range of 1.35-23.38 µg/kg (7.865 average) (Tanita et al., 1976).

(e) Animals

cis-Chlordane was present in the carcasses of 10/37 bald eagles at concentrations of 0.11-7.4 mg/kg (0.30 median) and in the brains of 7 of the birds at concentrations of 0.05-1.7 mg/kg (0.11 median) (Cromartie et al., 1975). Fish eggs taken from Iowa rivers in 1971 were found to have chlordane residues of 24-350 µg/kg (Johnson & Morris, 1974).

(f) Occupational exposure

A 1974 National Occupational Hazard Survey in the US indicated that workers primarily exposed to chlordane were those in gas and other service industries, disinfecting and exterminating occupations and cigarette manufacture (National Institute for Occupational Safety & Health, 1977).

2.3 Analysis

A review of analytical methods for chlordane residues has been published (Fitzhugh et al., 1976); extraction and clean-up methods have also been evaluated (US Food & Drug Administration, 1975b). Methods used for the analysis of chlordane in environmental samples are listed in Table 1.

Other analytical methods designed to isolate or identify chlordane include gel-permeation chromatography (Johnson et al., 1976) and gas chromatography/mass spectrometry (Keith et al., 1976).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Epstein (1976) reported a previously unpublished study by the International Research and Development Corporation, carried out in 1973, in which groups of 100 male and 100 female Charles River CD-1 mice, 6 weeks of age, were fed technical-grade chlordane (purity not given) at three dose levels, 5, 25 and 50 mg/kg diet, for 18 months. Excluding 10 animals sacrificed from each group for interim study at 6 months, mortality at 18 months ranged from 27-49%, with the exception of males and females receiving the
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granules</td>
<td>Extract (acetone) in Soxhlet, evaporate to dryness, dissolve (carbon disulphide), evaporate, repeat dissolution in carbon disulphide and evaporation 4 times, dry, dissolve (carbon disulphide)</td>
<td>IR</td>
<td></td>
<td>Malins (1973)</td>
</tr>
<tr>
<td>Pesticides</td>
<td>Extract (acetone), filter or centrifuge</td>
<td>TLC</td>
<td></td>
<td>Bontoyan &amp; Jung (1972)</td>
</tr>
<tr>
<td>Emulsifiable concentrates</td>
<td>Dilute (toluene), dechlorinate</td>
<td>Titration</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Dusts, granular impregnates &amp; wettable powders</td>
<td>Extract (benzene) in Soxhlet, dechlorinate</td>
<td>Titration</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Liquids, high-concentration solids</td>
<td>Dilute (methanol-benzene)</td>
<td>Colorimetry</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Low-concentration solids</td>
<td>Extract (pentane) in Soxhlet</td>
<td>Colorimetry</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Soil</td>
<td>(a) Extract (hexane-acetone-methanol) in Soxhlet, transfer to hexane</td>
<td></td>
<td></td>
<td>Nash et al. (1973)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
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<tr>
<td>Foods</td>
<td>(b) Wet sample with ammonium chloride solution, extract (hexane-acetone), decant, repeat extraction</td>
<td>GC/ECD; TLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crops</td>
<td>(c) Prepare Florisil column, add soil, extract (hexane-acetone-methanol) on column, wash with water</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>Extract (acetonitrile), filter, liquid/liquid partition, CC</td>
<td>GC/ECD</td>
<td>0.005 mg/kg</td>
<td>Cochrane et al. (1975)</td>
</tr>
<tr>
<td></td>
<td>Extract (acetone), filter or centrifuge</td>
<td>TLC</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
</tbody>
</table>

Abbreviations: IR - infra-red spectrometry; TLC - thin-layer chromatography; CC - column chromatography; GC/ECD - gas chromatography/electron capture detection
50 mg/kg diet level, in which mortalities of 86 and 76%, respectively, were seen. In addition to high mortality, a relatively large number of animals were lost by autolysis. A dose-related increased incidence of liver nodules was reported in the 25 and 50 mg/kg diet test groups; a dose-related increased incidence of hepatocytomegaly was found in all test groups; and a dose-related increased incidence of nodular hyperplasia, which was statistically significant at the 25 and 50 mg/kg diet levels (P<0.01), was reported. Subsequent re-evaluation of the histology of this study, however, revealed a significant incidence of hepatocellular carcinomas compared with controls. In males receiving 0, 5, 25 or 50 mg/kg diet, hepatocellular carcinomas were found in 3/33, 5/55, 41/52 and 32/39 animals, respectively; in females, the respective incidences were 0/45, 0/61, 35/20 and 26/37.

Groups of 50 male and 50 female B6C3Fl hybrid mice, 5 weeks of age, were fed analytical-grade chlordane, consisting of 94.8% chlordane (71.7% cis-chlordane and 23.1% trans-chlordane), 0.3% heptachlor, 0.6% nonachlor, 1.1% hexachlorocyclopentadiene, 0.25% chlordene isomers and other chlorinated compounds for 80 weeks. Males received initial levels of 20 and 40 mg/kg diet, and females 40 and 80 mg/kg diet; time-weighted average dietary concentrations were 30 and 56 mg/kg diet for males and 30 and 64 mg/kg diet for females. There were 20 male and 10 female matched controls and 100 male and 80 female pooled controls. Survival in all groups was relatively high: over 60% in treated males and over 80% in treated females, and over 90% in male and female controls. A dose-related increase in the incidence of hepatocellular carcinomas was found in males and females in the high-dose group. The incidences were 43/49 and 34/49 in high-dose males and females, respectively, and 16/48 and 3/47 in low-dose males and females, respectively, compared with 2/18 and 0/19 in male and female matched controls, respectively (National Cancer Institute, 1977).

Rat: Groups of 50 male and 50 female, 5-week-old Osborne-Mendel rats were administered analytical-grade chlordane in the diet for 80 weeks, at initial dose levels of 400 and 800 mg/kg for males and 200 and 400 mg/kg for females. These were reduced during the experiment due to adverse toxic effects; the time-weighted average dietary concentrations were 407 and 203 mg/kg diet for males and 241 and 121 mg/kg diet for females. There were 10 male and 10 female matched controls and 60 male and 60 female pooled controls. Survivors were killed at 80 weeks, at which time approximately 50% of treated and control males and 60% of treated females and 90% of control females were still alive. In all treated animals combined there was an excess incidence of follicular-cell thyroid neoplasms (10/75 in treated females and 7/65 in treated males versus 0/10, 3/58, 0/6 and 4/51 in matched and pooled female and male controls); there was an excess of malignant fibrous histiocytomas in all treated males (8/88 versus 0/8 and 2/58 in matched and pooled controls) (National Cancer Institute, 1977).
3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The acute oral LD_{50} of chlordane is 335+40 mg/kg for male rats and 430+40 mg/kg bw for female rats (Gaines, 1960). The oral LD_{50} for mice is 430 mg/kg bw.

Commercial samples of chlordane may contain hexachlorocyclopentadiene (see section 1.4), whose toxicity has been described (WHO, 1968). When chlordane is given orally to rats at a dose of 25 mg/kg bw/day for 15 days it has no toxic effects, while 50 mg/kg bw or more result in toxic effects and death; it has cumulative toxic effects (Ambrose et al., 1953). The toxic effects of chlordane in rats include stimulation of the central nervous system, stomach ulcers, inflammation of the intestine, nephritis, hepatitis, an increase in liver weight, coma and death (Boyd & Taylor, 1969).

Chlordane induces hepatic drug-metabolizing enzymes in all species examined (reviewed by Fouts, 1970). Oestradiol-17β and oestrone metabolism were also stimulated by chlordane pretreatment in mice and rats, respectively (Welch et al., 1971).

Chlordane decreased fertility in female and male rats (Ambrose et al., 1953) and in female mice (Welch et al., 1971).

Embryotoxicity and teratogenicity

In an abstract, it was reported that mice maintained for 4 months on a diet containing 100 mg/kg diet chlordane had decreased viability of offspring (Deichmann & Keplinger, 1966). Ambrose et al. (1953) also reported reduced survival of offspring.

Absorption, distribution, excretion and metabolism

Rats excreted about 5% of an oral dose of chlordane in the urine and the rest in the faeces over 7 days. Only small amounts of unchanged chlordane were detected; the several metabolites have various degrees of dechlorination and ring hydroxylation (Barnett & Dorough, 1974). Oxychlordane (α-chloroepoxide) was the major residue in fat, liver and kidney (Barnett & Dorough, 1974; Street & Blau, 1972); it was also detected in the milk of cows administered chlordane (Lawrence et al., 1970).

Both cis- and trans-chlordane were metabolized in rats via 1,2-dichlorochlordene (I) and oxychlordane (II) to 1-exo-hydroxy-2-chlorochlordene (III) and 1-exo-hydroxy-2-endo-chloro-2,3-exo-epoxychlordene (IV) (see
Fig. 1), which are not readily metabolized further, and to various other hydroxylated products. Another major metabolic route for the cis isomer involves more direct hydroxylation to form 1-exo-hydroxydihydrochlordene and 1,2-trans-dihydroxydihydrochlordene. The cis isomer was excreted as hydroxylated metabolites more readily than the trans isomer, which was more readily converted to oxychlordane. Heptachlor was a minor metabolite of both isomers (Tashiro & Matsumura, 1977).

Mutagenicity and other related short-term tests

Pure chlordane was not mutagenic in any strain of Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, TA100) that was tested (Tardiff et al., 1976). Chlordane induced gene conversions in Saccharomyces cervisiae strain D4 (Chambers & Dutta, 1976).

cis-Chlordane weakly inhibited sporulation in Helminthosporium sativum (Pero & Owens, 1971). Chlordane (60% pure) was not mutagenic in a spot test in the reverse mutation assay with Escherichia coli WP2 (try') (Ashwood-Smith et al., 1972).

A 0.01 mM concentration of chlordane induced ouabain-resistant mutants in Chinese hamster V79 cells (Ahmed et al., 1977a).

Neither cis-chlordane (42, 58 and 290 mg/kg bw i.p., or 5 daily oral doses of 75 mg/kg bw) nor the trans isomer (5 daily oral doses of 50 mg/kg bw) had a significant effect in the dominant lethal assay in mice (Epstein et al., 1972). Similar negative results were reported in dominant lethal studies with mice that were given single doses (50 or 100 mg/kg bw) of technical-grade chlordane either by oral intubation or by i.p. administration (Arnold et al., 1977).

trans-Chlordane (99.8% pure) inhibited division of L-5178Y cells in culture but did not inhibit DNA synthesis (Brubaker et al., 1970); cis-chlordane had no effect on DNA repair synthesis in HeLa cells (Brandt et al., 1972). In concentrations of 1, 10, 100 and 1000 μM, chlordane induced unscheduled DNA synthesis (measured autoradiographically) in SV-40 transformed human cells (VA-4) in culture, but the effect disappeared when rat liver microsomes were added to the culture during treatment. The DNA repair kinetics and the size of the repaired regions resulting from chlordane treatment (studied by 313 nm photolysis of repaired regions containing bromodeoxyuridine) were similar to that after exposure to 254 nm ultra-violet radiation (Ahmed et al., 1977b).

Technical-grade chlordane contains a volatile component (not specified) which causes mutations in S. typhimurium TA100, but not in TA1535, TA1537, TA1538 or TA98 (Tardiff et al., 1976).

(b) Humans

Symptoms of acute chlordane poisoning in man include nervousness, convulsions and loss of coordination (Aldrich & Holmes, 1969). An oral
Figure 1. Simplified metabolism of chlordane in rats (adapted from Tashira & Matsumura, 1977)
dose of 100 mg/kg bw was fatal (Derbes et al., 1955).

In a case of acute chlordane poisoning in a 2-year-old child, the half-life of serum chlordane was about 21 days; 300 times more chlordane entered the fat than the urine (Curley & Garrettson, 1969).

In 1976, when a segment of a municipal water system was contaminated with chlordane, 13 persons showed gastrointestinal (nausea, vomiting) or neurological symptoms (Harrington et al., 1978).

Metabolites of chlordane, trans-nonachlor and oxychlordane, have been found in the tissues of non-occupationally exposed people in the US (Sovocool & Lewis, 1975); 0.03-0.40 mg/kg oxychlordane have been found in adipose tissue in the general population (Biros & Enos, 1973).

3.3 Case reports and epidemiological studies

Several clinical studies have been made of men exposed to chlordane during its manufacture or during its use as a pesticide (Alvarez & Hyman, 1953; Fishbein et al., 1964; Infante & Roan, 1969; Princi & Spurbeck, 1951) [The Working Group noted that these studies were uninformative with regard to the carcinogenicity of chlordane, since each study had serious limitations, e.g., small numbers, disproportionate number of current employees, short follow-up time since first exposure].

Infante et al. (1978) reviewed 25 previously reported cases of blood dyscrasias associated with exposure to chlordane or heptachlor, either alone or in combination with other drugs, in conjunction with 3 newly diagnosed cases of aplastic anaemia and 3 of acute leukaemia associated with a prior history of exposure to technical-grade chlordane containing 3-7% heptachlor. During the period December 1974-February 1976, 5 of 14 children with neuroblastoma admitted to one paediatric hospital had a positive history of pre- or postnatal exposure to technical-grade chlordane containing 3-7% heptachlor; history of exposure to chlordane had not yet been ascertained for the remaining 9 cases.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Chlordane (analytical grade) was tested in one experiment in mice and in one in rats by oral administration. It produced hepatocellular carcinomas in mice of both sexes; in rats, the results were inconclusive. A re-evaluation of unpublished studies involving the oral administration of technical-grade chlordane to mice of another strain confirmed the hepatocarcinogenicity of chlordane for mice of both sexes.

Chlordane induced gene conversions in yeast but was not shown to be mutagenic in bacteria. It induced mutations in mammalian cells in culture but was negative in dominant lethal tests in mice.
4.2 Human data

Case reports suggest a relationship between exposure to chlordane or heptachlor (either alone or in combination with other compounds) and blood dyscrasias. Another publication has also suggested an association with acute leukaemia; an association between both pre- and postnatal exposure to technical-grade chlordane and the development of neuroblastomas in children was also suggested.

No epidemiological studies were available to the Working Group.

The extensive production and use of chlordane over the past several decades, together with the persistent nature of the compound, indicate that widespread human exposure occurs. This is confirmed by many reports of its occurrence in the general environment and in human tissues.

4.3 Evaluation

There is sufficient evidence that chlordane is carcinogenic in mice. A report of a number of cases of cancer in humans was also available, but these data do not allow an evaluation of the carcinogenicity of chlordane to humans to be made.
5. References


Mercier, M. (1975) Preparatory Study for Establishing Criteria (Dose/Effect Relationships) For Humans on Organochlorine Compounds, i.e. Pesticides and their Metabolites, Doc. No. 1347/75e, Luxembourg, Commission of the European Communities, pp. 27, 58-59, 177a, 211-212


Safe Drinking Water Committee (1977) *Drinking Water and Health*, Washington DC, National Academy of Sciences, pp. 556-561


US Food & Drug Administration (1975a) Compliance Program Evaluation, Total Diet Studies: FY 1973 (7320.08), Washington DC, Bureau of Foods, Table 3


Literature on the environmental effects of chlordecone has been reviewed recently (Black, 1977; Huff & Gerstner, 1978). A review on chlordecone is available (Epstein, 1978).

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 143-50-0

Chem. Abstr. Name: 1,1a,3,3a,4,5,5a,5b,6-Decachlorooctahydro-1,3,4-metheno-2H-cyclobuta[cd]pentalen-2-one

Synonyms: Decachloroketone; decachlorooctahydro-1,3,4-metheno-2H-cyclobuta[cd]pentalen-2-one; decachloropentacyclo(5.2.1.0²⁶.0³⁹.0⁵,⁸)decan-4-one; decachlorotetracyclodecanone

Trade names: Compound 1189; ENT 16391; CC 1189; Kepone; Merex

1.2 Structural and molecular formulae and molecular weight

\[ C_{10}Cl_{10}O \]

Mol. wt: 490.6

1.3 Chemical and physical properties of the pure substance

From Spencer (1973) unless otherwise specified

(a) Description: Tan-to-white solid

(b) Melting-point: Sublimes with some decomposition at about 350°C
(c) **Solubility:** Practically insoluble in water (0.4% at 100°C); soluble in strongly alkaline aqueous solutions; readily soluble in acetone, less soluble in benzene and light petroleum; soluble in alcohols, ketones and acetic acid (Windholz, 1976)

(d) **Volatility:** Vapour pressure is < $3 \times 10^{-7}$ mm at 25°C (Allied Chemical Corp., undated).

(e) **Stability:** Stable to about 350°C

(f) **Reactivity:** Readily forms hydrates on exposure to standard temperatures and humidities; noncorrosive

1.4 **Technical products and impurities**

Chlordecone was available in the US until 1976 as a technical grade, typically containing 94.5% of the chemical (72.3% chlorine content), 0.30% methanol insolubles, 5.09% water, 0.01% sulphate and 0.10% hexachlorocyclopentadiene. Chlordecone was also available as a wettable powder containing 50% of the chemical, an emulsifiable concentrate containing 2 pounds per US gallon, (~ 200 g/l), and granules and dusts containing 5 or 10% (Spencer, 1973).

2. **Production, Use, Occurrence and Analysis**

A review on chlordecone has been published (Sterrett & Boss, 1977).

2.1 **Production and use**

(a) **Production**

Synthesis of chlordecone was first reported in 1952 (Gilbert & Giolito, 1952), by the dimerization of hexachlorocyclopentadiene catalysed by sulphur trioxide. This method has been used for its commercial production (Sterrett & Boss, 1977).

Commercial production of chlordecone in the US was first reported in 1966 (US Tariff Commission, 1968) and was last reported by a government agency in 1973 (US International Trade Commission, 1975). Production during that period was by a single company and is reported to have been intermittent; however, in 1974 continuous operation at the rate of 1350–2700 kg/day was initiated. Between 1968 and 1974, 720 thousand kg were produced (Epstein, 1978). Another plant, which operated for 18 months, produced 770 thousand kg chlordecone before it was closed down in late July 1975. Over 90% of the chemical produced during this period was exported to Latin America, Europe and Africa (Library of Congress, 1977; Sterrett & Boss, 1977).
Chlordecone is believed to be produced by one company in Europe (Epstein, 1978). It has never been produced or imported into Japan.

(b) Use

The only known use for chlordecone is as an insecticide. In the US, products containing this chemical are classified as 'accessible' or 'inaccessible' products: examples of 'inaccessible' products are household ant and roach traps containing a small amount of confined chlordecone; 'accessible' products are those which are applied to crops or structures for control of insects. Until 1 August 1976 (Epstein, 1978) chlordecone was registered in the US for use on bananas, non-bearing citrus trees, tobacco and ornamental shrubs and for control of insects that attack structures (US Environmental Protection Agency, 1973).

On 17 June 1976, the US Environmental Protection Agency (EPA) announced that it had notified the sole producer of chlordecone of the cancellation of the registration of their 12 products containing chlordecone (US Environmental Protection Agency, 1976). Cancellation was effective 45 days from the date of the notice. Agreement was reached in July 1977 between the EPA and the registrants of several inaccessible chlordecone products that the products would be voluntarily cancelled as of 1 May 1978. This agreement provides that all stocks of these inaccessible chlordecone products that were in existence before 1 May, 1978 may be sold, distributed and used indefinitely (Anon., 1977a). In October 1977, the EPA ruled that existing stocks of accessible products containing chlordecone could not be sold in the US (Anon., 1977b). On 27 January, 1978, the EPA revoked all residue tolerances for chlordecone in or on raw agricultural commodities. This action prevents the introduction of bananas containing residues of chlordecone into the US (US Environmental Protection Agency, 1978).

In February 1976, the US National Institute for Occupational Safety and Health recommended that chlordecone be controlled in the workplace so that its airborne concentration be no greater than 1 \( \mu g/m^3 \) of breathing zone air. This standard is part of a programme to protect workers during up to a 10-hr workday in a 40-hr work week over a working lifetime (Anon., 1976a).

2.2 Occurrence

Chlordecone is not known to occur as a natural product, but it is a degradation product of the insecticide mirex (Carlson et al., 1976; see monograph, p. 283).

Chlordecone was detected in soil at a level of 0.02 \( \mu g/g \) 12 years after application of 1 \( \mu g/g \) mirex, and was found in a shallow pond at a level of 10 \( \mu g/g \) 5 years after the crash of an aircraft containing mirex (Carlson et al., 1976).
In the US, detectable levels of chlordecone have been found in 400 samples of air, drinking-water, plant life and municipal waste in a town where chlordecone was manufactured. Sludge near the town's sewage treatment plant contained 200-600 mg/kg chlordecone; waste-water at the sewage treatment plant contained levels of 0.1-10 mg/l of the chemical; fish and shellfish in a nearby river had 0.1-20 mg/kg; and water in the river, 0.1-4 μg/l. Studies showed that the air in a town about 16 miles from the plant had levels of 0.1-20 ng/m³, while samples 100 metres from the plant showed 0.2-50 mg/m³ during the 1-year sampling period. At that time, chlordecone comprised about 1-40% of the total suspended particulates in air in some areas (Anon., 1975).

Tests run by the state of Maryland in July 1976 on Chesapeake Bay water showed chlordecone levels of 0.04-0.08 mg/l (Anon., 1976b).

A single application of chlordecone as a wettable powder containing 50% of the chemical to apple trees at a rate of 2 pounds/acre (2.2 kg/ha) resulted in an initial residue level of 1.4 mg/kg, which decreased to 0.3 mg/kg after approximately 3 months. When treatment involved 8 fortnightly applications over 3.5 months, residues fell from 5.0 mg/kg at the end of treatment to 1.4 mg/kg by harvest time 2 months later (Brewerton & Slade, 1964).

In February 1976, a study sponsored by the US Environmental Protection Agency reported chlordecone in 9 of 200 mother's milk samples taken in southeastern US (Anon., 1976c).

Chlordecone was found at levels of 0.165-26 μg/ml in the blood of 32 workers who manufactured chlordecone (Epstein, 1978). A 1974 US National Occupational Hazard Survey determined that workers in the disinfecting and exterminating industries are exposed to chlordecone (National Institute for Occupational Safety & Health, 1977a).

2.3 Analysis

Methods used for the analysis of chlordecone in environmental samples are listed in Table 1.

Chromatographic methods, including thin-layer chromatography (Roscher & Onley, 1977) and gas chromatography/electron capture detection (Blanke et al., 1977), have also been used to separate and quantitate chlordecone.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F1 hybrid mice, approximately 6 weeks of age, were fed technical-grade chlordecone (about 98% pure)
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentrates and wettable powders</td>
<td>Extract (acetone), decant, evaporate to dryness, dissolve (decane), boil, cool</td>
<td>IR</td>
<td>(C = 0 hand)</td>
<td>Allied Chemicals Corp. (1966)</td>
</tr>
<tr>
<td>Technical-grade</td>
<td>Extract (acetone-decane), heat to remove acetone, boil, cool</td>
<td>IR</td>
<td>(C = 0 hand)</td>
<td>Allied Chemicals Corp. (1966)</td>
</tr>
<tr>
<td>Air</td>
<td>Trap on filter and back-up impinger containing sodium hydroxide solution, extract filter (benzene-methanol), acidify extract (benzene), bulk extracts</td>
<td>GC/ECD</td>
<td>0.1 µg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977b)</td>
</tr>
<tr>
<td>Food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apples</td>
<td>Extract (benzene), decant, filter</td>
<td>GC/ECD</td>
<td>0.08 mg/kg</td>
<td>Brewerton &amp; Slade (1964)</td>
</tr>
<tr>
<td>Potatoes</td>
<td>Extract (methylene chloride), CC</td>
<td>TLC (revelation: silver nitrate/ultra-violet)</td>
<td>0.2 mg/kg</td>
<td>Proszynska (1977)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC/ECD</td>
<td>0.005 mg/kg</td>
<td>Proszynska (1977)</td>
</tr>
<tr>
<td>Bananas</td>
<td>Extract (isopropanol-benzene), evaporate to dryness, dissolve (hexane), liquid/liquid partition, extract (benzene)</td>
<td>GC/microcoulo-</td>
<td>0.003 mg/kg</td>
<td>Allied Chemical Corp. (1963)</td>
</tr>
</tbody>
</table>

Abbreviations: IR - infra-red spectrometry; GC/ECD - gas chromatography/electron-capture detection; CC - column chromatography; TLC - thin-layer chromatography
at two levels in the diet for 80 weeks; there were 20 male and 10 female matched controls and 50 male and 40 female pooled controls. Males received initial levels of 40 mg/kg diet, and females 40 and 80 mg/kg diet; these levels were reduced during the experiment due to adverse toxic effects. The time-weighted average dietary concentrations were 20 and 23 mg/kg diet for males and 20 and 40 mg/kg diet for females. Survivors were sacrificed 90 weeks after the start of treatment; survival at that time was 58 and 50% in low- and high-dose male mice, respectively, in contrast with over 80% in all other groups (low- and high-dose females and controls). Well-differentiated hepatocellular carcinomas were found in over 80% of all treated males: in 39/48 low- and 43/49 high-dose males, compared with 6/19 matched male controls; and in 26/50 low- and 23/49 high-dose females, compared with none in female controls (National Cancer Institute, 1976).

Rat: Epstein (1978) reported a previously unpublished study by Larson et al., carried out in 1961, in which groups of 40 male and 40 female albino rats of an unspecified strain were administered technical chlordecone (approximately 94% pure) at 6 dose levels in the diet for 24 months, starting at an unspecified 'young age'. The dietary concentrations were 1, 5, 10, 25, 50 and 80 mg/kg diet for both males and females. Groups of 12-14 animals for each dose and for each sex were killed for interim histological examination at 13, 52 and 56 weeks. All remaining survivors were killed 24 months after the start of treatment. All males and females receiving 50 and 80 mg/kg diet had died by 25 weeks; mortality was also high in those given 25 mg/kg diet and in all males given more than 1 mg/kg diet; about 25% of controls were still alive at 2 years. Hepatocellular carcinomas were seen in 2/3 male survivors in the 25 mg/kg diet group, in 3/9 female survivors in the 10 mg/kg diet group and in 1/3 female survivors in the 25 mg/kg diet group. None were observed in other groups or in controls.

Groups of 50 male and 50 female Osborne-Mendel rats, approximately 6 weeks of age, were administered chlordecone (about 98% pure) in the diet for 80 weeks; there were 10 male and 10 female matched controls and 105 male and 100 female pooled controls. Initial dose levels were 15 and 30 mg/kg diet for males and 30 and 60 mg/kg diet for females; these levels were reduced during the experiment due to adverse toxic effects. The time-weighted average dietary concentrations were 8 and 24 mg/kg diet for males and 18 and 26 mg/kg diet for females. Survivors were killed 112 weeks after the start of treatment, at which time survival was low in all treated groups. An increased incidence of hepatocellular carcinomas was found in female rats given the high dose: 10/45 compared with 0/100 pooled controls (P<0.0001); and there were 3/44 hepatocellular carcinomas in high-dose males compared with 0/105 in pooled controls (P<0.05). Neoplastic nodules were diagnosed in 2 low-dose male rats, but none in the controls or in the high-dose group, and in 2 high-dose female rats, with 1 in the controls and none in the low-dose group. Extensive liver hyperplasia, fatty infiltration and degeneration were also found in rats of both sexes in both dose groups, while no such changes were seen in
controls. Increased incidences of thyroid carcinomas and adenomas were observed in low-dose males and of reproductive tract tumours in both low- and high-dose females, but the differences were not statistically significant (National Cancer Institute, 1976).

3.2 Other relevant biological data

The toxicity of chlordecone (including its cumulative effects) has been reviewed (Epstein, 1978).

(a) Experimental systems

Toxic effects

The single oral LD$_{50}$ of chlordecone in rats is 125 mg/kg bw; the LD$_{50}$ by dermal application is > 2000 mg/kg bw (Gaines, 1969). The single oral LD$_{50}$ for hens is 480 mg/kg bw and between 220 and 440 mg/kg bw when chlordecone is incorporated in the diet for longer periods (Sherman & Ross, 1961). The estimated maximum tolerated dose for a 6-week dietary exposure was 30 mg/kg diet for male rats, 60 mg/kg diet for female rats and 40 and 80 mg/kg diet for male and female mice, respectively (National Cancer Institute, 1976).

Both rats and mice administered high doses of chlordecone exhibited nervous tremors (National Cancer Institute, 1976). In mice fed diets containing 30-100 mg/kg diet chlordecone, the size of the liver was increased, and focal necrosis, cellular hypertrophy, hyperplasia and congestion were observed, depending on the length of treatment (Huber, 1965). Quail livers were also markedly enlarged by chlordecone exposure (Atwal, 1973; McFarland & Lacy, 1969).

Chicks, quail and fish showed neurotoxic symptoms on exposure to chlordecone (Couch et al., 1977; McFarland & Lacy, 1969; Sherman & Ross, 1961). A strong correlation was shown between the neurotoxic effects of chlordecone and the inhibition of Mg$^{2+}$-ATPases in fish brain (Desaiah & Koch, 1975; Yap et al., 1975) and rat liver (Desaiah et al., 1977).

Feeding mice and rats for 2 weeks with 50 mg/kg diet chlordecone induced hepatic mixed-function oxidase activity (Fabacher & Hodgson, 1976; Mehendale et al., 1977).

Female mice maintained on 40 mg/kg diet chlordecone failed to reproduce; the animals appeared to be in constant oestrus, and developed large ovarian follicles but no corpora lutea. The effects were consistent with a partial blockage of the release of luteinizing hormone from the pituitary (Huber, 1965). Chlordecone had an oestrogen-like effect on the oviducts of immature female quail and on the testes of males (Eroschenko & Wilson, 1975).
Embryotoxicity and teratogenicity

The size and numbers of litters were decreased in female mice fed doses as low as 10 mg/kg diet chlordecone for one month before mating (Good et al., 1965).

Chlordecone was given by gastric intubation in doses of 2, 6 and 10 mg/kg bw/day to rats and 2, 4, 8 and 12 mg/kg bw/day to mice on days 7-16 of gestation. In rats, 19% of dams that received 10 mg/kg bw/day died; the foetuses of those which survived exhibited a variety of toxic effects, such as reduced body weight, reduced degree of ossification, oedema, undescended testes, enlarged renal pelvis and cerebral ventricles. Male rats showed no reproductive impairment. Lower dose levels only reduced foetal weight and degree of ossification. In mice, foetotoxicity occurred only in the highest dose group and was manifested by increased foetal mortality and clubfoot (Chernoff & Rogers, 1976).

In an abstract, it was reported that rats were exposed by gastric intubation to 1, 2 or 4 mg/kg bw/day chlordecone beginning on day 2 of gestation and ending at weaning. At parturition, all control animals and those receiving 1 mg/kg bw/day delivered healthy pups. Two-thirds of pregnant females that received 2 mg/kg bw/day and all those that received 4 mg/kg bw aborted or had stillbirths. Electroencephalograms and visual-evoked responses obtained in the offspring at 24 days of age indicated that chlordecone induces central nervous system impairment in the perinatal rat (Rosenstein et al., 1977).

Chlordecone also decreased egg production in hens; and chicks of chlordecone-fed hens exhibited neurotoxic symptoms (Naber & Ware, 1965).

Absorption, distribution, excretion and metabolism

After mice were exposed to chlordecone for 5 months, maximum accumulation of residues occurred mainly in the liver; residues were also found in brain, kidneys and body fat. On withdrawal of treatment, liver chlordecone levels decreased, and the neurotoxic effects were reversed. There was no evidence of metabolism (Huber, 1965).

Chlordecone was well absorbed and distributed throughout the body after its oral administration to rats. It had a long half-life and disappeared more slowly from the liver than from other tissues. By 84 days, 66% of the dose had been excreted in the faeces and less than 2% in the urine (Egle et al., 1978). Faecal excretion of chlordecone in rats was increased by the administration of an anionic exchange resin, cholestyramine (Boylan et al., 1977, 1978).

When chlordecone was fed to dairy cows in concentrations of 0.25-5.0 mg/kg in hay and in feed-concentrate for 60 days, the highest residue level in milk recorded from an individual cow was 0.44 mg/l. No measurable amounts of chlordecone were present in milk 83 days after treatment was discontinued (Smith & Arant, 1967).
Hens were fed 75 or 150 mg/kg diet chlordecone in their feed for 16 weeks. After 5 weeks of treatment, the chlordecone content of egg yolk was 163 and 336 mg/kg, respectively, for the two dosage levels. By the 13th week it was 100 and 214 mg/kg, respectively; and 3 weeks after treatment had ceased, the chlordecone content was 26 and 70 mg/kg, respectively (Naber & Ware, 1965).

**Mutagenicity and other related short-term tests**

It was reported in an abstract that no dominant lethal mutations were observed in male rats given 5 consecutive oral doses of 3.6 or 11.4 mg/kg bw/day chlordecone prior to mating (Simon et al., 1978).

**(b) Humans**

Industrial workers exposed by inhalation, oral ingestion and skin contact to chlordecone showed signs of nervousness, tremors, visual deficiencies, pleural pain, weight loss, joint pain, tachycardia and hepatomegaly. Abnormal liver function tests, changes in electroencephalogram and electromyogram patterns, demyelination of peripheral nerves and oligospermia with decreased sperm mobility were noted. Dermatitis was seen in 60% of workers; skin rashes and nervous effects were also seen in family members of the workers. The severity of the symptoms was proportional to the blood levels of chlordecone (Cannon et al., 1978; Cohn et al., 1978; Epstein, 1978; Martinez et al., 1978; Taylor et al., 1978).

High concentrations of chlordecone were found in liver and body fat of workers exposed to the compound (Cohn et al., 1978), and it has been determined in blood of workers (see section 2.2, p. 69). The serum half-life of chlordecone ranged from 63-148 days (Adir et al., 1978).

Chlordecone undergoes extensive biliary excretion and enterohepatic circulation. Excretion in the faeces, unchanged and as the alcohol derivative, was the major route of elimination. Administration of cholestyramine, an anionic exchange resin which binds to chlordecone, increased faecal excretion, presumably by interfering with reabsorption from the intestine (Cohn et al., 1976, 1978).

Most of a group of workers severely poisoned by chlordecone in Virginia in 1975 had severe neurological abnormalities, and some were reported to have become infertile (Whorton et al., 1977).

3.3 **Case reports and epidemiological studies**

No data were available to the Working Group.
4. Summary of Data Reported and Evaluation

4.1 Experimental data

Chlordecone was tested in one experiment in mice and in two in rats by oral administration: it produced hepatocellular carcinomas in males and females of both species.

Chlordecone impairs fertility and is foetotoxic.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and the widespread use of chlordecone and its persistence in the environment (where it may also occur as a result of degradation of the pesticide mirex) indicate that human exposure occurs. This is confirmed by many reports of its occurrence in human body fluids. A group of highly exposed workers is known to exist. Oligospermia with hypomobility of the sperm has been reported in heavily exposed workers.

4.3 Evaluation

There is sufficient evidence that chlordecone is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard chlordecone as if it presented a carcinogenic risk to humans.
5. References


Allied Chemical Corporation (1963) Determination of Kepone (CC-1189) Residues in crops, 26 June, Morristown, NJ

Allied Chemical Corporation (1966) Assay method for Kepone®, 8 March, Morristown, NJ

Allied Chemical Corporation (undated) Summary of Basic Information - Kepone® Insecticide, Morristown, NJ

Anon. (1975) End of line for Kepone. Chem. Week, 117, 10


Anon. (1976b) Mandel says Kepone no problem in Bay. The News American, 16 July, p. 5A

Anon. (1976c) EPA-sponsored study finds mirex in tissue samples taken in southeast. Environ. Rep., 7, 506


National Cancer Institute (1976) Report on Carcinogenesis Bioassay of Technical Grade Chlordecone (Kepone), Bethesda, MD, Carcinogenesis Program, Division of Cancer Cause & Prevention


1,2-DIBROMO-3-CHLOROPROPANE

This substance was considered by a previous Working Group, in February 1977 (IARC, 1977). Since that time new data have become available and these have been incorporated into the monograph and taken into account in the present evaluation.

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 96-12-8
Chem. Abstr. Name: 1,2-Dibromo-3-chloropropane
Synonyms: 3-Chloro-1,2-dibromopropane; DBCP; dibromochloropropane
Trade names: BBC 12; Fumagon; Fumazone; Fumazone 86; Fumazone 86E; Nemabrom; Nemaocene; Nemagon; Nemagon 20; Nemagon 90; Nemagon 20G; Nemagon Soil Fumigant; Nemanax; Nemapaz; Nemaset; Nematox; OS 1897

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{C}_3\text{H}_5\text{Br}_2\text{Cl} & \\
\text{Mol. wt: } & 236.3
\end{align*}
\]

1.3 Chemical and physical properties of the pure substance

From Spencer (1973), unless otherwise specified
(a) Description: Dark-amber to dark-brown liquid with pungent odour
(b) Boiling-point: 196°C
(c) Density: \(d_{20}^0 \approx 2.08\) (Martin & Worthing, 1977)
(d) Spectroscopy data: Infra-red, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).
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(e) **Refractive index:** $n^*_D = 1.5518$

(f) **Solubility:** Slightly soluble in water (0.1% w/w); miscible with liquid hydrocarbons, ethanol, methanol, isopropanol and halogenated hydrocarbons

(g) **Vapour pressure is 0.8 mm at 21°C.**

(h) **Stability:** Stable in neutral and acidic media; hydrolysed by alkali to 2-bromoallyl alcohol; dehalogenated by soil bacteria to n-propanol (Castro, 1977)

(i) **Reactivity:** Corrodes aluminium, magnesium, tin and alloys containing these metals; attacks rubber materials and coatings (US Occupational Safety & Health Administration, 1977a)

(j) **Conversion factor:** 1 ppm in air is equivalent to approximately 10 mg/m³.

1.4 Technical products and impurities

1,2-Dibromo-3-chloropropane is available in the US as a technical grade containing not less than 95% of the pure chemical (Johnson & Lear, 1969), as emulsifiable concentrates containing 70.7-87.8%, as solutions containing 47.2%, as granules containing 5.25-34%, and in fertilizer mixtures containing 0.6-5% (US Environmental Protection Agency, 1974).

A technical grade available in the USSR contains 97-98% of the pure chemical and 1-3% of other halogenated hydrocarbons. A technical grade available in Japan contains at least 99% of the pure chemical.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) **Production**

1,2-Dibromo-3-chloropropane was first prepared by Oppenheim in 1833 by the addition of bromine to allyl chloride (Prager et al., 1918); this is the method used currently for its production in the US and Japan.

1,2-Dibromo-3-chloropropane was first produced commercially in the US in 1955 (US Tariff Commission, 1956). In 1969, US production was 3.9 million kg (US Tariff Commission, 1971); in 1974, estimated production
by one source was 9 million kg (Kelso et al., 1976). In 1976, 3 US companies reported commercial production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977); by 1977, only 2 US companies were producing it (US Environmental Protection Agency, 1977a). 1,2-Dibromo-3-chloropropane has been imported into the US from the Federal Republic of Germany and Israel (US Occupational Safety & Health Administration, 1977a) and from Mexico and Japan (US Occupational Safety & Health Administration, 1978).

Production in the Benelux, France, Italy, Spain, Switzerland and the UK has been estimated to be 3-30 million kg annually.

1,2-Dibromo-3-chloropropane was first produced commercially in Japan in 1960. In 1974, the single Japanese producer manufactured 496 thousand kg; in 1975, production dropped to 159 thousand kg and in 1976 to 154 thousand kg.

(b) Use

The only known use for 1,2-dibromo-3-chloropropane is as a soil fumigant for control of nematodes. Its nematocidal activity was first reported in 1955 (McBeth & Bergeson, 1955). About 5.4 million kg were used in 1972 in the US (US Occupational Safety & Health Administration, 1978), where it is used mainly for soil treatment for soya beans, pineapples, peaches, grapes and citrus fruits; minor uses are for turf, ornamental shrubs and vegetable crops. Some of these uses, particularly on vegetables, may be discontinued due to recent suspension actions (US Environmental Protection Agency, 1977a). In 1971, US farmers used 1.6 million kg on crops (US Department of Agriculture, 1974); and in 1977, a total of 378 thousand kg were used in California alone, mostly on grapes and tomatoes (California Department of Food & Agriculture, 1978).

On 22 September 1977, the US Environmental Protection Agency (EPA) issued a notice of rebuttable presumption against renewal of registration (RPAR) (see General Remarks on Substances Considered, p. 31) of all pesticide products containing 1,2-dibromo-3-chloropropane, on the basis of carcinogenic and reproductive effects (US Environmental Protection Agency, 1977a). Four days later, the EPA issued an order suspending registration of those pesticide products containing 1,2-dibromo-3-chloropropane which were found to pose an 'imminent hazard' to humans or to the environment. The suspended products were those intended for use on 19 food crops in which residues are likely to occur in edible portions. Conditional suspensions were declared for those products used on other crops, pending label changes to restrict use to certified applicators wearing protective clothing and respirators (US Environmental Protection Agency, 1977b).

The US Food and Drug Administration has established maximum residue levels of 1.5 mg/l in raw milk and 0.05 mg/kg in all other raw agricultural
commodities (Anon., 1977). Tolerance levels of 5-130 mg/kg had previously been established on some 30 food crops (US Environmental Protection Agency, 1974).

On 9 September 1977, the US Occupational Safety and Health Administration established an emergency temporary health standard for exposure to 1,2-dibromo-3-chloropropane as an air contaminant. This requires that an employee's exposure to the chemical not exceed an 8-hr time-weighted average of 100 μg/m³ (10 ppb) in the workplace air in any 8-hr work shift of a 40-hr week, with a ceiling level of 500 μg/m³ (50 ppb) for any 15-min period during the 8-hr day. The emergency temporary standard was to be superseded by a permanent standard within 6 months (US Occupational Safety & Health Administration, 1977a). A proposed permanent standard was issued on 1 November, 1977. This proposal reduced the time-weighted average from 10 ppb to 1 ppb and the ceiling from 50 ppb to 10 ppb (US Occupational Safety & Health Administration, 1977b). The proposed time-weighted average of 1 ppb became a permanent standard, effective 17 April, 1978. In the final ruling, the ceiling exposure requirement of 10 ppb was eliminated since it was judged to be adequately covered by the time-weighted average standard (US Occupational Safety & Health Administration, 1978).

No data were available on use of 1,2-dibromo-3-chloropropane in Japan; it is used as a soil fumigant in Europe.

2.2 Occurrence

1,2-Dibromo-3-chloropropane is not known to occur as a natural product. It is present at a level of 0.05% or 0.002% in the flame retardant tris(2,3-dibromopropyl) phosphate (see monograph, p. 575) (Prival et al., 1977).

(a) Soil

1,2-Dibromo-3-chloropropane has been applied to various types of agricultural soils in California by injection, flooding and sprinkling. The chemical was still present 40 weeks after application; and its distribution in soil was proportional to the size of soil particles, with the greatest concentration found in sandy soils and the lowest in clay (Hodges, 1972).

In field experiments, 1,2-dibromo-3-chloropropane was detected in soil at levels in the mean range of 0.008-1.64 mg/kg from 1 day to 16 weeks after application at the rate of 13.75 kg/ha (Newsome et al., 1977).

(b) Food

The US Environmental Protection Agency has estimated that human dietary exposure to 1,2-dibromo-3-chloropropane is in the range of 2.2-61.0 x 10⁻⁶ mg/kg/day (US Environmental Protection Agency, 1977b).
1,2-Dibromo-3-chloropropane was detected in carrots in the range of 0.009-1.5 mg/kg and in radishes in the range of 0.03-0.194 mg/kg after application of 13.75 kg/ha to soil. In the same study, the compound was detected in carrot peel and pulp in concentrations of 0.339 and 0.607 mg/kg, respectively. After unpeeled carrots were boiled for 5 min, they still contained 0.251 mg/kg 1,2-dibromo-3-chloropropane (Newsome et al., 1977).

(c) Occupational exposure

Occupational exposure to 1,2-dibromo-3-chloropropane in production or formulation plants at levels which caused physiological changes has been reported for: (1) 41 employees in California; (2) 86 employees in Arkansas; and (3) a total of 50 employees in Colorado and Alabama. One US manufacturer of 1,2-dibromo-3-chloropropane estimated that employee exposure ranged from < 1-6 mg/m³ (100-600 ppb) over 3 years. The US Occupational Safety and Health Administration has estimated that 2000-3000 employees have recently been or may currently be exposed during the manufacture and formulation of 1,2-dibromo-3-chloropropane (US Occupational Safety & Health Administration, 1977a,b).

Whorton et al. (1977) have detected an average of 4 mg/m³ (0.4 ppm) 1,2-dibromo-3-chloropropane over an 8-hr day in a manufacturing plant. In another factory, levels of 1-6 mg/m³ (0.1-0.6 ppm) have been estimated during the past 3 years (US Occupational Safety & Health Administration, 1977a).

2.3 Analysis

Methods used for the analysis of 1,2-dibromo-3-chloropropane in environmental samples are listed in Table 1.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Two groups of 50 male and 50 female B6C3F1 hybrid mice, 5-6 weeks old, were fed technical-grade 1,2-dibromo-3-chloropropane (minimum 90% purity) in corn oil by gavage on 5 consecutive days per week. Approximate time-weighted average doses were 114 and 219 mg/kg bw for males and 110 and 209 mg/kg bw for females. Two groups, each of 20

¹The Working Group was aware of a completed but as yet unpublished study involving the i.p. administration of 1,2-dibromo-3-chloropropane to mice and of studies in progress by inhalation exposure in rats and mice and by skin application in mice (IARC, 1978).
### TABLE 1. METHODS FOR THE ANALYSIS OF 1,2-DIBROMO-3-CHLOROPROPAINE

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquids</td>
<td>Dilute (chloroform)</td>
<td>GC/TCD</td>
<td></td>
<td>US Environmental Protection Agency (1976)</td>
</tr>
<tr>
<td>Dry formulations</td>
<td>Extract (chloroform), filter</td>
<td>GC/TCD</td>
<td></td>
<td>US Environmental Protection Agency (1976)</td>
</tr>
<tr>
<td>Emulsifiable</td>
<td>Dilute (carbon disulphide), dry</td>
<td>IR</td>
<td></td>
<td>US Environmental Protection Agency (1976)</td>
</tr>
<tr>
<td>concentrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granules</td>
<td>Extract (acetone), filter, evaporate to dryness (with care), take up in carbon disulphide</td>
<td>IR</td>
<td></td>
<td>US Environmental Protection Agency (1976)</td>
</tr>
<tr>
<td><strong>Air</strong></td>
<td>Trap in dimethyl sulphoxide</td>
<td>Polarography</td>
<td>7 mg/m³</td>
<td>Novik &amp; Plyngyu (1973)</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td>Extract (petroleum ether)</td>
<td>Polarography</td>
<td></td>
<td>Novik &amp; Kozlova (1971)</td>
</tr>
<tr>
<td></td>
<td>Extract (hexane)</td>
<td>GC/ECD</td>
<td>1 mg/kg</td>
<td>Johnson &amp; Lear (1969)</td>
</tr>
<tr>
<td><strong>Soil</strong></td>
<td>Extract (acetone), decant</td>
<td>GC/ECD</td>
<td>1 mg/kg</td>
<td>Gutenmann &amp; Lisk (1968)</td>
</tr>
<tr>
<td></td>
<td>Extract (hexane)</td>
<td>GC/ECD</td>
<td>1 mg/kg</td>
<td>Johnson &amp; Lear (1969)</td>
</tr>
<tr>
<td></td>
<td>Extract (ether-water)</td>
<td>Polarography</td>
<td>0.1 mg/kg</td>
<td>Novik &amp; Kozlova (1973)</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td>Extract (absolute ethanol) in blender, filter, add sodium chloride solution, extract (hexane), dry, CC</td>
<td>GC/ECD</td>
<td>2 μg/kg</td>
<td>Newsome et al. (1977)</td>
</tr>
</tbody>
</table>

Abbreviations: GC/TCD - gas chromatography/thermal conductivity detection; IR - infra-red spectrometry; ECD - electron capture detection; CC - column chromatography
males and 20 females, were used as vehicle-treated and untreated controls. Low-dose animals and vehicle controls had to be killed at 60 and 59 weeks and high-dose animals at 47 weeks because of high mortality related to tumours; untreated male and female controls were sacrificed at 78 and 90 weeks. Animals dying with tumours were observed in high-dose groups as early as 27 weeks. In males, 40/50 of the high-dose group had died by the end of week 47, and 42/50 of the low-dose group had died by week 59. In females, 30/50 of the high-dose group had died by the end of week 47, and 41/50 of the low-dose group had died by week 60. Squamous-cell carcinomas of the forestomach occurred in 43/46 low-dose males, 47/49 high-dose males, 50/50 low-dose females and 47/48 high-dose females. This lesion occurred with frequent metastases to the abdominal viscera and the lungs. No gastric neoplasms occurred in either vehicle or untreated controls (National Cancer Institute, 1978).

Rat: Two groups of 50 male and 50 female Osborne-Mendel rats, 6-7 weeks old, were fed 1,2-dibromo-3-chloropropane (minimum 90% pure) in corn oil by gavage at approximately time-weighted average dosages of 15 and 29 mg/kg bw on 5 consecutive days per week. Two groups, each of 20 males and 20 females, were used as vehicle-treated and untreated controls. Low- and high-dose females were treated for 73 and 64 weeks, respectively, and then killed because of high mortality related to tumours. High-dose males were treated for 64 weeks and then killed; low-dose males were treated for 78 weeks and killed at 83 weeks. Vehicle-treated controls were killed after 83 weeks, and untreated controls at 109 weeks. Animals dying with tumours were observed in high-dose groups as early as 33 weeks. Of males, 40/50 in the high-dose group had died by week 62, and 45/50 in the low-dose group had died by week 83; of females, 47/50 in the high-dose group had died by week 61, and 42/50 in the low-dose group had died by week 73. Squamous-cell carcinomas of the forestomach occurred in 47/50 both low- and high-dose males, 38/50 low-dose females and 29/49 high-dose females. These lesions occurred with frequent metastases to the abdominal viscera and the lungs. No gastric carcinomas occurred in either vehicle or untreated controls. In females, adenocarcinomas of the mammary gland occurred in 24/50 of the low-dose group, in 31/50 of the high-dose group, in 2/20 untreated controls and in none of the vehicle controls (National Cancer Institute, 1978).

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The LD$_{50}$ of 1,2-dibromo-3-chloropropane by oral intubation is 150-370 mg/kg bw in male rats, 260-620 mg/kg bw in female rats and 150-300 mg/kg bw in male guinea-pigs (Torkelson et al., 1961). The percutaneous LD$_{50}$ in rabbits is 1400 mg/kg bw (Kodama & Dunlap, 1956).
Daily oral administration of 70 mg/kg bw (20% of the acute LD₅₀) to rats was lethal after 3 weeks of dosing. Degenerative effects were noted in the vascular system and in all internal organs (Faidysh et al., 1970).

1,2-Dibromo-3-chloropropane (97% pure) was given by gavage to 190 rats either in a dose of 100 mg/kg bw (single dose), or in repeated doses of 10 mg/kg bw for 5 months. After the single dose, the animals developed symptoms of acute poisoning - mostly nervous system depression - and weight loss. Following repeated treatment, an effect on spermatogenesis was observed in males, and the number and viability of spermatozoa were decreased; oestrus was inhibited in females (Reznik & Sprinchan, 1975). Severe atrophy and degeneration of the testes were observed in rats, guinea-pigs and rabbits (Torkelson et al., 1961). Testicular atrophy was also observed in rats during the long-term oral carcinogenicity study reported in section 3.1 (National Cancer Institute, 1978).

1,2-Dibromo-3-chloropropane induced skin irritation and irritation of the eyes in rabbits (Kodama & Dunlap, 1956). Inhalation of concentrations of over 600 mg/m³ (60 ppm) in air caused irritation of the skin, eyes, mucous membranes and respiratory tract, hepatic degeneration, neurotoxicity and nephrotoxicity in rats (Torkelson et al., 1961).

No data on the embryotoxicity, teratogenicity, absorption, distribution, excretion or metabolism of 1,2-dibromo-3-chloropropane were available to the Working Group.

**Mutagenicity and other related short-term tests**

1,2-Dibromo-3-chloropropane was mutagenic in Salmonella typhimurium TA100, TA1530 and TA1535, but not in TA1538, both in the presence and absence of a liver microsomal activation system (Blum & Ames, 1977; Prival et al., 1977; Rosenkranz, 1975).

(b) **Humans**

Sperm counts were determined for 36 workers potentially exposed to 1,2-dibromo-3-chloropropane (the extent of exposure to other pesticides is not clear). Of these, 11 were found to be vasectomized. Of the remaining 25, 3 had sperm counts between 10 and 30 million/ml; 11 who had normal counts (>40 million/ml) had had a short duration of exposure (less than 3 months); 11 who had significantly decreased sperm counts (<1 million/ml) had been exposed for at least 3 years. Of the latter, 9 had no detectable sperm cells (Whorton et al., 1977). In a later report (Whorton et al., 1979), among 142 non-vasectomized workers (including the ones mentioned above) providing semen samples, the median sperm count was 46 million/ml for 107 men exposed to 1,2-dibromo-3-chloropropane and 79 million/ml for 35 men never exposed.
Glass et al. (1979) found that 24 pesticide applicators who were exposed to 1,2-dibromo-3-chloropropane for 2 months or more during the year in which they were studied had a mean sperm count of 22 million/ml. Thirty-one applicators who were exposed for less than 2 months but more than 2 weeks had a mean sperm count of 39 million/ml, while the mean count for 19 men exposed for less than 2 weeks was 46 million/ml. Twenty-two applicators who reported no exposure to 1,2-dibromo-3-chloropropane had a mean count of 62 million/ml. This trend was statistically significant ($P = 0.018$); however, only the men exposed for 2 months or more had counts which were significantly lower ($P < 0.01$) than the rest. Serum levels of follicle stimulating hormone (FSH) increased with increasing period of exposure ($P < 0.05$). Neither the depression of sperm counts nor the increased FSH levels were associated with exposure in prior years, suggesting that these effects develop quickly after exposure to the chemical and are apparently reversible when exposure to the chemical is removed.

Of 86 other workers examined, 24% had aspermia and 46% had oligospermia. Of workers from two other factories, 7/11 and 20/27 had sperm counts of 40 million/ml or less (US Occupational Safety & Health Administration, 1977a).

Of 18 workers exposed to 1,2-dibromo-3-chloropropane for 6-18 months, 16 had abnormal incidences (greater than 2%) of Y-chromosomal nondisjunction (Kapp et al., 1979).

Spermatogenic activity was either significantly decreased or absent in 7/10 men with a history of exposure to 1,2-dibromo-3-chloropropane (Biava et al., 1978).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

1,2-Dibromo-3-chloropropane was tested in one experiment in mice and one in rats by oral administration: it produced squamous-cell carcinomas of the forestomach in animals of both species and adenocarcinomas of the mammary gland in female rats.

1,2-Dibromo-3-chloropropane is mutagenic in Salmonella typhimurium.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.
The extensive production of 1,2-dibromo-3-chloropropane and its use as a pesticide over the past two decades indicate that widespread human exposure occurs. This is confirmed by reports of its presence in soils and vegetables following experimental application and by the observation of increased sterility in identified industrial groups.

4.3 Evaluation

There is sufficient evidence that 1,2-dibromo-3-chloropropane is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard 1,2-dibromo-3-chloropropane as if it presented a carcinogenic risk to humans.
5. References


Blum, A. & Ames, B.N. (1977) Flame-retardant additives as possible cancer hazards. The main flame retardant in children's pajamas is a mutagen and should not be used. Science, 195, 17-23


Gutenmann, W.H. & Lisk, D.J. (1968) Gas chromatographic analysis of Nemagon fumigant in extracts of soil on porous polymer beads. J. Gas Chromatogr., 6, 124-125


IARC (1977) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, 15, Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals, Lyon, pp. 139-147


Reznik, J.B. & Sprinchan, G.K. (1975) Experimental data on gonadotoxic action of Nemagon (Russ.). Gig. Sanit., 6, 101-102

Rosenkranz, H.S. (1975) Genetic activity of 1,2-dibromo-3-chloropropane, a widely-used fumigant. Bull. environ. Contam. Toxicol., 14, 8-12


US Environmental Protection Agency (1977a) Rebuttable presumption against registration and continued registration of pesticide products containing dibromochloropropane (DBCP). Fed. Regist., 42, 48026-48031


DICHLORVOS

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: 2,2-Dichloroethenyl phosphoric acid dimethyl ester

Synonyms: Chlorvinphos; DDVP; dichlorophos; 2,2-dichlorovinyl dimethyl phosphate; 2,2-dichlorovinyl dimethyl phosphoric acid ester; dichlorovos; dimethyl 2,2-dichloroethenyl phosphate; dimethyl dichlorovinyl phosphate; dimethyl 2,2-dichlorovinyl phosphate; vinylophos

Trade names: Atgard; Atgard V; Bibesol; Brevinyl; Brevinyl E50; Canogard; Dedevap; Dichlorman; ENT-20738; Equigard; Equigel; Estrosel; Estrosol; Herkol; Mafu Strip; Mopari; Nerkol; Nogos; Nogos 50; Nogos G; No-Pest Strip; Nuvan; Nuvan 100 EC; OMS 14; SD 1750; Szklarniak; TAP 9VP; Task; Unifos; Unifos 50 EC; Vapona; Vapona Insecticide; Vaponite

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{C}_4\text{H}_7\text{Cl}_2\text{O}_4\text{P} & \quad \text{Mol. wt: 221.0} \\
\end{align*}
\]

1.3 Chemical and physical properties of the pure substance

From Spencer (1973), unless otherwise specified

(a) **Description:** Colourless-to-amber liquid

(b) **Boiling-point:** 140°C at 20 mm; 84°C at 1 mm (Windholz, 1976)
(c) **Density:** \( d_{25}^1 1.1415 \)

(d) **Refractive index:** \( n_{D}^{25} 1.4523 \)

(e) **Spectroscopy data:** Infra-red, ultra-violet (Gore *et al*., 1971) and Raman spectral data (Nicholas *et al*., 1976) have been tabulated.

(f) **Solubility:** Soluble in water (1 g/100 ml), glycerol (0.5 g/100 ml) (Windholz, 1976) and kerosene (2-3 g/100 g); miscible with aromatic and chlorinated hydrocarbon solvents and alcohols (Hawley, 1977)

(g) **Vapour pressure** is \( 1.2 \times 10^{-2} \) mm at 20°C.

(h) **Stability:** Practically nonflammable (Windholz, 1976). A saturated aqueous solution is hydrolysed at the rate of 3% per day.

(i) **Reactivity:** Hydrolyses rapidly in alkali. Corrosive to iron and mild steel but noncorrosive to stainless steel, aluminium, nickel, Hastelloy 13 and Teflon

1.4 **Technical products and impurities**

Dichlorvos is available in the US as a technical grade containing not less than 93 wt % of the pure chemical and not more than 7 wt % of insecticidally active related compounds (Shell Chemical Company, 1973). Technical grade dichlorvos can contain trichlorphon (O,O-dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate), O,O-dimethyl 2-chlorovinyl phosphate, O,O-dimethyl methylphosphonate, O,O,O-trimethyl phosphate and chloral (trichloroacetaldehyde) (Gillett *et al*., 1972a).

Dichlorvos is formulated as solutions (fogging concentrates), emulsifiable concentrates, dilute spray solutions, baits and resin strips (Shell Chemical Company, 1973).

2. **Production, Use, Occurrence and Analysis**

2.1 **Production and use**

(a) **Production**

Dichlorvos was prepared independently in several laboratories in the period 1951-1955. It can be prepared by the reaction of trimethyl phosphite and chloral (the commercial process) or by the dehydrochlorination of trichlorphon (Spencer, 1973).
Commercial production of dichlorvos in the US was first reported in 1961 (US Tariff Commission, 1962). In the period 1961-1972, only one US company reported commercial production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977). Kelso et al. (1976) estimated that 0.9 million kg dichlorvos were produced in the US in 1974.

Six companies in Benelux, the Federal Republic of Germany, Spain and Switzerland produce an estimated 1-10 million kg dichlorvos annually. Imports and exports are in the range of 100-1000 thousand kg for most of these regions. Production in the eastern European countries is estimated to be less than 100 thousand kg dichlorvos annually, and imports and exports are each less than 100 thousand kg.

In Japan, dichlorvos was first produced commercially in 1963. In 1976, 3 companies produced a total of 1.1 million kg, of which 573 thousand kg were exported; 4000 kg were imported.

(b) Use

The only known uses of dichlorvos are as an insecticide and as an anthelminthic for swine and dogs. It is registered for use in flea collars for pets; in the control of external parasites on livestock, insects in buildings and outdoor areas, insects affecting certain greenhouse crops and insects on harvested tomatoes; and on mushrooms in mushroom houses (US Environmental Protection Agency, 1973). It is also used for mosquito and fly control (US Environmental Protection Agency, 1976a).

In 1971, 16 thousand kg were used on crops in the US and 1.1 million kg on livestock and in livestock buildings (US Department of Agriculture, 1974). In 1975, 80% of the dichlorvos produced in the US was formulated into resin strips containing 20% of the compound and used primarily in households. Aerosol sprays containing dichlorvos are also used by pest control operators in households and elsewhere (US Environmental Protection Agency, 1976a).

Use of dichlorvos in Europe in 1968 was reviewed (WHO, 1968), but no data on its use in Japan were available.

In November 1970, the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues recommended tolerances for preharvest and postharvest treatment of many commodities: the range was from 0.02 mg/kg for milk to 5 mg/kg for cocoa beans; 0.5 mg/kg was recommended for fresh vegetables and tomatoes (WHO, 1971). Residue tolerances established on commodities in the US are generally in the range of 0.02 mg/kg in meat and milk to 1 mg/kg on lettuce (US Environmental Protection Agency, 1976b).

The US Environmental Protection Agency reported on 20 January 1978 that dichlorvos may qualify as a candidate for issuance of a notice of a rebuttable presumption against renewal of registration (RPAR) (see
General Remarks on the Substances Considered, p. 31) on the basis of mutagenic, reproductive and foetotoxic effects and possible carcinogenicity. A decision on this possible course of action awaits the recommendations of the Carcinogen Assessment Group of the US Environmental Protection Agency (Anon., 1978).

A maximum acceptable daily intake of dichlorvos for humans of 0-0.004 mg/kg bw was established at the Joint Meeting of the FAO Working Group of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues in December 1974 (WHO, 1975). This was confirmed in December 1977 (FAO/WHO, 1978).

The US Occupational Safety and Health Administration standards for exposure to air contaminants require that an employee's exposure to dichlorvos not exceed an 8-hr time-weighted average of 1 mg/m³ (about 0.1 ppm) in the working atmosphere in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977). The corresponding standard in the Federal Republic of Germany is also 1 mg/m³ (about 0.1 ppm), and the acceptable ceiling concentration in the USSR is 0.2 mg/m³ (about 0.02 ppm) (Winell, 1975).

2.2 Occurrence

Although dichlorvos is not known to occur as a natural product, it does occur in organs and muscles of cattle as a residue after its application as a pesticide and as a conversion product of the insecticide trichlorphon (O,O-dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate) (Nepoklonov & Metelitsa, 1971). In the US, over 600 thousand kg trichlorphon were used on livestock in 1971.

Dichlorvos has been found in mouse brain after i.p. injection of trichlorphon (Nordgren et al., 1978); it is formed by heating trichlorphon at 70°C (Holmstedt et al., 1978).

(a) Air and food

Dichlorvos has been detected in: (1) stored wheat, at levels of 2.4-6.0 mg/kg, which decreased to 0.5 mg/kg or less during 6 weeks of storage (Vardell et al., 1973); (2) cereal products and flour, at levels of 0-5.8 mg/kg (Raffke & Wirthgen, 1976); (3) crude soya bean oil and meal, at levels of < 1 mg/kg (La Hue et al., 1975); and (4) malt and worts, at levels of 0-2 mg/kg (Leuzinger, 1975). Dichlorvos has also been detected in: (1) mushrooms and the air above them (< 0.2 mg/m³) 8 hrs after spraying (Gruebner, 1972); (2) raspberries, at levels of 0.2-7 mg/kg (Romanuk, 1976); (3) milk and milk products (Konrad et al., 1975); and (4) vegetable food products (0.24 mg/kg) (Lyubenko et al., 1973).

Dichlorvos has been found in prepared foods at concentrations of 0.005-1.653 mg/kg after experimental exposure to air containing dichlorvos
in concentrations ranging from 0.035-0.577 mg/m³ (0.003-0.06 ppm) (Dale et al., 1973).

Dichlorvos has been found in households in which commercial pest strips were used, in concentrations of 0-0.24 mg/m³ (0-0.026 ppm) in ambient air and <0.01-0.12 mg/kg in the foods prepared therein (Collins & DeVries, 1973; Elgar & Steer, 1972; Elgar et al., 1972a; Leary et al., 1974). It has also been detected in the air of food shops where the strips were used, at mean concentrations of <0.01-0.03 mg/m³ (<0.001-0.003 ppm), and in the foods in the shops, at concentrations of <0.05 mg/kg (Elgar et al., 1972b).

Seven days after application of trichlorphon, dichlorvos was found in sheep organs, at concentrations of 0.8-1.2 mg/kg (Nepoklonov & Bukshtyynov, 1971); in the tissue of cattle, 15-22 days after application (Nepoklonov & Metelitsa, 1971); and in the leaves of cabbages and onion plants, at low levels during the first 7 days after application (Baida, 1975).

(b) Water

Dichlorvos has been detected in: (1) a water reservoir and a water supply-irrigation system in the USSR (Akimov & Babich, 1975); (2) the polluted waters of 4 rivers (Drevenkar et al., 1975); and (3) the waste-water from a dichlorvos production plant in Bulgaria (16 g/l) (Andreeva et al., 1973).

(c) Occupational exposure

Dichlorvos has been detected in the workplace environment: (1) in concentrations of 0.7 mg/m³ (0.077 ppm) in air, during the production and processing of a dichlorvos-releasing vaporizer (Menz et al., 1974); and (2) in average concentrations of 1.19 mg/m³ (0.13 ppm) in air during the spraying of an orchard. In the latter case, the rate of skin contamination was 0.072 mg/100 cm²/hr (Sawinsky et al., 1973).

2.3 Analysis

Methods used for the analysis of dichlorvos in environmental samples are listed in Table 1.

Other analytical methods used to isolate and identify dichlorvos include: gel-permeation chromatography (Johnson et al., 1976); gas chromatography on packed columns (Thompson et al., 1975) or on capillary columns (Krijgsman & Van De Kamp, 1976); gas chromatography/mass spectrometry (Rosen & Pareles, 1974); high-pressure liquid chromatography (Szalontai, 1976); thin-layer chromatography (Štefanac et al., 1976); polarography (Seifert & Davidek, 1974); and spectrophotometry (Fitak & Gwiazda, 1975; Mukherjee et al., 1973; Ogata et al., 1975; Rajak & Krishnamurthy, 1974; Turner, 1974).
TABLE 1. METHODS FOR THE ANALYSIS OF DICHLORVOS

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
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<tbody>
<tr>
<td>Formulations</td>
<td>Dissolve (chloroform), centrifuge, filter</td>
<td>IR</td>
<td></td>
<td>Goza (1972)</td>
</tr>
<tr>
<td>Fly bait</td>
<td>Extract (chloroform) on CC</td>
<td>IR</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Spray in hydrocarbon solvents</td>
<td>Wash (alkali)</td>
<td>IR (on hydrocarbon phase)</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Air</td>
<td>Trap in acetone</td>
<td>Spectrophotometry of resorcinol complex at 490 nm</td>
<td>0.14 mg/m³</td>
<td>Leu &amp; Suwalska (1977)</td>
</tr>
<tr>
<td>Water</td>
<td>Extract (benzene or chloroform)</td>
<td>Spectrophotometry of ortho-tolidine complex at 400-500 nm; or TLC (revelation: sodium carbonate/resorcinol)</td>
<td>50 μg/l</td>
<td>Babina et al. (1972)</td>
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<tr>
<td></td>
<td>Extract (dichloromethane)</td>
<td>Spectrophotometry of resorcinol derivative of dichlorvos dichloroacetaldehyde adduct at 487 nm</td>
<td>40 μg/l</td>
<td>Novikova &amp; Mel'tser (1973)</td>
</tr>
<tr>
<td>Food &amp; drinks</td>
<td>Blend, absorb on Celite, extract (acidified ethyl acetate/hexane), filter, CC</td>
<td>GC/flame photometry</td>
<td>5 μg/kg</td>
<td>Dale et al. (1973)</td>
</tr>
<tr>
<td>Whole meals</td>
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<tr>
<td>Sample Type</td>
<td>Extraction/Clean-Up</td>
<td>Detection</td>
<td>Limit of Detection</td>
<td>Reference</td>
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<td>----------------------------------------------------------</td>
<td>----------------------------------</td>
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<td>------------------------------------------</td>
</tr>
<tr>
<td>Beverages</td>
<td>Acidify, extract (hexane)</td>
<td>GC/flame photometry</td>
<td>5 µg/kg</td>
<td>Dale et al. (1973)</td>
</tr>
<tr>
<td>Margarine</td>
<td>Dissolve (ethyl acetate-hexane), CC</td>
<td>GC/flame photometry</td>
<td>5 µg/kg</td>
<td>Dale et al. (1973)</td>
</tr>
<tr>
<td>Cereals &amp; pulses</td>
<td>Extract (hexane) in Soxhlet, liquid/liquid partition, CC</td>
<td>GC/flame photometry</td>
<td>0.008-1.01 ng/sample</td>
<td>Aoki et al. (1975)</td>
</tr>
<tr>
<td>Grain</td>
<td>Grind, homogenize (methanol), concentrate, add acetone</td>
<td>GC/flame photometry or thermionic detection</td>
<td>20 µg/kg</td>
<td>Panel on Malathion &amp; Dichlorvos Residues in Grain (1973)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Extract (acetonitrile)</td>
<td>TLC (revelation: sodium carbonate-resorcinol)</td>
<td>0.25 µg/ml</td>
<td>Kavetskii (1974)</td>
</tr>
<tr>
<td>Mixed feed</td>
<td>Extract (acetone), transfer to water, filter, extract (chloroform)</td>
<td>TLC (revelation: sodium carbonate-resorcinol)</td>
<td>0.5-0.8 mg/kg</td>
<td>Konyukhov (1974)</td>
</tr>
<tr>
<td>Vegetables &amp; fruit</td>
<td>Extract (chloroform), purify (activated charcoal)</td>
<td>TLC (revelation: enzymatic technique)</td>
<td>0.01 mg/kg</td>
<td>Zadrozinska (1973)</td>
</tr>
<tr>
<td>Milk</td>
<td>Coagulate (acetone), extract supernatant (petroleum ether)</td>
<td>Spectrophotometry of resorcinol derivative of dichlorvos dichloro-acetaldehyde adduct at 487 nm</td>
<td>0.1 mg/l</td>
<td>Novik &amp; Mel'tser (1973)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Homogenize (acetone), liquid/liquid partition, gel permeation chromatography</td>
<td>GC/thermionic detection</td>
<td>50 µg/kg</td>
<td>Pflugmacher &amp; Ebing (1974)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
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<td>-------------------</td>
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<tr>
<td>Biological</td>
<td></td>
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<td></td>
<td></td>
<td>nitrobenzylpyridine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human tissues</td>
<td>Extract (hexane or acetone), slurry of</td>
<td>TLC (revelation: silver</td>
<td>10 µg/kg</td>
<td>Tewari &amp; Harpalani</td>
</tr>
<tr>
<td></td>
<td>sodium sulphate, liquid/liquid partition</td>
<td>nitrate or palladium</td>
<td></td>
<td>(1977)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chloride reagents)</td>
<td></td>
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</tr>
<tr>
<td>Animal organs &amp;</td>
<td>Extract (chloroform or acetone), liquid/</td>
<td>TLC (revelation: silver</td>
<td>1-5 µg</td>
<td>Kazanovskii (1975)</td>
</tr>
<tr>
<td>tissues</td>
<td>liquid partition</td>
<td>nitrate)</td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: IR - infra-red spectrometry; CC - column chromatography; GC - gas chromatography; TLC - thin-layer chromatography
Dichlorvos

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 50 male and 50 female 5-7-week-old B6C3F1 hybrid mice were fed technical-grade dichlorvos (94% minimum purity) in their diet. Initially, high-dose animals received 2000 mg/kg diet, and low-dose animals received 1000 mg/kg diet; however, after 2 weeks these doses were reduced to 600 mg/kg and 300 mg/kg diet, respectively, because of severe toxicity. Test animals were maintained at these dietary levels for 78 weeks, followed by 12-14 weeks on dichlorvos-free diets, after which time (90-94 weeks) the animals were killed and necropsied. The measured, time-weighted, average doses were 635 (high dose) and 318 (low dose) mg/kg diet. Groups of 10 male and 10 female mice that served as matched controls were maintained on dichlorvos-free diets for 92 weeks. Further control data were obtained from pooled control animals (100 males and 80 females), in order to increase the scope of the statistical analysis. In the female low-dose groups, 13/50 animals died before week 90; survival to 90 weeks was greater than 84% in all other groups. Histopathology was performed on all organ systems in 94% or more of animals entered into the experiment. Average weights of high-dose mice of both sexes were generally lower than those of low-dose and control groups, but the differences never exceeded 10%. In male mice, 29/92 in the pooled control group that were examined histopathologically developed tumours, compared with 1/10 in matched controls, 21/50 of the low-dose group and 14/50 in the high-dose group. In female mice, the respective tumour incidences were 14/79 in pooled controls, 1/9 in matched controls, 11/49 in low-dose animals and 8/50 in high-dose animals. There were no significant differences between test and control groups in the age at observation of any tumours. The only unusual findings were 2 squamous-cell carcinomas (in 1 low-dose male and 1 high-dose female), 1 papilloma of the oesophagus (high-dose female), and 3 cases of focal hyperplasia of the oesophageal epithelium (2 low-dose males and 1 high-dose female) (National Cancer Institute, 1977).

Rat: Groups of 50 male and 50 female 5-7-week-old Osborne-Mendel rats were fed diets containing technical-grade dichlorvos (94% minimum purity). High-dose animals received 1000 mg/kg diet for 3 weeks; this level was reduced to 300 mg/kg diet for the rest of the study after severe toxicity was observed. Low-dose animals received 150 mg/kg diet. Both groups were fed dichlorvos for 80 weeks and were maintained for a further 30 weeks on a dichlorvos-free diet. Time-weighted average doses were 326 mg/kg and 150 mg/kg diet, respectively. Groups of 10 animals of each sex were used as matched controls, and groups of 60 animals of each sex as pooled controls. Weight gain was consistently lower in high-dose groups compared with low-dose and control groups: 76% of high-dose males, 84% of high-dose females, 64% of low-dose males and 80% of low-dose females survived for
more than 105 weeks. There was no evidence of dose-related mortality and no significant difference in survival between treated and control groups. Histopathology of all organ systems was performed on 94% or more of the animals entered into the study. The numbers of tumour-bearing males, excluding those with tumours of the reproductive tract, were: pooled controls, 37/58; matched controls, 6/10; low-dose, 20/48; high-dose, 33/50; males with tumours of the reproductive tract were: 2/58, 0/10, 3/48 and 2/50, respectively. The numbers of tumour-bearing females, excluding those with tumours of the reproductive tract, were: pooled controls, 38/60; matched controls, 8/10; low-dose, 34/48; high-dose, 30/50; females with tumours of the reproductive tract were: 19/60, 5/10, 17/48 and 10/50, respectively. The incidence of malignant fibrous histiocytomas in male rats was the only one that showed a statistically significant trend (2/58 pooled controls; 4/48 low-dose; 8/50 high-dose; $P = 0.018$); however, the occurrence of malignant fibrous histiocytoma in 1/10 animals in the matched-control group does not support the suggestion of a treatment-related effect. Furthermore, on the basis of the variability of both incidence and type of spontaneous lesions and the lack of significant increases in tumour yield or decreases in time to first tumour in dosed groups, no significance could be attached to the trend in tumours seen in dichlorvos-fed rats (National Cancer Institute, 1977).

(b) Inhalation and/or intratracheal administration

Rat: Groups of 50 male and 50 female 5-week-old Carworth Farm E strain rats were exposed continuously to atmospheres containing 0 (control), 0.05, 0.5 or 5 mg/m$^3$ (0.0055, 0.05 or 0.55 ppm) technical-grade dichlorvos (purity greater than 97%) for 104 weeks. The mean values for the entire test period were 0.05, 0.48 and 4.7 mg/m$^3$, all ± 20%. All treated groups showed decreases in weight gain compared with controls, this being most marked in those given 5 mg/m$^3$. The numbers of males still alive at 104 weeks were 11/50 controls, 21/50 given 0.05 mg/m$^3$, 15/50 given 0.5 mg/m$^3$, and 32/50 given 5 mg/m$^3$; females still alive at that time were 22/47 controls, 27/47 given 0.05 mg/m$^3$, 26/47 given 0.5 mg/m$^3$ and 34/47 given 5 mg/m$^3$. Complete necropsy and histopathology were performed on 20-32% of male rats and 20-36% of females, reducing the effective numbers of animals per group to between 10 and 18. No significantly increased risk of tumour incidence could be attributed to treatment with dichlorvos (Blair et al., 1976) [The Working Group noted the very low doses used, the small number of animals submitted for complete necropsy and the high incidence of tumours in control groups].

3.2 Other relevant biological data

The toxicology, biochemistry and possible health hazards of dichlorvos have been reviewed (Anon, 1974; Attfield & Webster, 1966; Gillett et al., 1972a,b; WHO, 1971; Wright et al., 1979).
(a) Experimental systems

Toxic effects

The LD$_{50}$ by inhalation is 75-108 mg/kg bw in mice, 56-65 mg/kg bw in rats, and 25 mg/kg bw in rabbits; the LD$_{100}$ for cats is 50 mg/kg bw (Sasinovich, 1967). The oral LD$_{50}$ for chicks is 15 mg/kg bw (Sherman & Ross, 1961); for rats, 56-80 mg/kg bw (Durham et al., 1957); and for mice, about 140-275 mg/kg bw (Anon, 1974; Holmstedt et al., 1978). The dermal LD$_{50}$ for rats is 75-900 mg/kg, depending on the solvent (Jones et al., 1968). In mice, the i.p. LD$_{50}$ is 28-41 mg/kg bw; the s.c. LD$_{50}$, 20-26 mg/kg bw; and the i.v. LD$_{50}$, 8-10 mg/kg bw (Holmstedt et al., 1978).

The LC$_{100}$ for rats was exposure to more than 30 mg/m$^3$ (3.3 ppm) dichlorvos in air for 5-83 hrs (Durham et al., 1957).

Feeding dichlorvos at up to 1000 mg/kg diet for 90 days caused no signs of intoxication in rats, but dietary levels as low as 50 mg/kg diet produced definite reductions of plasma and erythrocyte cholinesterase levels. Rats exposed to dichlorvos vapours in air [6.0 decreasing to 0.1 mg/m$^3$ (0.66-0.011 ppm) over 2 weeks] showed no signs of organic phosphate poisoning, but slight reductions in plasma and erythrocyte cholinesterase levels were observed. The erythrocyte and plasma cholinesterase levels in monkeys similarly exposed fell rapidly during exposure but recovered after exposure was discontinued. Three monkeys treated daily with dermal doses of 50, 75 and 100 mg/kg bw dichlorvos in xylene for 5 days per week died after 8, 10 and 4 doses, respectively. The erythrocyte cholinesterase activity fell rapidly and remained depressed for the period of the experiment; plasma cholinesterase levels fell, then returned to normal (Durham et al., 1957).

In 48 male rats that received daily topical applications of 21.4 mg/kg bw dichlorvos in ethanol on 5 days/week for 90 days, no gross or histological changes associated with dichlorvos exposure were seen in the skin or testes (Dikshith et al., 1976).

In male rats fed dichlorvos, non-neoplastic lesions were observed, including aggregates of alveolar macrophages in the lungs, interstitial fibrosis of the myocardium and focal follicular-cell hyperplasia of the thyroid. Focal hepatocytomegaly and chronic nephritis were also observed (National Cancer Institute, 1977).

Cholinesterase activity in the plasma and brains of male and female rats exposed to 0.5 and 5 mg/m$^3$ in air was reduced significantly compared with control values. The cholinesterase activity of erythrocytes was reduced significantly in males and females exposed to 5 mg/m$^3$ and in females exposed to 0.5 and 0.05 mg/m$^3$. No dichlorvos-related changes were seen in brain acetylcholine or choline levels after 2 years' exposure. Respiratory tissues showed no ultrastructural changes attributable to exposure to 5 mg/m$^3$ dichlorvos for 2 years (Blair et al., 1976).
Nursing female rats were given repeated oral doses of 30 mg/kg bw dichlorvos. Their litters showed normal plasma and erythrocyte cholinesterase activities and normal weight-gain curves. Two cows suckling calves showed normal erythrocyte cholinesterase levels while ingesting 200 mg dichlorvos/kg diet daily; however at 500 mg/kg diet, a severe depression in these levels occurred, and a single dose of 27 mg/kg bw caused cholinergic collapse, followed by recovery. The cholinesterase levels of the calves remained normal throughout the 78-day test. Five horses exposed continuously to vapours of 0.5 mg dichlorvos/ft$^3$ of air [17.7 mg/m$^3$ (2 ppm)], giving a range of 0.24-1.5 mg/m$^3$ (0.026-0.16 ppm), in a closed barn for 22 days showed mild erythrocyte cholinesterase depression after 7 days, which returned to normal at 11-22 days. Plasma cholinesterase levels remained normal during the experiment (Tracy et al., 1960).

Dogs, cats and rabbits were exposed continuously for 8 weeks to dichlorvos atmospheres in air ranging from 0.05-0.3 mg/m$^3$ (0.0055-0.033 ppm). No effects were found on general health, behaviour, plasma or erythrocyte cholinesterase activities or electroencephalographic patterns (Walker et al., 1972).

Thirty-two rhesus monkeys were given pellets of polyvinyl chloride resin formulations containing dichlorvos orally at doses ranging from 5-80 mg/kg bw, daily or twice daily for 10-21 days. Plasma and erythrocyte cholinesterase activities were significantly inhibited in all treated animals (Hass et al., 1972).

**Embryotoxicity and teratogenicity**

When dichlorvos was given by i.p. injection to rats on day 11 of pregnancy at a dose of 15 mg/kg bw, 3 of 41 foetuses developed malformations (omphaloceles) (Kimbrough & Gaines, 1968).

Groups of 15 rats were exposed to atmospheres containing 0.25, 1.25 and 6.25 mg/m$^3$ (0.027-0.69 ppm) for 23 hrs, daily, from days 1 to 20 of pregnancy. The treatment had no effect on the pregnancies, number of foetal resorptions or late foetal deaths, litter size or mean weight per foetus. The observation of only one malformed foetus in the group given 0.25 mg/m$^3$ (skeletal defects and gastroschisis) was regarded as unrelated to exposure of the dam to dichlorvos (Thorpe et al., 1972).

In studies reported as abstracts, concentrations of up to 500 mg/kg diet dichlorvos given to rats through 3 generations and 12 mg/kg bw given orally to rabbits during the period of major organogenesis had no teratogenic effects (Vogin et al., 1971; Witherup et al., 1971). Mean foetal weight was slightly depressed in offspring of rabbits that inhaled 4 mg/m$^3$ (0.44 ppm) dichlorvos in air from days 1-28 of gestation; this was considered to be the result of toxic effects on the mother (Thorpe et al., 1972).
In two abstracts, it was reported that doses of 800 mg/animal dichlorvos fed daily to pigs through gestation, or from 18-56 days before parturition, did not interfere with development of the offspring (Batte et al., 1969); reproduction was not impaired when male and female swine were fed for up to 37 months on a diet containing up to 500 mg/kg diet dichlorvos (Collins et al., 1971).

No abortions or malformations were induced in a pregnant cow fed 6.2 mg/kg bw/day dichlorvos for 134 days before parturition (Macklin & Ribelin, 1971).

A single oral dose of 40 μg/kg bw induced a drastic reduction in germinal epithelium of mouse testis (Krause & Homola, 1972).

[The Working Group noted that the low doses used in many of the above studies might explain the lack of embryotoxicity or teratogenicity reported].

Absorption, distribution, excretion and metabolism

Studies using 32P-, 36Cl-, [vinyl-14C]- and [methyl-14C]-dichlorvos in pigs, rats and mice, have shown that dichlorvos is degraded rapidly, whether it is administered orally or by inhalation (reviewed by Blair et al., 1975). After oral administration of [vinyl-1-14C]-dichlorvos to male rats, 42% of the radioactivity was recovered as metabolites during the first 24 hrs. After 4 days, 39% of the radioactivity was recovered as 14C-carbon dioxide, 13% was excreted in the urine and 3.4% in the faeces, and 16% was found in the carcass. At least 9 metabolites were detected in the urine; 14C-labelled metabolites were dichloroethyl β-D-glucopyranosiduronic acid, demethyl-dichlorvos, hippuric acid, N-benzoyl glycine and urea. Four days after dosing, 5% of the radioactivity of the administered dose was associated with liver, largely in the protein fraction as 14C-glycine and 14C-serine. Similar results were obtained in rats exposed by inhalation to 14C-dichlorvos (Hutson et al., 1971a,b).

Exposure of rats to 10 mg/m3 (1.1 ppm) for 4 hrs was required before dichlorvos could be detected reliably, and then only in kidneys; the half-life of dichlorvos in kidneys of animals exposed to 50 mg/m3 (5.5 ppm) for 4 hrs was 13.5 min. With 90 mg/m3 (10 ppm), which is equivalent to 60% of full air saturation, dichlorvos could be detected in most tissues. In mice similarly exposed, dichlorvos was found in most tissues, but at 1/10 of the levels found in rats (Blair et al., 1975).

The metabolism of dichlorvos has been reviewed (Hathway, 1975; Wright et al., 1979); it is metabolized via two major pathways: (1) hydrolysis and (2) O-demethylation. (1) The primary products of the esterase-catalysed hydrolysis of the P-O (vinyl) bond are dimethyl phosphate, which is excreted in the urine, and dichloroacetaldehyde, which is rapidly degraded to dichloroethanol. This may be glucuronidated.
and excreted in the urine or dehalogenated to a 2-carbon fragment, which may then enter pathways of intermediary metabolism. (2) O-Demethylation of dichlorvos can proceed via (a) oxidative demethylation catalysed by microsomal mono-oxygenases, with formation of formaldehyde and demethyl-dichlorvos, or (b) S-methyl transferase-catalysed monomethylation, to yield S-methylglutathione and demethyldichlorvos. Of the two major metabolic routes (1) and (2), esterase-catalysed hydrolysis is quantitatively more important and occurs in a wide range of tissues. The tissue distribution of methyl transferases is less well defined, but such activities have been demonstrated in liver and kidney.

**Reaction with macromolecules**

Dichlorvos alkylates bacteriophage and bacterial and mammalian nucleic acids in vitro (Lawley et al., 1974; Löffroth, 1970; Löffroth et al., 1969; Shooter, 1975; Wennerberg & Löffroth, 1974).

When [methyl-\(^{14}\)C]-dichlorvos (36.6 Ci/mol) was reacted with salmon sperm DNA, *Escherichia coli* DNA, *E. coli* cells and HeLa cells, it was found that dichlorvos broadly resembles methyl methanesulphonate (MMS) in its pattern of alkylation. In DNA, 7-methylguanine was the major product (63-93%), and 3-methyladenine was the principle minor product (8.8-13.7%) (except in *E. coli* cells, where there was rapid excision of 3-methyladenine); \(\text{O}^6\)-methylguanine was detected only in trace amounts. This pattern of methylation is ascribed to the \(S,2\) mechanism of alkylation characteristic of agents such as MMS and dimethylsulphate; however, dichlorvos methylated DNA at about 1/4 the rate of MMS and to 1/15 the extent per unit time under comparable conditions. Dichlorvos methylated cellular proteins more rapidly than it did the nucleic acids of *E. coli* cells and HeLa cells (Lawley et al., 1974). Studies of the effect of dichlorvos on the survival of bacteria and Chinese hamster cells suggest that dichlorvos caused DNA-strand breakage by an indirect mechanism (probably by alkylation of cellular protein and subsequent uncontrolled nuclease activity), and to a lesser extent by direct methylation of DNA (Green et al., 1974; Lawley et al., 1974).

Mice were exposed to \([^{14}\text{C}-\text{methyl}]\)- or \([^{3}\text{H}-\text{methyl}]\)-dichlorvos (3.2 Ci/mol or 0.7 Ci/mol, respectively), by inhalation or intraperitoneally, at doses ranging from about 5-45 mg/kg bw. Peaks of radioactivity (10-30 cpm/ml) coincident with markers of hypoxanthine and 7-methylguanine, together with peaks for unidentified material, were detected in column chromatograms of 24-hr urine samples collected from exposed mice. The most probable explanation for these results was said to be a chemical, non-enzymatic methylation of guanine moieties by dichlorvos. No data showing levels of alkylation of tissue macromolecules of exposed mice were given (Wennerberg & Löffroth, 1974).

Twenty male rats were exposed to \([^{14}\text{C}-\text{methyl}]\)- or \([^{3}\text{H}-\text{methyl}]\)-dichlorvos (113 Ci/mol) for 12 hrs, giving a total inhaled dose of 6 \(\mu\)g/rat (\(~\)0.03 mg/kg bw). Traces of radioactivity were detected in RNA, DNA and protein of
major soft-tissue organs; these ranged, in DNA, from 0.83 dpm/mg (testis) to 9.9 dpm/mg (spleen); in RNA, from 1.46 dpm/mg (brain) to 5.54 dpm/mg (heart/lung); and in protein, from 1.93 dpm/mg (brain) to 20.8 dpm/mg (heart/lung). Analysis of the DNA and RNA from total soft tissues revealed no 7-methylguanine, the limits of detection of methylation being 1 methyl group per $6 \times 10^{11}$ nucleotides DNA and $2 \times 10^9$ nucleotides RNA. Chromatographic analysis of urine from exposed rats revealed no radioactivity associated with added marker 7-methylguanine (Wooder et al., 1977).

Mutagenicity and other related short-term tests

The mutagenicity of dichlorvos has been reviewed (Wild, 1975).

Dichlorvos induced reverse mutations to streptomycin-independence in *E. coli* B (Sd-4) (Löfroth et al., 1969). In plate tests with *E. coli* WP2, dichlorvos induced trp reversions (Ashwood-Smith et al., 1972; Nagy et al., 1975); although, in the same system, negative (Dean, 1972a) and variable results (Bridges et al., 1973) have also been reported. In liquid tests with the same bacterial strain, a time-dependent increase in trp reversions was observed with 1–3 hrs' treatment with 13 mM dichlorvos (Bridges et al., 1973). Also in liquid tests, Wild (1973, 1975) recorded a time- and concentration-dependent increase in the frequency of forward mutations to streptomycin-resistance in a streptomycin-sensitive *E. coli* B strain with up to 10 hrs' treatment with 5–25 mM dichlorvos. Similar results were obtained by Mohn (1973) with much lower concentrations, i.e., up to 6 hrs' treatment with 0.3–3.2 mM dichlorvos, for the induction of forward mutations to 5-methyltryptophan resistance in *E. coli* K12.

Positive results have also been obtained (i) in plate tests with *Serratia marcescens* (Dean, 1972a), *Streptomyces coelicolor* (Carere et al., 1976) and *Salmonella typhimurium* strains TA1535, 1537 and 1538 (Shirasu et al., 1976); (ii) in liquid tests with *Pseudomonas aeruginosa* strain PA038 and *S. typhimurium* strains C117 and TA1535 (Carere et al., 1978a,b; Dyer & Hanna, 1973); (iii) in fluctuation tests with *Klebsiella pneumoniae*, *E. coli* K12, *Citrobacter freundii* and *Enterobacter aerogenes* (Voogd et al., 1972); and (iv) in *rec* assays (disc assays on nutrient agar plates) with *Bacillus subtilis* strain M45 rec− (Shirasu et al., 1976). An *E. coli* strain deficient in DNA polymerase (pol A) was more susceptible than the wild type to the lethal and mutagenic actions of dichlorvos (Bridges et al., 1973; Rosenkranz, 1973).

The results with bacteria (Bridges et al., 1973; Mohn, 1973; Shirasu et al., 1976) suggest that dichlorvos induces base-pair substitution type mutations. The mutation process is largely error-prone (i.e., *exrA*- and *recA*-dependent). The pattern of response of strains of *E. coli* WP2 that are deficient at 4 different loci concerned with DNA repair (polA, *wmA*, *recA*, *exrA*) is qualitatively similar with dichlorvos and with the methylating agent MMS, with regard both to survival and
mutation induction. Thus, the mutagenic action of dichlorvos is most probably a result of DNA alkylation (Bridges et al., 1973).

Dichlorvos induced point mutations, mitotic crossing-over and non-disjunction in Aspergillus nidulans (Bignami et al., 1977). It was not mutagenic to conidia of Neurospora crassa exposed to an atmosphere containing dichlorvos, but the actual concentration of dichlorvos in the cell environment was unknown (Michalek & Brockman, 1969). In Saccharomyces cerevisiae strain D4, dichlorvos produced a concentration-dependent increase in the frequency of mitotic gene convertants at the ade and trp loci, with exposure for 5 hrs to 5-40 mM (Dean et al., 1972; Fahrig, 1973). Host-mediated assays, involving S. typhimurium and Serratia marcescens bacteria as indicator organisms and mice injected subcutaneously with 25 mg/kg bw dichlorvos as hosts, were negative (Buselmaier et al., 1972; Voogd et al., 1972).

In those microbial systems in which positive results have been recorded, dichlorvos is much less effective than 'reference' alkylating agents such as MMS or N-nitrosomethylguanidine, i.e., the concentration of dichlorvos that produced a given mutagenic effect was 20-50 times higher than for MMS and about 100 times higher than for the nitrosamine (Bridges et al., 1973; Fahrig, 1973; Wild, 1973).

Dichlorvos induced chromosome aberrations in onion root tips (Sax & Sax, 1968). When barley seeds were treated with 0.25-0.75 nM dichlorvos for 6 or 18 hrs, there was an increased frequency of chromosome aberrations in the root-tip preparations of the seedlings, but no chlorophyll mutations were observed in the M2 generation (Bhan & Kaul, 1975).

No significant effects were noted in tests for sex-linked lethal mutations in male Drosophila melanogaster raised in a medium containing 0.009-0.09 mg/kg dichlorvos (Jayasuriya & Ratnayake, 1973; Kramers & Knaap, 1978). The observation by Gupta & Singh (1974) of a high incidence (10%) of aberrations in the salivary gland chromosome of third instar larvae grown in food containing 1 mg/kg dichlorvos is difficult to interpret, since it is very unlikely that a chemical would produce such a high frequency of chromosome aberrations but no sex-linked lethal mutations.

A significant increase in the frequency of autosomal lethal mutations in flies reared in a dichlorvos-containing medium was found in studies in which populations were exposed continuously to a dichlorvos-containing medium over about 30 generations (Hanna & Dyer, 1975). During this period, larvae developed increasing resistance to dichlorvos, and its concentration had to be raised from 0.1 mg/kg to 0.75 mg/kg in the course of the experiment. The results of this study are therefore not directly comparable with those from standard recessive lethal tests.

No induction of 8-azaguanine-resistant mutations was detected in V79 Chinese hamster cells that had been treated in serum-containing culture medium for 2 hrs with up to 1 mM dichlorvos (Wild, 1975). In
another study with human peripheral blood lymphocytes treated \textit{in vitro} with up to 0.18 mM dichlorvos for different durations, no significant cytogenetic changes were observed (Dean, 1972b).

No significant effect of dichlorvos was found in any \textit{in vivo} mammalian study. Negative results were reported in dominant lethal studies: (1) with male mice that received 5 x 10 mg/kg bw dichlorvos orally or 13 and 16.5 mg/kg bw by i.p. injection (Epstein \textit{et al.}, 1972) or were exposed to atmospheres containing dichlorvos at concentrations of 30 and 55 mg/m$^3$ of air for 16 hrs or to 2.1 and 5.8 mg/m$^3$ for 23 hrs, daily for 4 weeks (Dean & Thorpe, 1972a); and (2) with female mice that received 25 and 50 mg/kg bw dichlorvos orally or were exposed to atmospheres containing up to about 8 mg/m$^3$ dichlorvos in air (Dean & Blair, 1976). In cytogenetic studies, no effects were seen when male mice were exposed to dichlorvos by inhalation of 64-72 mg/m$^3$ of air for 16 hrs or of 5 mg/m$^3$ of air for 21 days; and none were seen in male Chinese hamsters exposed by inhalation and orally to high concentrations of dichlorvos. In chromosome preparations made from bone marrow and spermatocytes of exposed mice and hamsters, the incidence of chromosome abnormalities did not differ from that in controls (Dean & Thorpe, 1972b). The incidence of sperm abnormalities in dichlorvos-treated male mice was increased slightly (Wyrobek & Bruce, 1975).

Dichloroacetaldehyde, a metabolite of dichlorvos, was positive in the dominant lethal test when given intraperitoneally to mice at a dose of 176 mg/kg bw saline (Fischer \textit{et al.}, 1977).

Trimethyl phosphate, an impurity of dichlorvos, was also positive in the dominant lethal assay in mice when given as 5 oral doses of 500 mg/kg bw or as a single i.p. dose of 700-2000 mg/kg bw (Epstein \textit{et al.}, 1972).

(b) Humans

The numerous studies of the effects of dichlorvos on human subjects have been reviewed (Cavagna & Vigliani, 1970; Gillett \textit{et al.}, 1972a,b; WHO, 1965, 1967, 1968, 1971).

**Toxic effects**

In a study of household exposure to dichlorvos, families were exposed intermittently to maximum concentrations of approximately 0.1 mg/m$^3$ (0.01 ppm) for periods ranging from 2-6 months in their homes. Other volunteers were exposed cutaneously to dichlorvos for 30 min daily for 5 days. No significant degree of inhibition of plasma and erythrocyte cholinesterase resulted from either exposure (Zavon & Kindel, 1966).

Plasma and erythrocyte cholinesterase activities were measured in groups of hospital patients exposed to dichlorvos concentrations ranging from 0.02-0.28 mg/m$^3$ (0.002-0.03 ppm), for 16-24 hrs per day, for periods
ranging from 3-29 days. Control values for plasma and erythrocyte cholinesterase activities were established for 250 healthy male and 100 healthy female subjects not exposed to dichlorvos. Of 66 adult males without liver disease, 5 who were exposed for 24 hrs/day to levels of over 0.1 mg/m$^3$ (0.01 ppm) had plasma cholinesterase levels that were 35-72% lower than the control value; there was no depression of erythrocyte cholinesterase. Depression of plasma cholinesterase was seen only in those sick babies and children exposed to clothes disinfected with dichlorvos vapour and in healthy women exposed during labour or post-partum when the dichlorvos level was more than 0.1 mg/m$^3$ (0.001 ppm). All of 6 patients with liver disease showed a 25-66% reduction in plasma cholinesterase when exposed to <0.1 mg/m$^3$ (<0.01 ppm) and above. None of these subjects showed clinical symptoms of organophosphate poisoning. The amount of inhaled dichlorvos that caused a reduction in plasma cholinesterase was about the same for children and adults, i.e., 0.028-0.030 mg/kg bw/day (corresponding to a daily inhalation of 0.2 mg in children and to 1.7 mg in adults) (Cavagna et al., 1969).

It was reported in an abstract that plasma and erythrocyte cholinesterase levels were normal in 22 healthy babies, at birth and after 5 days' exposure for 18 hrs/day to a time-weighted concentration of 0.05 mg/m$^3$ (0.005 ppm) dichlorvos. Another group of 22 babies exposed to 0.152-0.159 mg/m$^3$ (0.017 ppm) dichlorvos also showed no acute adverse effects (Vigliani, 1971).

Eleven male and 2 female factory workers producing and processing a dichlorvos-releasing product were monitored for haematology, blood chemistry (including plasma and erythrocyte cholinesterase) and urinalysis throughout an 8-month exposure period and for 4 months after exposure had ceased. Plasma cholinesterase activity was inhibited by approximately 60%, and erythrocyte cholinesterase by 35%, as a result of repeated exposure to an average dichlorvos concentration of 0.7 mg/m$^3$ (0.077 ppm) for up to 216 hrs/month for 8 months. One month after exposure had ceased both esterases had returned to normal levels. No other effects, in the blood picture, blood chemistry, urinalysis or general health, attributable to dichlorvos exposure were noted (Menz et al., 1974). Chow & Bellin (1975) challenged both the statistical analysis and the conclusions of Menz et al. and surmized that '... the observed large decreases in blood cholinesterases [following dichlorvos] exposure may well be injurious to the health of workers even in the absence of overt clinical symptoms....'

Absorption, distribution, excretion and metabolism

In one man who ingested 5 mg [$^{14}$C-vinyl]-dichlorvos, a large proportion of the dose was excreted as $^{14}$C-CO$_2$; 8 hrs after administration the yield of $^{14}$C-CO$_2$ was 27%. A total of 9% of the dose was excreted in the urine over a period of 48 hrs. The rates and routes of excretion of radioactivity from rats, mice, hamsters and humans after oral ingestion of [$^{14}$C-vinyl]-dichlorvos suggest that the metabolic fate of the compound in these species is similar (Hutson & Hoadley, 1972).
Two male subjects were exposed for 10 and 20 hrs to atmospheres containing 0.25 mg/m\textsuperscript{3} (0.027 ppm) and 0.7 mg/m\textsuperscript{3} (0.077 ppm) dichlorvos, respectively. Blood samples taken within 1 min after exposure contained no detectable dichlorvos (detection limit, 0.1 μg/g; 4.5 x 10\textsuperscript{-7}M). The half-life of dichlorvos (5 x 10\textsuperscript{-6}M) added to human blood in vitro was found to range from 7-11 min at 37°C (data from 4 subjects), and the degradation was shown to be enzyme-catalysed, with a K\textsubscript{m} of the order of 3.2 x 10\textsuperscript{-6}M (Blair et al., 1975).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Dichlorvos was tested in one experiment in mice and in one in rats by oral administration: no statistically significant excess of tumours was observed. However, in mice, a few oesophageal tumours, rarely seen in untreated animals, were found. Dichlorvos was also tested by inhalation in a small number of rats, using low exposure levels; no conclusive evaluation of this study could be made.

Dichlorvos is an alkylating agent and binds to bacterial and mammalian nucleic acids. It is a mutagen in a number of microbial systems; but there is no evidence of its mutagenicity in mammals, in which it is rapidly degraded.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and the widespread use of dichlorvos since the early 1960s in agricultural, veterinary and household products indicate that widespread human exposure occurs. This is confirmed by a number of reports of its occurrence in the general environment. A group of people intentionally exposed to specific levels of dichlorvos is known to exist.

4.3 Evaluation

The available data do not allow an evaluation of the carcinogenicity of dichlorvos to be made.
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HEPTACHLOR AND HEPTACHLOR EPOXIDE

These substances were considered by a previous Working Group, in October 1973 (IARC, 1974). Since that time new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.

A review is available (Mercier, 1975).

1. Chemical and Physical Data

1.1 Synonyms and trade names

**Heptachlor**

Chem. Abstr. Services Reg. No.: 76-44-8

Chem. Abstr. Name: 1,4,5,6,7,8,8-Heptachloro-3a,4,7,7a-tetrahydro-4,7-methanol-1H-indene

Synonyms: 3-Chlorochlordene; 3,4,5,6,7,8,8a-heptachlorodicyclopentadiene; 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-endo-methanoindene; 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; 1(3a),4,5,6,7,8,8-heptachloro-3a(1),4,7,7a-tetrahydro-4,7-methanoindene; 3a,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methylene indene; 1,4,5,6,7,10,10-heptachloro-4,7,8,9-tetrahydro-4,7-methyleneindene; 1,4,5,6,7,10,10-heptachloro-4,7,8,9-tetrahydro-4,7-endo-methyleneindene

Trade names: Aahepta; Agroceres; Drinocl; E 3314; ENT 15,152; GPKh; H34; Heptachlorane; Heptagran; Heptamul; Rhodiachlor; Velsicol 104

**Heptachlor epoxide**

Chem. Abstr. Services Reg. No.: 1024-57-3

Chem. Abstr. Name: 2,3,4,5,6,7,7-Heptachloro-1a,1b,5,5a,6,6a-hexahydro-2,5-methano-2H-indeno(1,2-b)oxirene
Synonyms: Epoxyheptachlor; HCE; 1,4,5,6,7,8,8-heptachloro-2,3-epoxy-3a,4,7,7a-tetrahydro-4,7-methanoindan

Trade names: ENT 25,584; Velsicol 53-CS-17

1.2 Structural and molecular formulae and molecular weights

Heptachlor

\[
\text{C}_{10}\text{H}_8\text{Cl}_7 \quad \text{Mol. wt: 373.5}
\]

Heptrachlor epoxide

\[
\text{C}_{10}\text{H}_8\text{Cl}_7\text{O} \quad \text{Mol. wt: 389.4}
\]

1.3 Chemical and physical properties of the substances

From Fairchild et al. (1976a), unless otherwise specified

Heptachlor (99% pure)

(a) Description: White, crystalline solid

(b) Boiling-point: 135-145°C at 1-1.5 mm

(c) Melting-point: 93°C

(d) Spectroscopy data: \(\lambda_{\max} = 236 \text{ nm (E}_1^1 = 1611), 309 \text{ nm (E}_1^1 = 270), 328 \text{ nm (E}_1^1 = 203}\) (in ethanol) (Grasselli & Ritchey, 1975); infra-red (Gore et al., 1971) and Raman spectral data (Nicholas et al., 1976) have also been published.

(e) Solubility: Practically insoluble in water (0.056 mg/l); soluble in ethanol (4.5 g/100 ml), xylene (102 g/100 ml), carbon tetrachloride (112 g/100 ml), acetone (75 g/100 ml) and benzene (106 g/100 ml)
HEPTACHLOR AND HEPTACHLOR EPOXIDE

(f) **Volatile**: Vapour pressure is 0.0003 mm at 25°C.

(g) **Stability**: Stable in daylight, air, moisture and moderate heat (160°C); oxidized biologically to heptachlor epoxide (Whetstone, 1964)

Heptachlor epoxide (99.5% pure)

(a) **Melting-point**: 160-161.5°C

(b) **Solubility**: Insoluble in water

1.4 Technical products and impurities

**Heptachlor**

Technical heptachlor available in the US has the following specifications: waxy solid; assay, 72% min; related compounds, 28% max; hexachlorocyclopentadiene content, 1% max; melting range, 46.1-73.9°C (typical); density at 68.9°C, 1.61 (typical); and storage stability, one year minimum. It is available as dusts, dust concentrates, emulsifiable concentrates, wettable powders and oil solutions (Berg, 1978).

**Heptachlor epoxide**

Heptachlor epoxide is not available as a commercial product in the US. It is not normally present in commercial heptachlor but is apparently formed by biological and chemical transformation of heptachlor in the environment.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Heptachlor was isolated in about 1946 as a constituent of chlordane (Lawless et al., 1972). It is manufactured by the chlorination of chlordene in the presence of a catalyst such as Fuller's earth (Whetstone, 1964).

Commercial production of heptachlor in the US was first reported in 1953 (US Tariff Commission, 1954). In 1976, only one US company reported production of an undisclosed amount (see preamble, p. 16). US production in 1971 has been estimated at 2.7 million kg (Johnson, 1972); on the basis of the manufacturer's estimated production figures for the last 6 months of 1975, a total of approximately 4.5 million kg heptachlor (for uses
other than subsurface ground insertion for termite control and the
dipping of roots and tops of nonfood plants) were to be produced during
the 18-month period from July 1975-December 1976 (US Environmental

No data on its production in Europe were available. It has never
been produced commercially in Japan and was last imported in 1972, in a
quantity of about 71 thousand kg.

(b) Use

The only known use of heptachlor is as an insecticide. As of 4 June
1971, it was registered for use in the US on 22 agricultural crops,
involving both foliar and seed treatment (US Environmental Protection
Agency, 1971). An estimated 930 thousand kg were used in the US in
1974, as follows: on corn, 58%; by pest control operators, 26.8%; as
a seed treatment, 13.2%; and for miscellaneous other uses (including
use to control fire ants, use on pineapple and possibly on citrus), 2%
(US Environmental Protection Agency, 1976a).

On 6 March 1978, the US Environmental Protection Agency's heptachlor/
chlordane cancellation proceeding was terminated and a settlement reached
for the contested uses (US Environmental Protection Agency, 1978). The
settlement allows for use of technical heptachlor on corn cutworms until
1 August 1980. A maximum of 2.27 million kg heptachlor may be produced
for this use from the date of the settlement. A total of 443 thousand
kg may be used until 1 July 1983 for sorghum seed treatment and until
1 September 1982 for barley, oats, wheat, rye and corn seed treatment.
The settlement allows for use of smaller amounts of technical heptachlor
for other purposes. These are listed below by crop, location (in some
cases), maximum time interval for permitted use and amount allowed for
specific uses: (1) citrus, Florida, until 31 December 1979, 18.2 thousand
kg; (2) pineapples, Hawaii, 31 December 1982, 68.1 thousand kg; and
(3) narcissus bulbs, 31 December 1980, 204.3 kg (Anon., 1978a). After
1 July 1983, the only approved use for heptachlor will be for underground
termite control (Anon., 1978b).

No data on use of heptachlor in Europe were available. It has
been used in Japan as an insecticide; however, its registration was
cancelled in 1972 and it is no longer used there.

In November 1971, the Joint Meeting of the FAO Working Party of
Experts on Pesticide Residues and the WHO Expert Committee on Pesticide
Residues recommended practical residue limits in 15 commodities, ranging
from 0.01 mg/kg for citrus fruit to 0.5 mg/kg for crude soya bean oil,
with a limit of 0.05 mg/kg for vegetables and 0.15 mg/kg for milk and
HEPTACHLOR AND HEPTACHLOR EPOXIDE

Tolerances for total residues of heptachlor and heptachlor epoxide in or on raw agricultural commodities have been established by the US Environmental Protection Agency as follows: 0.1 mg/kg in or on cabbage, lettuce, rutabagas (yellow turnips) and snap beans; and none in or on a variety of about 30 vegetable, fruit and field crops, and in meat and milk (US Environmental Protection Agency, 1976b).

The Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues in 1970 established an acceptable daily intake (ADI) for humans of 0-0.0005 mg/kg bw (WHO, 1972).

The US Occupational Safety and Health Administration's health standards require that an employee's dermal exposure to heptachlor not exceed 0.5 mg/m³ in the workplace in any 8-hr work shift of a 40-hr week (US Occupational Safety & Health Administration, 1977). The corresponding standard in the Federal Republic of Germany is also 0.5 mg/m³, and the acceptable ceiling concentration in the USSR is 0.01 mg/m³ (Winell, 1975).

2.2 Occurrence

Heptachlor

Heptachlor is not known to occur as a natural product. It is a contaminant of technical chlordane (about 10%) (see monograph, p. 45).

A review of the environmental distribution of heptachlor is available (Fairchild et al., 1976b).

(a) Air

Air was sampled in 9 US cities (representative of both urban and agricultural areas) for pesticides and their metabolites during 2 weeks of each month over 6 months. Heptachlor was detected in 37 samples of air from 1 city (maximum level, 19.2 ng/m³) and in 7 air samples from another (maximum level, 2.3 ng/m³) (Stanley et al., 1971).

Weekly air samples were taken in the middle of a primary cotton-growing area during 1972, 1973 and 1974. The maximum level of heptachlor found was 0.8 ng/m³ (Arthur et al., 1976).

(b) Water

Heptachlor has been found in drinking-water, ground-water, chemical plant effluents, river-water (Shackelford & Keith, 1976) and in sediments, lakes and rivers at 18 US and European locations (Eurocop-Cost, 1976).

In a 1958-1965 survey of US rivers, heptachlor was found in 17% of the samples at average concentrations up to 3 ng/l (Safe Drinking Water Committee, 1977). It has been detected in ambient water in Nova Scotia
at levels up to 0.46 µg/l (Burns et al., 1975).

In 1977, a study was conducted in 2 US counties on the effects of agricultural practices on the pesticide residue levels in rural drinking-water samples from 1 out of 100 households. Heptachlor was detected in 62.5% of samples from one county, at a mean level of 15 µg/l, and in 45.5% of those from the other, at a mean level of 9 µg/l (Sandhu et al., 1978).

(c) Soil

The half-life of heptachlor in soil is 9-10 months when used at agricultural rates (Anon., 1976).

Pesticide residues were measured in cropland soils from 43 states and in noncropland soils from 11 states during fiscal year 1969, as part of the US National Pesticide Monitoring Program. Heptachlor was detected in 68 of 1729 samples analysed; levels ranged from 0.01-0.97 mg/kg in soil used for corn, cotton, general farming and hay and in irrigated land and vegetable fruit cropping regions. Heptachlor was not detected in noncropland soil samples (Wiersma et al., 1972a). It was also detected in soil samples from 7/8 US cities taken in 1969; levels ranged from 0.01-0.53 mg/kg (Wiersma et al., 1972b).

Heptachlor residues in the soil of 7/16 farms ranged from trace amounts to 0.24 mg/kg (Harris & Sans, 1971). Residues were also detected in soil samples from 6 of the 12 states in the Corn Belt region of the US, in an average of 5.7% of the sites, at levels ranging from 0.01-0.84 mg/kg (Carey et al., 1973).

In 1973, a study was performed to determine the persistence of pesticides in tobacco fields. Heptachlor was applied to 3 plots of soil at a rate of 2.24 kg/ha active ingredient; the soil was rototilled to a depth of 15 cm; soil samples were taken at 0-15 cm depth; and tobacco plants were planted 6 days later. When soil samples were taken at 0-15 cm and 15-23 cm nearly 3 months later, slightly more heptachlor was found in the later 0-15 cm sample (0.37 mg/kg) than in the earlier one (0.34 mg/kg) (1 day after planting); 0.04 mg/kg was found in the later 15-23 cm samples. The authors suggested that, due to soil compaction during the 3 months, some of the insecticide that was initially deposited below 15 cm appeared in the 0-15 cm samples (Townsend & Specht, 1975).

Heptachlor was detected in sediments from stream beds and natural drainage ditches, at maximum levels of 174 and 4.8 µg/kg, respectively (Burns et al., 1975).

(d) Food

Samples of raw oil and oil in various stages of processing (neutralized, hydrogenated, decolourized and deodorized oils and shortenings) were
taken at 7 cooking-oil processing factories. Heptachlor was present at 9 μg/kg in raw oil and at 2 μg/kg in neutralized oil, but none was found in the remaining samples (Hashemy-Tonkabony & Soleimani-Amiri, 1976).

Heptachlor residues were not found in any food composites collected during the 9th year (August 1972–July 1973) of the Total Diet Study of the US Food and Drug Administration (Johnson & Manske, 1976).

(e) Animals

Heptachlor was found in 3/15 seals at levels of 0.003, 0.017 and 0.039 mg/kg, respectively (Clausen et al., 1974).

Heptachlor epoxide

Heptachlor epoxide is not known to occur as a natural product.

(a) Air

Heptachlor epoxide was detected at a maximum level of 9.3 ng/m³ in weekly air samples taken in the middle of a primary cotton-growing area (Arthur et al., 1976).

(b) Water and sediments

Heptachlor epoxide has been found in drinking-water, ground-water, land-runoff effluent and river-water at 7 US and European locations (Shackelford & Keith, 1976) and in sediments, lakes, rivers, tap-water and effluent water from a biological sewage treatment plant at 28 US and European locations (Eurocop-Cost, 1976).

In a 1958–1965 survey of US rivers, heptachlor epoxide was found in 25% of the samples at average concentrations of <1–8 ng/l (Safe Drinking Water Committee, 1977).

Heptachlor epoxide levels in tributary streams of Lake Michigan averaged <0.6, 2.1 and 2.9 ng/l in 1970, 1971 and 1972, respectively, and annual ranges were <0.2–1.0, 0–5.4 and 1.2–4.5 ng/l. Average concentrations of heptachlor epoxide in sewage treatment plant effluents were <0.3, 5.4 and 2.8 ng/l, respectively, and annual ranges were 0.2–0.7, 0.3–17.2 and 1.2–7.8 ng/l (Schacht, 1974).

Heptachlor epoxide was detected in 57% of water samples in Nova Scotia, at levels up to 6.1 μg/l (Burns et al., 1975). In a study of water supplies in 2 US counties, heptachlor epoxide was detected in 41.7% of samples from 1 county, at a mean level of 8 ng/l, and in 63.6% of those from the other, at a mean level of 18 ng/l (Sandhu et al., 1978).
(c) Soil

Heptachlor epoxide was detected in the soil of 7/16 farms at levels ranging from trace amounts to 0.24 mg/kg (Harris & Sans, 1971). It was also found in 139 of 1729 samples of cropland soil analysed as part of the US National Pesticide Monitoring Program in fiscal year 1969; levels ranged from 0.01-1.08 mg/kg in all the cropping regions sampled. It was also detected at a level of 0.01 mg/kg in 2/199 samples of noncropland soil (Wiersma et al., 1972a).

In a study of organochlorine pesticide residues in soil in the US Corn Belt region, heptachlor epoxide was detected in 7 of the 12 states in the region, at levels ranging from 0.01-0.31 mg/kg at an average of 8% of sites (Carey et al., 1973). It was also detected in hayfield soils in 9 US states at 1.1% of sites, at a maximum level of 0.15 mg/kg, on a dry-weight basis (Cowen et al., 1976).

In a study of pesticide residues in tobacco fields, no heptachlor epoxide was found in the soil immediately after application of heptachlor. After nearly 3 months, heptachlor epoxide was detected at levels of 0.03 and 0.01 mg/kg at depths of 0-15 cm and 15-23 cm, respectively (Townsend & Specht, 1975).

(d) Food

During the period August 1972-July 1973, market basket surveys were carried out in 30 US cities, which ranged in population from less than 50,000 to 1,000,000 or more, to measure pesticide residues by food class. Heptachlor epoxide was found in 21 samples of dairy products at levels from trace amounts to 2 µg/kg; in 24 samples of meat, fish and poultry, from trace amounts to 2 µg/kg; and in one sample of potatoes in trace amounts (Johnson & Manske, 1976). It has been found in soya bean oil at levels up to 0.01 mg/kg (Yang et al., 1976).

(e) Animals

Heptachlor epoxide was found in muscle tissue of fish collected from a river in British Columbia, in 14 of 61 samples at levels of up to 86.6 µg/kg, and in 4 of 11 samples of shellfish collected from the estuary at levels up to 23 µg/kg (Albright et al., 1975). The edible portions of four species of fish were found to contain 0.1 mg/kg bw or less (Schacht, 1974).

In breast muscle samples from doves from 15 US states, levels of heptachlor epoxide ranged from 0.14-8.7 mg/kg lipid weight (<0.006-0.17 mg/kg wet weight) (Kreitzer, 1974). It was detected in starlings from approximately 97% of 126 collection sites, at levels ranging from trace amounts to 0.31 mg/kg wet weight (White, 1976).
Heptachlor epoxide was found in most species of arctic mammals: levels ranged from 0.005 mg/kg in a ringed seal to 0.49 mg/kg in a polar bear (Clausen et al., 1974).

(f) Humans

Trace amounts of heptachlor epoxide have been found in fat in the general population in most countries (Abbott et al., 1968, 1972; Curley et al., 1973; Davies et al., 1971; Edwards, 1970; Fournier et al., 1972; Hayes et al., 1965; Wassermann et al., 1970, 1972a,b,c). Maximum levels were reported in France (0.28-0.36 mg/kg) (Fournier et al., 1972). In the US, levels of 0.24 mg/kg were found in 1964 (Hayes et al., 1965), which had decreased to 0.05 mg/kg by 1969 (Davies et al., 1971).

2.3 Analysis

Analytical methods used to determine heptachlor and its epoxide have been reviewed (Fairchild et al., 1976b). Methods used for the analysis of heptachlor and its epoxide in environmental samples are listed in Table 1.

More than 80% of heptachlor and heptachlor epoxide is recovered in the method of the Association of Official Analytical Chemists (US Food & Drug Administration, 1975). Other analytical investigations designed to isolate and identify heptachlor include paper chromatography (Dyatlovitiskaya et al., 1972), thin-layer chromatography (Yurkova & Klisenko, 1970) and gas chromatography/electron capture detection (Arthur et al., 1976).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Epstein (1976) reported a previously unpublished study by the Food & Drug Administration, carried out in 1965, in which 3 groups of 100 male and 100 female C3H mice were fed heptachlor or heptachlor epoxide at a concentration of 10 mg/kg diet for 24 months or received a standard diet. Data were reported for males and females combined in a summary memorandum form. The numbers of mice still alive at 24 months were 62 controls, 60 given heptachlor and 19 given heptachlor epoxide. The incidences of hepatic hyperplasia and benign hepatomas were doubled in mice treated with heptachlor and heptachlor epoxide in comparison with control animals. The incidence of hepatic carcinomas, diagnosed on the basis of pulmonary metastases or extrahepatic invasion, was the same in heptachlor-treated and control groups, but doubled in the group given heptachlor epoxide. When all malignant tumours were combined, their incidence in
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emulsifiable concentrates</td>
<td>Dechlorinate</td>
<td>Titration</td>
<td></td>
<td>Horwitz (1970)</td>
</tr>
<tr>
<td>Granules and dusts</td>
<td>Dechlorinate</td>
<td>Titration</td>
<td></td>
<td>Horwitz (1970)</td>
</tr>
<tr>
<td>Liquids</td>
<td>Extract (carbon disulphide)</td>
<td>GC/FID</td>
<td></td>
<td>Horwitz (1970)</td>
</tr>
<tr>
<td>Solids</td>
<td>Extract (pentane) in Soxhlet</td>
<td>GC/FID</td>
<td></td>
<td>Horwitz (1970)</td>
</tr>
<tr>
<td><strong>Air</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap in ethylene glycol</td>
<td>GC/ECD</td>
<td>0.1 ng/m³</td>
<td>Arthur et al. (1976)</td>
</tr>
<tr>
<td><strong>Soil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sediments and sewage sludge</td>
<td>Centrifuge, extract solid (acetone), liquid/liquid partition, transfer into trimethylpentane, treat to remove sulphur, isolate in trimethylpentane</td>
<td>GC/ECD</td>
<td>1-10 μg/kg</td>
<td>Jensen et al. (1977)</td>
</tr>
<tr>
<td>Soil</td>
<td>Add acetone, extract (petroleum ether or hexane), filter, wash (water) to remove acetone, CC</td>
<td>GC/ECD</td>
<td>1 μg/kg</td>
<td>Harris &amp; Sans (1971)</td>
</tr>
<tr>
<td>Soil</td>
<td>Extract (hexane-isopropanol), filter, wash (water) to remove isopropanol, filter, dry</td>
<td>GC/ECD</td>
<td>10 μg/kg</td>
<td>Wiersma et al. (1972a,b)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
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<tr>
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</tr>
<tr>
<td>Soil</td>
<td>Extract (acetone-hexane), add benzene to extract, evaporate to dryness, dissolve in hexane, CC</td>
<td>GC/ECD</td>
<td></td>
<td>Townsend &amp; Specht (1975)</td>
</tr>
<tr>
<td>Soil</td>
<td>Wet sample, extract (hexane-isopropanol), filter, wash (water) to remove isopropanol, dry</td>
<td>GC/ECD</td>
<td>10 µg/kg</td>
<td>Carey et al. (1973)</td>
</tr>
<tr>
<td>Food</td>
<td>Extract (acetonitrile), dilute (water), extract (petroleum ether), CC</td>
<td>GC/ECD, thermionic detection</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td></td>
<td>Extract (hexane-acetone), dry, filter, wash filtrate (water), distill, CC</td>
<td>GC/ECD</td>
<td>4 µg/kg</td>
<td>Albright et al. (1975)</td>
</tr>
<tr>
<td>Fish, crabs, shellfish</td>
<td>Dilute (water), add hexane, shake, add isopropanol, shake, wash (water), separate hexane layer, dry, filter</td>
<td>GC/ECD</td>
<td>10 µg/kg</td>
<td>Yang et al. (1976)</td>
</tr>
<tr>
<td>Molasses</td>
<td>Blend with water-acetonitrile, decant, separate liquid, concentrate, extract (hexane), transfer to hexane, liquid/liquid partition, transfer to hexane, CC</td>
<td>GC/ECD</td>
<td>10 µg/kg</td>
<td>Carey et al. (1973)</td>
</tr>
<tr>
<td>Crops</td>
<td>Extract (hexane)</td>
<td>TLC/oscillo-polarography on TLC plate</td>
<td>20 µg/kg</td>
<td>Kommatyi &amp; Büblik (1974)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>--------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Water Rural potable</td>
<td>Extract (hexane), CC</td>
<td>GC/ECD</td>
<td>10 ng/l</td>
<td>Sandhu et al. (1978)</td>
</tr>
<tr>
<td>Biological Adipose tissue</td>
<td>Extract (hexane), re-extract (petroleum ether, chloroform-methanol, acetonitrile or acetone-hexane), dry, dissolve (hexane), CC</td>
<td>GC/ECD and TLC</td>
<td></td>
<td>Clausen et al. (1974)</td>
</tr>
<tr>
<td>Wildlife tissues</td>
<td>Grind with sodium sulphate, extract (ethyl ether-petroleum ether) in Soxhlet, CC</td>
<td>GC/ECD</td>
<td>5 µg/kg</td>
<td>White (1976)</td>
</tr>
<tr>
<td>Plant tissues</td>
<td>Blend in acetonitrile, extract (hexane), wash (water), evaporate to dryness, dissolve (hexane), CC</td>
<td>GC/ECD</td>
<td></td>
<td>Townsend &amp; Specht (1975)</td>
</tr>
</tbody>
</table>

Abbreviations: GC/FID - gas chromatography/flame-ionization detection; GC/ECD - gas chromatography/electron capture detection; CC - column chromatography; TLC - thin-layer chromatography; PC - paper chromatography
controls was approximately double that in the two test groups. Following histological reevaluation, however, a significant excess (P<0.001) of liver carcinomas was found in males and females treated with heptachlor and heptachlor epoxide when compared with controls, as shown below in Table 2.

**TABLE 2. NUMBER OF LIVER CARCINOMAS IN UNTREATED MICE AND IN THOSE RECEIVING 10 MG/KG DIET OF HEPTACHLOR AND HEPTACHLOR EPOXIDE FOR 2 YEARS**

<table>
<thead>
<tr>
<th>Controls</th>
<th>Heptachlor</th>
<th>Heptachlor Epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>22/73</td>
<td>64/87</td>
</tr>
<tr>
<td></td>
<td>73/79</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>2/54</td>
<td>57/78</td>
</tr>
<tr>
<td></td>
<td>77/81</td>
<td></td>
</tr>
</tbody>
</table>

Epstein (1976) also reviewed and reevaluated unpublished studies carried out in 1973 by the International Research and Development Corporation, in which groups of 100 male and 100 female Charles River CD-1 mice were each fed a mixture of 75% heptachlor epoxide and 25% heptachlor at levels of 1, 5 and 10 mg/kg diet, for 18 months starting at 7 weeks of age. Excluding groups of 10 mice from each group that were sacrificed for interim histology at 6 months, mortality at 18 months in all groups ranged from 34-49%, with the exception of the males and females given 10 mg/kg diet, which had mortalities of approximately 70%; in addition, comparatively large numbers of animals from all groups were lost to histology by autolysis. A dose-related incidence of 'compound-related liver masses' and 'compound-related nodular hyperplasia' was reported in test groups; the incidence in those receiving 1 mg/kg diet decreased to the level of negative controls. Histological reevaluation revealed an excess of liver carcinomas in both sexes given the 10 mg/kg diet level and in males given 5 mg/kg diet (P<0.01; see Table 3). The pathology of these liver carcinomas was reported by Reuber (1977).

**TABLE 3. NUMBER OF LIVER CARCINOMAS IN UNTREATED MICE AND IN THOSE RECEIVING 1, 5 AND 10 MG/KG DIET OF A MIXTURE OF 75% HEPTACHLOR EPOXIDE AND 25% HEPTACHLOR**

<table>
<thead>
<tr>
<th>Controls</th>
<th>1 mg/kg</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0/62</td>
<td>2/61</td>
<td>18/68</td>
</tr>
<tr>
<td>Females</td>
<td>6/76</td>
<td>1/70</td>
<td>6/65</td>
</tr>
</tbody>
</table>
Groups of 50 male and 50 female B6C3Fl hybrid mice, 5 weeks of age, were fed technical-grade heptachlor (72% heptachlor, 18% trans-chlordane and 2% cis-chlordane) in the diet for 80 weeks. Males received initial dietary concentrations of 10 and 20 mg/kg diet and time-weighted average concentrations of 6 and 14 mg/kg diet; females received initial concentrations of 20 and 40 mg/kg diet and time-weighted average concentrations of 9 and 18 mg/kg diet. Initial dose levels were reduced during the experiment due to adverse toxic effects. Matched controls consisted of 20 males and 10 females; and pooled controls consisted of 100 males and 80 females. Survival in all groups was relatively high: over 70% of test and control males and 60% of test and control females were still alive at 90 weeks. Liver carcinomas were found in 34/47 males (P<0.01) and 30/42 females (P<0.01) that received the higher dose, and in 11/46 males and 3/47 females in the lower dose group, compared with 5/19 male and 2/10 female matched controls (National Cancer Institute, 1977).

Rat: Epstein (1976) reported a previously unpublished study by Kettering Laboratories, carried out in 1955, in which heptachlor of unspecified purity was administered to groups of 20 male and 20 female CF rats, 10 weeks of age, at concentrations of 1.5, 3, 5, 7 and 10 mg/kg diet, by spraying alcoholic solutions onto Purina Chow Pellets, for 100 weeks. Mortality in all test groups was stated to be random, although it was generally elevated in male test groups (50-75%). Liver-cell abnormalities were reported in males and females of the 7 and 10 mg/kg diet test groups. In addition, an excess of heterogenous, multiple-site tumours was reported in all females, particularly in those given 5 and 7 mg/kg; these data were interpreted as insignificant. Subsequent statistical analysis revealed a significant incidence of all tumours combined in female groups given the higher levels of heptachlor (P<0.01).

Epstein (1976) also reported another unpublished study by Kettering Laboratories, carried out in 1959, in which groups of 25 male and 25 female CFN rats, 7 weeks of age, were fed heptachlor epoxide at concentrations of 0.5, 2.5, 5.0, 7.5 and 10.0 mg/kg diet, by spraying alcoholic solutions on Purina Chow pellets, for 108 weeks. Survival at that time was over 45% in test and control groups. The following changes were noted in test groups: hepatic-cell vacuolization (which was centrilobular in those given lower test doses and irregular in those on higher doses), an excess of hepatomas and a spectrum of unusual malignant tumours. Subsequent analysis revealed an excess of all tumours in all test groups combined (P<0.001). Histological reevaluation revealed an excess of hepatic carcinomas in females given 5 and 10 mg/kg diet (P<0.05); males given 10 mg/kg diet also showed an excess when hepatic carcinomas and hyperplastic nodules were combined.

A group of 95 male and female suckling Wistar rats were administered 10 mg/kg bw heptachlor (97% pure) in corn oil by gavage on 5 successive occasions at 2-day intervals starting at 10 days of age; 19 male and 27 female controls received corn oil alone. Excluding 9 male and 20 female
test animals sacrificed for interim histology at 60 weeks, survival in test and control groups was high and comparable. While the numbers of total tumours in test and control groups were comparable, 'lipomatosus' renal tumours were noted in two females treated with heptachlor (Cabral et al., 1972) [The Working Group noted the small number of doses administered and the short duration of treatment].

Groups of 50 male and 50 female 5-week-old Osborne-Mendel rats were fed technical-grade heptachlor (72% heptachlor, 18% trans-chlordane and 2% cis-chlordane) in the diet for 80 weeks. Males received initial concentrations of 80 and 160 mg/kg diet and time-weighted concentrations of 40 and 78 mg/kg diet; females received initial concentrations of 40 and 80 mg/kg diet and time-weighted concentrations of 26 and 51 mg/kg diet. Initial dose levels were reduced during the experiment due to adverse toxic effects. Matched controls consisted of 10 males and 10 females; pooled controls consisted of 60 males and 60 females. Survival in all groups was high: approximately 60% of all test and control groups were still alive at 110 weeks. An excess of follicular-cell thyroid neoplasms was noted in females that received the low dose (3/43) and in those that received the high dose (14/38) (P<0.01), compared with pooled female controls (3/58) (National Cancer Institute, 1977).

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD$_{50}$ for heptachlor in rats is 100 mg/kg bw in males and 160 mg/kg bw in females (Gaines, 1969), the i.v. LD$_{50}$ in mice is about 20 mg/kg bw (Radomski & Daviadow, 1953). The oral LD$_{50}$ of the epoxide in rats is 62 mg/kg bw (Sperling & Ewinike, 1969).

Daily oral administration of 2 or 5 mg/kg bw heptachlor for 78-86 days to pigs, sheep and rats induced hepatic necrosis and synthesis of smooth endoplasmic reticulum. Rats were the most sensitive species (Halačka et al., 1975). Chronic i.m. treatment of rats with daily doses of 3 and 15 mg/kg bw heptachlor and 1 and 5 mg/kg bw heptachlor epoxide decreased liver size but had no effect on other tissues. Certain hepatic and renal gluconeogenic enzymes were stimulated (Kacew et al., 1973).

Embryotoxicity and teratogenicity

Injection of 1.5 mg/egg heptachlor resulted in a 12% reduction in hatchability but no abnormal chicks (Smith et al., 1970). It was toxic to sea urchins and induced greatly abnormal embryos (Bresch & Arendt, 1977).
Absorption, distribution, excretion and metabolism

Rats metabolize intravenously administered C$^{14}$-labelled heptachlor to the epoxide (found in the tissues, faeces and urine) and to 4,5,6,7,8,8-hexachloro-1-exo-hydroxy-6,7-exo-epoxy-1,2,3a,4,7,7a-hexahydro-1,4-endo-methyleneindene (1,2,3,4,8,8-hexachloro-5-exo-hydroxy-6,7-exo-epoxy-1,4,4a,7a,5,6-hexahydro-1,4-endo-methyleneindene), a hydrophilic metabolite which is excreted in the urine. In rabbits, the radioactive label was found mainly in the urine (20% epoxide, 80% hydrophilic metabolite) (Klein et al., 1968). Another faecal metabolite (a dehydrogenated derivative of 1-hydroxy-2,3-epoxychlordene) was isolated from rats fed 10 mg/kg diet heptachlor epoxide for 30 days (Matsumura & Nelson, 1971).

Rats fed 30 mg/kg diet heptachlor had maximum concentrations of heptachlor epoxide in fat within 2-4 weeks; 12 weeks after exposure was discontinued, heptachlor epoxide had completely disappeared from adipose tissue (Radomski & Davidow, 1953). Heptachlor is also stored as heptachlor epoxide in the fat of steers (Bovard et al., 1971) and dogs (Davidow & Radomski, 1953).

Mutagenicity and other related short-term tests

Heptachlor showed no activity in the rec assay with Bacillus subtilis (Shirasu et al., 1976), and both heptachlor and heptachlor epoxide were nonmutagenic to Salmonella typhimurium strains TA1535, TA1536, TA1537 and TA1538 in the presence or absence of a rat liver microsomal activation system (Marshall et al., 1976).

In Drosophila melanogaster injected with aqueous solutions of 5 μg/ml heptachlor or 2.5 μg/ml heptachlor epoxide, there was no evidence of induction of X-linked recessive lethals in post-meiotic germ-cell stages (Benes & Sram, 1969).

Male albino mice that received single doses of heptachlor:heptachlor epoxide (25:75) either by oral intubation or by i.p. injection (7.5 or 15 mg/kg bw) were mated with untreated females (1 male:3 females) sequentially for 6 successive weeks. There was no evidence of an increase in dominant lethality (relative to controls) as measured by pregnancy rates, early deaths and number of live implants/female (Arnold et al., 1977).

In a study reported as an abstract, rats were fed on diets containing 1 and 5 mg/kg diet heptachlor for 3 generations, and treated males were then used in dominant lethal tests. There was a statistically significant increase in the number of resorbed foetuses, relative to controls. Investigation of chromosomal damage in bone-marrow cells of the test animals of the second and third generations showed an increased incidence of abnormal mitosis relative to controls (Cerey et al., 1973).
An increase in the frequency of chromosome aberrations was found in the bone-marrow cells of mice 21 hrs after i.p. injection of 5.2 mg/kg bw heptachlor (4% of the LD50 dose) (Markaryan, 1966).

In SV40 transformed human cells (VA-4) in vitro, both heptachlor and heptachlor epoxide induced unscheduled DNA synthesis (measured autoradiographically) at all concentrations tested – 8 hrs' exposure to 100 and 1000 μM heptachlor; 8 hrs' exposure to 10, 100 and 1000 μM heptachlor epoxide – but only in the presence of a rat liver microsomal activation system (Ahmed et al., 1977).

(b) Humans

Heptachlor epoxide has been found in human fat [see section 2.2 (f)]. It has also been found in the blood and fat of stillborn infants (levels of 0.01-0.3 mg/kg were found in fat; 0.001 mg/l in blood), indicating transplacental transfer to the foetus (Curley et al., 1969; Wassermann et al., 1972a,c; Zavon et al., 1969). It is excreted in human milk (0.001-0.003 mg/l) (Curley & Kimbrough, 1969).

In a clinical study, it was demonstrated that the sera of pregnant women in a rural agricultural area in the Mississippi Delta contained levels of residues of chlorinated hydrocarbon insecticides, including heptachlor epoxide (0.08-0.1 μg/l), that were comparable to those found in occupationally exposed men. Cordblood of offspring also contained significant residue levels (0.02 μg/l) (D'Ercole et al., 1976).

Chlorinated insecticides were found in the blood of all 35 mothers and 35 newborn infants examined in two Italian provinces. Heptachlor was found in 62/70 blood samples in high concentrations (up to 0.06 mg/l); heptachlor epoxide (up to 0.015 mg/l) was found in only 4 cases (Grasso et al., 1973).

3.3 Case reports and epidemiological studies

Infante et al. (1978) reviewed 25 previously reported cases of blood dyscrasia associated with exposure to chlordane or heptachlor, either alone or in combination with other drugs, in conjunction with 3 newly diagnosed cases of aplastic anaemia and 3 of acute leukaemia associated with a prior history of exposure to technical-grade chlordane containing 3-7% heptachlor. During the period December 1974-February 1976, 5 of 14 children with neuroblastoma admitted to one paediatric hospital had a positive history of pre- or postnatal exposure to technical-grade chlordane containing 3-7% heptachlor; history of exposure to chlordane/heptachlor had not yet been ascertained for the remaining 9 cases.
4. Summary of Data Reported and Evaluation

4.1 Experimental data

Heptachlor containing about 20% chlordane was tested in one experiment in mice and in one in rats by oral administration. It produced liver carcinomas in mice of both sexes. In rats, the results suggest a carcinogenic effect on the thyroid in females. Heptachlor (97% pure) was also inadequately tested in one experiment in rats by oral administration. A reevaluation of unpublished studies involving the oral administration of heptachlor of unspecified purity to mice and rats of other strains confirms the hepatocarcinogenicity of heptachlor for mice and suggests a carcinogenic effect in female rats.

The latter studies also suggested that heptachlor epoxide produced liver carcinomas in mice of both sexes and hepatomas in rats of both sexes.

Heptachlor and heptachlor epoxide were not mutagenic in *Salmonella typhimurium* or *Drosophila melanogaster* and were negative in dominant lethal tests in mice.

4.2 Human data

Case reports suggest a relationship between exposure to heptachlor or chlordane (either alone or in combination with other compounds) and blood dyscrasias. Another publication has also suggested an association with acute leukaemia; an association between both pre- and postnatal exposure to technical-grade chlordane containing heptachlor and the development of neuroblastomas in children was also suggested.

No epidemiological studies were available to the Working Group.

The extensive production of heptachlor and its use over the past several decades, together with the persistent nature of the compound, indicate that widespread human exposure occurs. This is confirmed by many reports of its occurrence in the general environment and by the finding of its epoxide in the fat and body fluids of human adults and stillborn infants.

4.3 Evaluation

There is sufficient evidence that heptachlor (containing chlordane) is carcinogenic in mice. There is limited evidence that heptachlor epoxide is carcinogenic in experimental animals. A report of a series of cases of human cancer associated with exposure to heptachlor was also available, but these data do not allow an evaluation of the carcinogenicity of heptachlor or heptachlor epoxide to humans to be made.
5. References


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Markarjan, D.S. (1966) Cytogenetic effect of some chlororganic insecticides on the nuclei of mouse bone-marrow cells (Russ.). Genetika, 1, 132-137


Mercier, M. (1975) Preparatory Study for Establishing Criteria (Dose/Effect Relationships) for Humans on Organochlorine Compounds, i.e. Pesticides and their Metabolites, Doc. No. 1347/75 e, Luxembourg, Commission of the European Communities, pp. 24-26, 63-66, 176-177, 219-220


HEXACHLOROBENZENE

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 118-74-1
Chem. Abstr. Name: Hexachlorobenzene
Synonyms: HCB; pentachlorophenyl chloride; perchlorobenzene
Trade names: Amatin; Anticarie; Bunt-cure; Bunt-no-more; Co-op Hexa; Granox NM; Julin's carbon chloride; No Bunt; No Bunt 40; No Bunt 80; No Bunt Liquid; Sanocide; Sniecitox

1.2 Structural and molecular formulae and molecular weight

\[ C_6H_4Cl_6 \]  
Mol. wt: 284.8

1.3 Chemical and physical properties of the pure substance

From Weast (1976), unless otherwise specified

(a) Description: White needles (Hawley, 1977)

(b) Boiling-point: Sublimes at 322°C

(c) Melting-point: 230°C

(d) Spectroscopy data: \( \lambda_{\text{max}} \) 291, 301 nm \( (E_i^1 = 7.7, 7.9) \) in isooctane; infra-red, ultra-violet and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(e) Solubility: Insoluble in water, sparingly soluble in cold ethanol and soluble in ether, benzene, chloroform and boiling ethanol (Hawley, 1977)
(f) **Volatile:** Vapour pressure is $1.089 \times 10^{-5}$ mm at 20°C (Mumma & Lawless, 1975).

(g) **Stability:** Very stable; nonreactive; inflammable, with a flash-point at 242°C (Hawley, 1977)

(h) **Reactivity:** Not broken down by physical or chemical processes in the environment (Mumma & Lawless, 1975); photolysis in methanol or hexane ($\lambda_{max} > 260$ or 220 nm) is rapid, giving penta- and tetrachlorobenzenes (Plimmer & Klingebiel, 1976)

1.4 Technical products and impurities

Hexachlorobenzene is available in the US as a technical grade, containing 98% hexachlorobenzene, 1.8% pentachlorobenzene and 0.2% 1,2,4,5-tetrachlorobenzene. Some commercial hexachlorobenzene is derived from residual tar obtained as a byproduct in the production of tetrachloroethylene. Since this tar also contains hexachlorobutadiene, it is a potential impurity in commercial hexachlorobenzene derived from this source.

Hepta- and octachlorodibenzofurans and octachlorodibenzo-para-dioxin have been found in commercial hexachlorobenzene (Villanueva et al., 1974).

Formulations include wettable powders containing 40 or 80%, liquids containing 12.4-33% and a flowable product containing 35.1% of the chemical (US Environmental Protection Agency, 1972). Other commercial dust formulations for fungicidal use contain 10-40% hexachlorobenzene.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) **Production**

Hexachlorobenzene was prepared by Lorentz in 1893 by heating carbon with chlorine in the presence of boric oxide (Prager et al., 1922). It can be produced commercially by reacting benzene with excess chlorine in the presence of ferric chloride at 150-200°C. However, at least one US producer isolates hexachlorobenzene from the distillation residues obtained as a byproduct in the manufacture of tetrachloroethylene.

Commercial production of hexachlorobenzene in the US was first reported in 1933 (US Tariff Commission, 1934). Three US producers made
HEXACHLOROBENZENE

it up to the end of 1973 (with an estimated total production of 300 thousand kg in 1973); but there was only one US producer in 1974, and only one company reported commercial production of an undisclosed amount in 1975 (see preamble, p. 16) (US International Trade Commission, 1977a). That company is believed to have discontinued production in early 1978.

Hexachlorobenzene is a byproduct or waste material in the production of many chemicals. The quantities produced in 1972 have been estimated in relation to various end-products: tetrachloroethylene, 0.8-1.6 million kg; trichloroethylene, 104-203 thousand kg; carbon tetrachloride, 90-181 thousand kg; chlorine, 90-176 thousand kg; dimethyl tetrachloroterephthalate, 36-45 thousand kg; vinyl chloride, 0-12 thousand kg; atrazine, propazine and simazine, as a group, 2-4 thousand kg; pentachloronitrobenzene, 1-3 thousand kg; and mirex, 0.5-0.9 thousand kg.

In 1975, imports through the principal US customs districts of Grannox NM Seed Treatment, a formulation of hexachlorobenzene in combination with maneb, were 100 thousand kg (US International Trade Commission, 1977b).

One company in Spain produces an estimated 150 thousand kg hexachlorobenzene annually. In Japan, about 300 thousand kg were obtained in 1977 as a byproduct in the production of tetrachloroethylene; almost all was incinerated.

(b) Use

In 1972, the principal use of hexachlorobenzene in the US was as a fungicide to control wheat bunt and smut fungi on other grains. Other applications in 1972 were as an additive for pyrotechnic compositions for military uses, as a porosity controller in the manufacture of electrodes, as a chemical intermediate in dye manufacture and organic synthesis and use as a wood preservative.

Minor amounts have been used as an additive for polymers and as a raw material for synthetic rubber. It has been used as a plasticizer for polyvinyl chloride (Plimma & Klingebiel, 1976). In 1974, the largest US producer reported that all of its production for several years had been committed for use as a rubber peptizing agent in the manufacture of nitroso and styrene-type rubbers.

Hexachlorobenzene is registered by the US Environmental Protection Agency as a treatment for control of fungi which infect the seeds of onions, sorghum and wheat. It is also used in combination with captan or maneb for the treatment of seeds of barley, beans, corn, flax, oats, peanuts, rye and soya beans (US Environmental Protection Agency, 1972). It is reported to be a candidate for the issuance of a notice of a rebuttable presumption against renewal of registration (RPAR) (see
General Remarks on the Substances Considered, p. 31) because of possible carcinogenicity, teratogenicity and mutagenicity (Anon., 1978).

From 1 August 1974, the use on lettuce and on seed-potatoes of pentachloronitrobenzene containing more than 0.1% hexachlorobenzene was prohibited in The Netherlands. From 1 May 1975, the same restriction was applied to its use on flower bulbs and to all other uses (WHO, 1975).

In December 1974, the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues established a value of 0-0.0006 mg/kg bw as a conditional acceptable daily intake in man (WHO, 1975).

2.2 Occurrence

Hexachlorobenzene is not known to occur as a natural product. It is a contaminant of various pesticides, including dimethyl tetrachloroterephthalate (Dacthal) and pentachloronitrobenzene (Cabral et al., 1977).

The distribution of hexachlorobenzene as a byproduct of the petrochemical industry has been reviewed (Laska et al., 1976). Reviews have been published on the occurrence of hexachlorobenzene residues in the environment in Italy (Leoni & D'Arca, 1976) and in Czechoslovakia (Mahelova et al., 1977).

(a) Water

Hexachlorobenzene has been found in 4 river-water samples, 8 finished drinking-water samples, 1 sample from a sewage treatment plant and in the effluent water from 7 chemical plants in various US and European locations (Shackelford & Keith, 1976). It has also been detected in urban rainwater runoff in the US, at levels of 0-339 ng/l (Dappen, 1974); in the Rhine River (Greve, 1972); in 108 samples of surface waters in Italy, at average levels of 2.5 ng/l (Leoni & D'Arca, 1976); and in most river-water residues in an industrialized region of the US, at levels of less than 2 µg/l, but as high as 90 µg/l in one sample (Laska et al., 1976).

(b) Soil and sediments

Hexachlorobenzene has been detected in: (1) greenhouse soil in the US, 19 months after application, at levels of 0.19 mg/kg in the top 2 cm of soil and of 0.11 mg/kg in the 2-4 cm layer (Beall, 1976); (2) soil in Belgium, at average levels of 0.44 and 0.85 mg/kg (Dejonckheere et al., 1976); (3) untreated and treated greenhouse and field soil in the Federal Republic of Germany, at levels of 0.002-1.03 mg/kg (Haefner, 1975, 1977); (4) the soil in farming areas in Italy, at levels of 40 µg/kg (Leoni & D'Arca, 1976); and (5) levee and ditch soil in an
industrialized region of the US, at levels ranging from 0 to nearly 900 µg/kg (wet-weight basis) and 1677 µg/kg (dry-weight basis) (Laska et al., 1976).

(c) Food and drink

In the Total Diet Program of the US Food and Drug Administration, hexachlorobenzene was detected in food composites in 30 US cities, at levels of 0.006-0.041 mg/kg (Johnson & Manske, 1976). As part of the same study, the average daily intake of hexachlorobenzene was calculated to be 0.3978 µg/day in fiscal year 1973 and 0.0725 µg/day in fiscal year 1974 (US Food & Drug Administration, 1977).

The average intake of hexachlorobenzene from cooked food samples taken from an Italian Navy mess was reported to be 4.11 µg/man/day (Leoni et al., 1975). In Japan, hexachlorobenzene residues were detected at low levels in 16 foods, e.g., beef, 12 µg/kg; pike, 11 µg/kg; salmon, 9 µg/kg; carp, 8 µg/kg; and pork, 7 µg/kg (Morita et al., 1975a,b). Residues of pesticides, including hexachlorobenzene, have been detected in foods representing an average Canadian diet, at levels of 0.001-0.085 mg/kg (Smith et al., 1975).

The contamination of milk and dairy products by organochlorine pesticides, including hexachlorobenzene, in The Netherlands between 1967 and 1973 has been reviewed (Tuinstra, 1974). Hexachlorobenzene residues have been detected in: (1) milk and milk products in the Federal Republic of Germany, at levels of up to 0.5 mg/kg (Heeschen et al., 1976) and 0-2 mg/l (Knöppler, 1976) on a fat basis; (2) whole cow's milk in Italy, at an average level of 4.2 µg/l (Leoni & D'Arca, 1976); (3) some Italian grating cheeses (Corvi et al., 1976); (4) milk in Spain, at a mean level of 0.654 mg/l (Pozo Lora et al., 1977); (5) butter from 5 Spanish regions, with a mean level of 0.15 mg/kg on a fat basis (Polo Villar et al., 1977); and (6) dairy products in France (Richou-Bac et al., 1974).

Hexachlorobenzene has also been detected in tinned vegetables and fruits (Biston et al., 1975) and in meat at mean levels of 0.08-0.064 mg/kg (Knöppler, 1976).

(d) Animals

Hexachlorobenzene has been detected in: (1) starlings from 126 US sites, at levels of 0-9.11 mg/kg (White, 1976); (2) wild ducks, at levels of 0-0.24 mg/kg (White & Kaiser, 1976); (3) eggs of common terns, at a level of 7.67 mg/kg (dry weight) (Gilbertson & Reynolds, 1972); (4) captive and free pheasants, at levels of 1.2-3.8 and 2.3-2.8 µg/kg, respectively (Mikulik et al., 1977); (5) the livers of birds, at levels of up to 7.2 mg/kg (Leoni & D'Arca, 1976); (6) wild foxes, boars and does, at levels of 0.02-3.11 mg/kg (Koss & Manz, 1976); and (7) swine, at an average level of 0.616 mg/kg, with 67% of the samples containing residues of more than 0.5 mg/kg (Lohse, 1975).
It has also been detected in: (1) fish in Lake Superior, at concentrations of < 0.1 mg/kg (Veith et al., 1977); (2) aquatic animals in Australia, at levels of 1-2 μg/kg (Thomson & Davie, 1974); (3) 8 species of fish, at mean levels of < 1 μg/kg to 16 mg/kg (Johnson et al., 1974); and (4) mosquito fish, at levels of 71.8-379.8 μg/kg, and commercial fish, at a level of 88 μg/kg, from an industrialized region of the US (Laska et al., 1976).

(e) **Humans**

Hexachlorobenzene residues have been detected in human milk in: (1) Ghana, at a level of 0.086 mg/l (Polishuk et al., 1977); (2) Australia, at levels of 0.012-0.034 mg/l (Stacey & Thomas, 1975); (3) Norway (Bakken & Seip, 1977); (4) Austria, at a mean concentration of 1.24 mg/l (Pesendorfer, 1975); (5) France, at average levels of 0.98 mg/l (Luquet et al., 1975); and (6) Spain, at levels of up to 0.08 mg/l (Trigo Lorenzo & Fernandez Garcia, 1976).

It has also been detected in human adipose tissue in: (1) Japan, at levels of <0.003-0.77 μg/g (Curley et al., 1973) and at a level of 0.21 μg/g (Morita et al., 1975a,b); (2) New Zealand, at a mean level of 0.31 μg/g (Solly & Shanks, 1974); (3) Canada, at levels of 0.001-0.520 μg/g (Mes et al., 1977); and (4) Italy, at an average level of 491 ng/g (Leoni & D'Arca, 1976).

Hexachlorobenzene has been detected in the blood of the umbilical cord in newborn infants and of their mothers in Argentina, at levels of up to 19 ng/l (Astolfi et al., 1974), and in the blood of children 1-18 years old in the Federal Republic of Germany at a maximum of 22 ng/l in boys and 17 ng/l in girls (Richter & Schmid, 1976).

(f) **Occupational exposure**

Hexachlorobenzene has been detected in: workplace air during the production of pentachlorophenol (Mel'nikova et al., 1975); the blood of workers in a factory making chlorinated solvents, at levels of 14-233 μg/l (Burns & Miller, 1975); and the blood of vegetable spraymen, at levels of 0-310 μg/l (Burns et al., 1974).

(g) **Other**

Hexachlorobenzene has been detected in: animal feeds (Richou-Bac et al., 1975); various grain samples, at mean levels of 0.27 mg/kg or less (Arrifai & Acker, 1975); and laboratory plastic wash bottles, at levels of 0.16-2.7 μg/bottle (Rourke et al., 1977).
HEXACHLOROFLUOROBENZENE

2.3 Analysis

A review of methods of analysis for hexachlorobenzene is available (Li et al., 1976).

Determination and confirmation of low levels of hexachlorobenzene residues is hampered by the presence of other organochlorine pesticides and polychlorinated biphenyls. Methods for analysing residual hexachlorobenzene include separation and clean-up procedures, specific gas-chromatographic columns and formation of chemical derivatives. Methods used for the analysis of hexachlorobenzene in environmental samples are listed in Table 1.

Other analytical methods to isolate and identify hexachlorobenzene include: gel-permeation chromatography (Johnson et al., 1976), gas chromatography/electron capture detection on various columns (Di Muccio et al., 1972; Szokolay et al., 1975) and gas chromatography/mass spectrometry (Lunde & Baumann Ofstad, 1976).

Recovery of hexachlorobenzene from a magnesium silicate (Florisil) column, eluted with methylene chloride-hexane-acetonitrile, has been investigated for use with fatty and non-fatty foods (US Food & Drug Administration, 1975).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 30-50 male and 30-50 female 6-7 week-old Swiss mice were fed diets containing 0, 50, 100 or 200 mg/kg diet hexachlorobenzene (> 99.5% pure) until the animals were 120 weeks old, at which time all survivors were killed. Another group of 30 male and 30 female mice were fed 300 mg/kg diet hexachlorobenzene for 15 weeks. At 90 weeks of age, the percentage survival rates in males and females in the five different groups were: 50 and 48, 30 and 40, 27 and 30, 4 and 0, 13 and 57, respectively. The incidence of lymphomas and lung tumours was not increased in treated animals; no liver-cell tumours were found.

1The Working Group was aware of studies in progress to assess the carcinogenicity of hexachlorobenzene in mice and rats by oral administration (IARC, 1978).
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td>Acidify, extract (hexane), GC, form pentachlorophenol derivative, liquid/liquid partition, acidify, extract (dichloromethane), evaporate to dryness, acetylate, dilute (ethyl acetate)</td>
<td>GC/colorimetric detection</td>
<td>0.3 mg/l</td>
<td>Alam (1977)</td>
</tr>
<tr>
<td>Air</td>
<td>Trap on GC packing, desorb by heating</td>
<td>GC/FID</td>
<td>10 μg/m³</td>
<td>Russell (1975)</td>
</tr>
<tr>
<td></td>
<td>Trap on chromosorb 101, extract (hexane)</td>
<td>GC/ECD</td>
<td>28 μg/m³</td>
<td>Mann et al. (1974)</td>
</tr>
<tr>
<td>Soil</td>
<td>Extract (hexane-acetone), liquid/liquid partition</td>
<td>GC/ECD</td>
<td>7 μg/kg</td>
<td>Babkina et al. (1976)</td>
</tr>
<tr>
<td>Sediments and sewage sludge</td>
<td>Centrifuge, extract solid (acetone), liquid/liquid partition, transfer into trimethylpentane, treat to remove sulphur, isolate in trimethylpentane</td>
<td>GC/ECD</td>
<td>1-10 μg/kg</td>
<td>Jensen et al. (1977)</td>
</tr>
<tr>
<td>Food</td>
<td>Mix sample with Florisil, extract (acetonitrile), liquid/liquid partition, CC</td>
<td>GC/ECD</td>
<td></td>
<td>Bong (1977)</td>
</tr>
<tr>
<td>Fat and oil</td>
<td>Mix sample with Florisil, extract (acetonitrile), liquid/liquid partition, CC</td>
<td>GC/ECD</td>
<td></td>
<td>Holden (1973)</td>
</tr>
<tr>
<td>Fish</td>
<td>Grind with sodium sulphate, extract (hexane), CC</td>
<td>GC/ECD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------------------------------</td>
<td>------------</td>
<td>--------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Dairy products,</td>
<td>Melt and filter if necessary, GC</td>
<td>GC/ECD</td>
<td>2 µg/kg</td>
<td>Smyth (1972)</td>
</tr>
<tr>
<td>Meat, Fat</td>
<td></td>
<td>TLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggs</td>
<td>Grind with sodium sulphate, filter, CC</td>
<td>GC/ECD</td>
<td>2 µg/kg</td>
<td>Smyth (1972)</td>
</tr>
<tr>
<td>Milk</td>
<td>Extract (petroleum ether-ether), CC</td>
<td>GC/ECD</td>
<td>5 µg/l</td>
<td>Goursaud et al. (1976)</td>
</tr>
<tr>
<td>Adipose tissues</td>
<td>Dissolve (hexane), form bis(2-chloroethyl)</td>
<td>GC/ECD</td>
<td>5 µg/kg</td>
<td>Cist et al. (1975)</td>
</tr>
<tr>
<td></td>
<td>hexachlorobenzene derivative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faeces</td>
<td>Grind, homogenize (benzene), extract (benzene-methanol-water) in Soxhlet, CC</td>
<td>TLC</td>
<td></td>
<td>Yang et al. (1975)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Extract (hexane), CC</td>
<td>GC/MS</td>
<td></td>
<td>Rourke et al. (1977)</td>
</tr>
<tr>
<td>Plastic wash bottles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CC - column chromatography; GC - gas chromatography; FID - flame-ionization detection; ECD - electron capture detection; TLC - thin-layer chromatography; LC/UV - liquid chromatography/ultra-violet spectrometry; MS - mass spectrometry
in the controls or in the group receiving 50 mg/kg diet. In the groups receiving 100, 200 and 300 mg/kg diet, the incidences of liver-cell tumours in the survivors (males and females) at the time the first liver-cell tumour was observed were: 3/12 and 3/12, 7/29 and 14/26, 1/3 and 1/10. The effective intake of hexachlorobenzene that induced liver-cell tumours was 12-24 mg/kg bw/day (Cabral et al., 1978, 1979¹).

Hamster: A total of 159 female and 157 male Syrian golden hamsters, 6 weeks of age, were administered dietary concentrations of 0, 50, 100 and 200 mg/kg diet hexachlorobenzene (> 99.5% pure) for lifespan, equivalent to 0, 4, 8 and 16 mg/kg bw/day. The incidences of hepatomas, liver haemangioendotheliomas and thyroid adenomas were increased by exposure to hexachlorobenzene. In females and males given 0, 50, 100 and 200 mg/kg diet hexachlorobenzene, hepatomas occurred in 0/39 and 0/40, 14/30 and 14/30, 17/30 and 26/30 and 51/60 and 49/57 animals, respectively; the first hepatoma (with multiple nodules, largest diameter 7 mm) was found in one female hamster after 18 weeks of treatment. The incidences of liver haemangioendotheliomas in males and females receiving the highest dose were 20/57 and 7/60; 3 of these gave metastases; no liver haemangioendotheliomas were found in the controls. Alveolar thyroid adenomas were found in treated animals, and a significant increase (P < 0.05) was found in males treated with 200 mg/kg diet (8/57 versus 0/40 controls); these tumours also occurred in 2/30 females given 50 mg, in 1/30 males and 1/30 females given 100 mg and in 3/60 females given 200 mg (Cabral et al., 1977).

(b) Intraperitoneal administration

Mouse: Groups of 20 male A/St mice, 6-8 weeks old, were given thrice weekly i.p. injections of 8, 20 or 40 mg/kg bw hexachlorobenzene in tricaprylin for 8 weeks. All survivors were killed 24 weeks after the first injection. The average numbers of lung tumours per mouse were 0.68, 0.28 and 0.75 in the treated groups, which were not significantly different from that in controls injected with tricaprylin (Theiss et al., 1977) [The Working Group noted the limitations of a negative result obtained with this test system; see General Remarks on the Substances Considered, p. 34].

¹It was also reported in this article that an increased incidence of liver-cell tumours was observed in a small group of MRC rats fed 100 mg/kg diet hexachlorobenzene (5 mg/kg bw/day) for 75 weeks.
3.2 Other relevant biological data

(a) Experimental systems

The toxicity and metabolism of hexachlorobenzene have been reviewed (Cooper, 1976, 1978).

Toxic effects

The oral LD$_{50}$ of hexachlorobenzene in rats varies from 3500-10,000 mg/kg bw; death is due to neurotoxic effects (Booth & McDowell, 1975).

The LD$_{50}$ of technical hexachlorobenzene (93-95% pure) in female rats given repeated administrations in the diet over 4 months was about 500 mg/kg diet, which was lower than for males. Effects of such chronic feeding included hepatocellular hypertrophy and necrosis, spleen enlargement and porphyria (Kimbrough & Linder, 1974). Porphyrins accumulate in urine, liver, kidney and spleen, suggesting an effect on the activity of uroporphyrinogen decarboxylase (Doss et al., 1976; Goerz et al., 1978; Kuiper-Goodman et al., 1977). Mice given 167 mg/kg diet hexachlorobenzene for 6 weeks became immunosuppressed, as indicated by decreased serum globulin levels and a decreased response of spleen lymphocytes to sheep red blood cells (Loose et al., 1977). In rats fed hexachlorobenzene for 4 weeks, subsequent food deprivation appeared to enhance the toxic response, implying decreased mobilization of hexachlorobenzene residues into fat and resulting in a higher plasma, liver, brain and adrenal accumulation of hexachlorobenzene (Villeneuve et al., 1977).

Doses ranging from 0.05-50 mg/kg bw/day hexachlorobenzene were administered to pigs for 90 days. Porphyria and death occurred in animals given the highest dose level. Increased urinary excretion of coproporphyrin was observed in groups receiving 0.5 and 5 mg/kg bw/day after 8 weeks; in those receiving 5 mg/kg bw, induction of microsomal liver enzymes, accompanied by increased liver weight, was also observed (den Tonkelaar et al., 1978).

Low dietary doses of hexachlorobenzene induced various hepatic mixed-function oxidases in rats (Grant et al., 1974; Mehendale et al., 1975; Stonard, 1975).

Hexachlorobenzene enhanced the hepatocarcinogenicity of polychlorinated terphenyls (PCT) in ICR mice: 0/28 animals had hepatocellular carcinomas with 250 mg/kg diet PCT, while 8/26 had these tumours with the same dose of PCT plus 50 mg/kg diet hexachlorobenzene (Shirai et al., 1978).
Embryotoxicity and teratogenicity

Placental transfer of hexachlorobenzene has been reported in mice and rats (Andrews & Courtney, 1976; Villeneuve & Hierlihy, 1975). A minimal teratogenic effect of hexachlorobenzene observed in Wistar rats could not be reproduced in the same laboratory with doses up to 120 mg/kg bw administered during organogenesis (Khera, 1974). In other studies with 100 mg/kg bw hexachlorobenzene and with pentachloronitrobenzene (PCNB) contaminated by hexachlorobenzene, cleft palate and some kidney malformations were found in mice (Courtney et al., 1976).

In a 4-generation test, groups of 10 male and 20 female Sprague-Dawley rats were treated with 0, 10, 20, 40, 80, 160, 320 or 640 mg/kg diet hexachlorobenzene from weaning. Suckling pups in the F1 generation were particularly sensitive, and many died prior to weaning when the mothers were fed concentrations of 320 or 640 mg/kg diet. No gross abnormalities were found (Grant et al., 1977).

Hexachlorobenzene decreased survival of chicks of Japanese quail treated with 20 mg/kg diet for 90 days (Schwetz et al., 1974). These results confirmed those of another study in which administration of 80 mg/kg diet for 90 days reduced egg production and hatchability (Vos et al., 1971).

Absorption, distribution, excretion and metabolism

Hexachlorobenzene administered orally to rats was absorbed slowly from the gut, mainly via the lymphatic system, and was stored extensively in the fat after 48 hrs (Iatropoulos et al., 1975). The quantitative recovery of intraperitoneally and orally administered $^{14}$C-hexachlorobenzene in rats was dose-dependent, but more $^{14}$C was recovered from faeces than from the urine. The major urinary metabolites were pentachlorophenol, tetrachlorohydroquinone and pentachlorothio phenol. The other urinary metabolites were tetrachlorobenzene, pentachlorobenzene, 2,4,5- and 2,4,6-trichlorophenols and 2,3,4,6- and 2,3,5,6-tetrachlorophenols; 2,3,4-trichlorophenol and other tetrachlorophenols were present in traces. These metabolites were excreted as conjugates or in free form in the urine. Unchanged hexachlorobenzene was found in the faeces and in fat (Engst et al., 1976; Koss et al., 1976; Mehendale et al., 1975; Renner & Schuster, 1977).

When 110 µg/day $^{14}$C-hexachlorobenzene were given orally to Macaca mulatta monkeys for 11-15 months, 50% of the radioactivity found in the urine was in pentachlorophenol and 25% in pentachlorobenzene, the remainder being in unidentified metabolites and unchanged hexachlorobenzene. In the faeces, 99% of the radioactivity was in unchanged hexachlorobenzene. During the last 10 days of the experiment, males excreted 7.2% of the administered dose in the urine and 52% in the faeces; females excreted 4.6 and 42.2%, respectively (Rozman et al., 1977).
Hexachlorobenzene was found in the milk of cows administered hexachlorobenzene (Fries & Marrow, 1976), and in organs of 18-day-old rats whose mothers were fed a diet containing hexachlorobenzene (Mendoza et al., 1975).

Mutagenicity and other related short-term tests

Hexachlorobenzene did not significantly increase the frequency of reversions to histidine and methionine auxotrophy in Saccharomyces cerevisiae (strain 632/4) in the absence of a metabolic activation system (Guerzoni et al., 1976).

In a dominant lethal test, male rats that received 20, 40 or 60 mg/kg bw hexachlorobenzene orally for 10 days were mated sequentially with untreated females (1 male x 2 females; 14 mating periods, each of 5-days' duration). There were no significant differences between the test and control groups with regard to the incidence of pregnancies, corpora lutea, live implants or deciduomas, at any dose level or in any of the mating periods (Khera, 1974).

(b) Humans

The occurrence of hexachlorobenzene in human tissues is described in section 2.2 (e).

An epidemic of 4000 cases of porphyria cutanea tarda occurred in Turkey between 1955 and 1959 as a result of human consumption of grain that had been treated with hexachlorobenzene. The estimated daily intake was 50-200 mg/day hexachlorobenzene over a relatively long period before the disease became apparent (Mazzei & Mazzei, 1973; Peters, 1976; Peters et al., 1966, 1978). The majority of the patients were children, mostly boys, aged 4-14 years old (Cam & Nigogosyan, 1963). A mortality rate of 14% was reported within several years (Peters et al., 1966, 1978). Children under the age of 4 rarely developed porphyria, but in breast-fed infants a condition known as 'pink-sore' was reported, with a mortality rate greater than 95% (Cam, 1960; Peters, 1976). Samples of breast milk from the mothers of these infant were shown to contain hexachlorobenzene (Peters et al., 1966). Follow-up studies of 32 of the patients have shown that abnormal porphyrin metabolism and active symptomatology persist 20 years after hexachlorobenzene ingestion (Peters et al., 1978).

Hexachlorobenzene levels in plasma of people living near a hexachlorobenzene manufacturing plant but not exposed occupationally averaged 3.6 μg/l; there was no evidence of porphyria, but plasma coproporphyrin levels were abnormally high (Burns & Miller, 1975).
Farm workers exposed occupationally to hexachlorobenzene-contaminated Dacthal (dimethyl-tetrachloroterephthalate) had average blood hexachlorobenzene concentrations of 0.040 mg/l, but no evidence of porphyria was found in this group (Burns et al., 1974).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Hexachlorobenzene was tested by oral administration in one experiment in mice and in one in hamsters. In mice, it produced liver-cell tumours in animals of both sexes. In hamsters of both sexes, it produced hepatomas, liver haemangiotheliomas and thyroid adenomas. An experiment involving intraperitoneal administration in mice was considered to be inadequate.

Hexachlorobenzene is foetotoxic and produces some teratogenic effects. It was not mutagenic in yeast and did not induce dominant lethal effects in male rats.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The production and use of hexachlorobenzene as a fungicide over the past several decades and its occurrence as a byproduct in the manufacture of other chemicals indicate that widespread human exposure occurs in both the general and working environments. This is confirmed by many reports of its occurrence in the general environment and in human body fluids.

A group of people who were accidentally exposed over a period of time is known to exist; many of these showed toxic manifestations, some lasting for as long as 20 years. No data on carcinogenic effects have been reported.

4.3 Evaluation

There is sufficient evidence that hexachlorobenzene is carcinogenic in mice and hamsters. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard hexachlorobenzene as if it presented a carcinogenic risk to humans.
5. References


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Weast, R.C., ed. (1976) CRC Handbook of Chemistry and Physics, 57th ed., Cleveland, Ohio, Chemical Rubber Co., p. C-165


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HEXACHLOROBUTADIENE

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 87-68-3

Chem. Abstr. Name: 1,1,2,3,4,4-Hexachloro-1,3-butadiene

Synonyms: HCBD; hexachloro-1,3-butadiene; perchlorobutadiene

Trade names: C 46; Dolen-Pur

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
&\text{C}_4\text{Cl}_6 \\
&\text{Mol. wt: 260.7}
\end{align*}
\]

1.3 Chemical and physical properties of the substance

From Hawley (1977), unless otherwise specified

(a) Description: Clear, colourless liquid

(b) Boiling range: 210 to 220°C

(c) Freezing range: -19 to -22°C

(d) Density: \(d_{15.5} = 1.675\)

(e) Refractive index: \(n_D^{20} = 1.552\)

(f) Spectroscopy data: \(\lambda_{\text{max}} 249\ \text{nm} \ (\varepsilon = 168); 220\ \text{nm} \ (\varepsilon = 704)\); infra-red, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(g) Solubility: Insoluble in water; soluble in ethanol and diethyl ether
1.4 Technical products and impurities

No data were available to the Working Group.

2. Production, Use, Occurrence and Analysis

A review on hexachlorobutadiene has been published (US Environmental Protection Agency, 1975a).

2.1 Production and use

(a) Production

Hexachlorobutadiene was first prepared in 1877 by the chlorination of hexyl iodide (Prager et al., 1918). The production of commercial quantities of hexachlorobutadiene in the US has never been reported (but see General Remarks on the Substances Considered, p. 16); however, until about 1974, it was recovered as a by-product in the production of tetrachloroethylene (US Environmental Protection Agency, 1975a).

In 1972, 3.3-6.6 million kg hexachlorobutadiene were present in US industrial wastes and as by-products of the following chemical products (percent of total hexachlorobutadiene produced): tetrachloroethylene (60), trichloroethylene (21), carbon tetrachloride (19) and chlorine (< 1) (US Environmental Protection Agency, 1975a).

Since 1974, all hexachlorobutadiene used commercially in the US has been imported from the Federal Republic of Germany; 91-227 thousand kg hexachlorobutadiene have been imported annually since then (US Environmental Protection Agency, 1975a). It is believed that all hexachlorobutadiene now produced as a by-product in the US is disposed of, mostly by incineration, although landfill has been used in the past and may still be used at some plants.

No data on its production in Europe were available; and no evidence has been found that hexachlorobutadiene has ever been produced or imported in Japan.

(b) Use

In 1975, hexachlorobutadiene was used in the US for recovery of chlorine-containing gas in chlorine plants, as a fluid for gyroscopes, as a chemical intermediate to produce lubricants, and as an intermediate in the manufacture of rubber compounds. No information was available on the quantities used.
HEXACHLOROBUTADIENE

The largest use of hexachlorobutadiene in the US in 1975 was for recovery of 'snift' (chlorine-containing) gas in chlorine plants. This gas occurs at the liquefaction unit and is cleaned by passing it through hexachlorobutadiene or carbon tetrachloride. Many US chlorine producers were reported to have changed to hexachlorobutadiene from carbon tetrachloride in recent years (US Environmental Protection Agency, 1975a).

It is used as a solvent for elastomers, as a heat-transfer liquid, in transformers and as hydraulic fluid (Hawley, 1977); it has been used by at least one US manufacture in the production of high-temperature fluorinated lubricants.

The USSR is believed to be one of the major users of hexachlorobutadiene; 600-800 thousand kg are used annually, mainly as a fumigant against Phyloxera on grapes (US Environmental Protection Agency, 1975a). It is also used as a fumigant in vineyards in France, Italy, Greece, Spain and Argentina.

2.2 Occurrence

Hexachlorobutadiene is not known to occur as a natural product.

(a) Air

The air over cultivated fields within a radius of ≥ 100 m of vineyards in which hexachlorobutadiene had been applied to the soil was found to have been contaminated with hexachlorobutadiene (Gul'ko et al., 1972).

Hexachlorobutadiene was found in air samples collected upwind and downwind from a tetrachloroethylene manufacturing plant and from the vicinity of a landfill area used by the plant for disposal of waste chemicals (Mann et al., 1974). In another study of 9 chemical manufacturing factories, the highest levels of hexachlorobutadiene were present in air samples associated with production of tetrachloroethylene and trichloroethylene (highest level reported, 463 μg/m³); low levels were encountered at plants associated with production of chlorine and triazine herbicide; and none was detected in samples from the penta-chloronitrobenzene production plant (Li et al., 1976).

(b) Water

The highest concentration of hexachlorobutadiene found in US drinking-water up to 1975 was 0.07 μg/l (US Environmental Protection Agency, 1975b). It has been detected in the effluent water from a US chemical manufacturing plant (Shackelford & Keith, 1976); in the effluent from a European chemical manufacturing plant, at a concentration of 6.4 μg/l; in the Rhine River, at 5 μg/l; and in European drinking-water at 0.27 μg/l (Eurocop-Cost, 1976).
Hexachlorobutadiene was found at a level of 0.13 μg/l in the Rhine and at levels of 0.13-0.20 μg/l and 0.05-0.07 μg/l in lakes fed by the Rhine (Goldbach et al., 1976). In a UK study, an average concentration of 0.004 μg/l and a maximum concentration of 0.03 μg/l hexachlorobutadiene were reported in sea-water (Pearson & McConnell, 1975). Mississippi River water contained 0.9-1.9 μg/l hexachlorobutadiene; water at sites removed from a transect of the levees contained < 0.7-1.5 μg/l (Laska et al., 1976). In another US study, highest levels of hexachlorobutadiene were detected in water at the sites of factories associated with the production of tetrachloroethylene and trichloroethylene (highest reported concentration, 244 μg/l) (Li et al., 1976).

(c) Soil and sediments

Concentrations of hexachlorobutadiene in sediments from Liverpool bay ranged from < 0.02 – > 8 mg/kg (Pearson & McConnell, 1975). Levee soil in Louisiana contained levels ranging from undetectable to 800 μg/kg, ditch mud levels ranged from undetectable to 500 μg/kg and soil samples collected from sites removed from a transect of the levees contained levels ranging from < 0.7-321.5 μg/kg (433.0 μg/kg corrected to dry weight) (Laska et al., 1976). In a US study, highest levels were detected in soil around factories associated with the production of tetrachloroethylene and trichloroethylene (highest reported concentration, 980 μg/g) (Li et al., 1976).

(d) Food and drink

Hexachlorobutadiene residues have been detected in must wine (< 0.01-0.45 μg/l) and grape juice in the USSR; however, no residues were detected in fermented wine or in pasteurized grape juices (Gorenshtein, 1973).

Hexachlorobutadiene residues were found in the following foods and feeds (μg/kg): evaporated milk (4), egg yolk (42), vegetable-oil margarine (33), chicken grain feed (39) and chicken laying rations (20) (Kotzias et al., 1975). In a study of foods collected within a 25-mile (40-km) radius of factories producing tetrachloroethylene or trichloroethylene, no hexachlorobutadiene residues were found in any of 15 egg samples or 20 samples of a variety of vegetables; of 20 milk samples collected, only one contained hexachlorobutadiene residues (1.32 mg/kg on a fat basis); in a later follow-up sample, no residues were detected (Yip, 1976).

Hexachlorobutadiene residues were reported in the following foods in the UK (μg/kg): fresh milk (0.08), butter (2), vegetable cooking oil (0.2), light ale (0.2), tomatoes (0.8) and black grapes (3.7) (McConnell et al., 1975).
(e) Marine organisms

Eight of 16 fish samples were found to contain hexachlorobutadiene residues ranging from traces (< 0.005 mg/kg) to 4.65 mg/kg (Yurawecz et al., 1976). Residues were also found in 10 samples from 28 fish collected from within 25 miles (40 km) of tetrachloroethylene or trichloroethylene production plant sites, at levels ranging from 0.01-1.2 mg/kg (Yip, 1976). The mean concentration of hexachlorobutadiene residues detected in mosquito fish in Louisiana ranged from 112.8-827.3 μg/kg and that in crayfish from 10.6-70.1 μg/kg (Laska et al., 1976).

Thirty fish from lakes fed by the Rhine River contained 0.11-2.04 mg/kg hexachlorobutadiene on a wet weight basis, and 3 species of invertebrates and detritus contained 0.03-2.41 mg/kg; 20 sea fish contained 0.008-0.136 mg/kg (Goldbach et al., 1976).

In a UK study, 14 species of invertebrates were found to contain hexachlorobutadiene residues at levels ranging from 0-7 μg/kg by weight of wet tissue; 5 species of marine algae, 0-8.9 μg/kg; various organs of 15 species of fish, 0-2.6 μg/kg; eggs or organs of 8 species of sea and freshwater birds, 0-9.9 μg/kg; and organs of 2 species of mammals, 0-3.6 μg/kg (Pearson & McConnell, 1975).

(f) Humans

Hexachlorobutadiene has been detected in post-mortem human tissue samples, at levels of 0.8-13.7 μg/kg (wet tissue) (McConnell et al., 1975).

2.3 Analysis

Methods used for the analysis of hexachlorobutadiene in environmental samples are listed in Table 1.

Other methods using spectrophotometry (Simonov et al., 1971) and gas chromatography/electron capture detection (Yip, 1976) have been proposed.
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>Trap on Chromosorb 101, extract (hexane)</td>
<td>GC/ECD</td>
<td></td>
<td>Mann et al. (1974)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap on Tenax GC, extract (hexane) in ultra-sound</td>
<td>GC/ECD</td>
<td></td>
<td>Li et al. (1976)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap on silica gel, extract (ether), prepare derivative with pyridine</td>
<td>Colorimetry</td>
<td>5 mg/m³</td>
<td>Lebedeva &amp; Klisenko (1970)</td>
</tr>
<tr>
<td></td>
<td>Trap on silica gel or in solvent (cyclohexane-hexane-petroleum ether)</td>
<td>UV</td>
<td>0.2 mg/m³</td>
<td>Gul'ko et al. (1972)</td>
</tr>
<tr>
<td>Water</td>
<td>Grab water</td>
<td>Extract (hexane)</td>
<td>GC/ECD</td>
<td>Li et al. (1976)</td>
</tr>
<tr>
<td></td>
<td>Extract (benzene)</td>
<td>GC/ECD</td>
<td></td>
<td>Lase ter et al. (1976)</td>
</tr>
<tr>
<td></td>
<td>Extract (ether), prepare derivative with pyridine</td>
<td>Colorimetry</td>
<td>0.2 mg/l</td>
<td>Lebedeva &amp; Klisenko (1970)</td>
</tr>
<tr>
<td>Food &amp; drink</td>
<td>Fish</td>
<td>Homogenize with sodium sulphate and acetone, filter, add sodium chloride to filtrate, extract (hexane), evaporate, take up in hexane, CC, transfer to benzene</td>
<td>GC/ECD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vegetable</td>
<td>Extract (petroleum ether), CC</td>
<td>GC/ECD</td>
<td>5 µg/kg</td>
</tr>
</tbody>
</table>
TABLE 1. METHODS OF ANALYSIS FOR HEXACHLOROBUTADIENE (continued)

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish, eggs</td>
<td>Grind, extract (petroleum ether), CC</td>
<td>GC/ECD</td>
<td>5 µg/kg</td>
<td>Yurawecz et al. (1976)</td>
</tr>
<tr>
<td>Milk</td>
<td>Extract fat solution (petroleum ether saturated with acetonitrile)</td>
<td>GC/ECD</td>
<td>40 µg/kg</td>
<td>Yurawecz et al. (1976)</td>
</tr>
<tr>
<td>Wine</td>
<td>Extract (hexane), purify with potassium dichromate</td>
<td>UV</td>
<td>5 µg/l</td>
<td>Vaintraub (1970)</td>
</tr>
<tr>
<td>Wine</td>
<td>Extract (petroleum ether), purify with potassium dichromate</td>
<td>TLC (revelation: silver nitrate)</td>
<td>5 µg/l</td>
<td>Vaintraub (1970)</td>
</tr>
<tr>
<td>Biological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Extract (heptane), prepare derivative with pyridine</td>
<td>Colorimetry</td>
<td>5 mg/l</td>
<td>Gauntley et al. (1975)</td>
</tr>
<tr>
<td>Urine</td>
<td>Extract (heptane), prepare derivative with pyridine</td>
<td>UV</td>
<td>0.05 mg/l</td>
<td>Gauntley et al. (1975)</td>
</tr>
<tr>
<td>Soil</td>
<td>Extract (hexane) in Soxhlet</td>
<td>GC/ECD</td>
<td>5 µg/kg</td>
<td>Laseter et al. (1976)</td>
</tr>
<tr>
<td></td>
<td>Extract (acetone), add benzene</td>
<td>GC/ECD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GC/ECD - gas chromatography/electron capture detection; UV - ultra-violet spectrometry; CC - column chromatography; TLC - thin-layer chromatography
3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Rat: Groups of 39 or 40 male and 40 female SPF Sprague-Dawley rats, 8-weeks old at the start of treatment, were fed diets containing hexachlorobutadiene (99% pure) at concentrations providing intakes of 0.2, 2.0 or 20 mg/kg bw/day. Ninety males and 90 females served as untreated controls. All male survivors were killed after 22 months, and all females after 24 months of test diet; median survival times were 17-19 months for males and 20-23 months for females. In males, tumour incidences were 39/90 controls, 24/40 low-dose, 13/40 mid-dose and 15/39 high-dose. In females, the tumour incidences were 82/90 controls, 35/40 low-dose, 37/40 mid-dose and 39/40 high-dose. A statistically significant increase (P ~ 0.05) of kidney tumours was observed in male and female rats fed the highest dose level (9/39 males versus 0/40 and 0/40 at lower doses and 1/90 in controls; 6/40 females versus 0/40, 0/40, 0/90). Six of the 39 high-dose males had adenocarcinomas (some bilateral); 2 developed adenomas only (another had an adenoma as well as adenocarcinomas); and 1 male had an undifferentiated carcinoma in one kidney and an adenocarcinoma with metastases to the lung in the other kidney. One control male had an adenoma; 3 females had kidney adenomas (uni- or bilateral), 1 developed an adenocarcinoma, 1 had an adenocarcinoma with metastases to the lung and 1 developed an undifferentiated, unilateral carcinoma (Kociba et al., 1977).

(b) Intraperitoneal administration

Mouse: Two groups of male A/St mice, 6-8 weeks of age, were given thrice weekly i.p. injections of 4 or 8 mg/kg bw hexachlorobutadiene in tricaprylin for a total of 12-13 injections (total doses, 52 and 96 mg/kg bw). All surviving mice (19 and 14 animals) were killed 24 weeks after the first injection and examined for lung tumours. The incidence of lung tumours per mouse was not increased compared with that in tricaprylin-injected controls (Theiss et al., 1977) [The Working Group noted the limitations of a negative result obtained with this test system; see General Remarks on Substances Considered, p. 34].

The Working Group was aware of studies in progress to assess the carcinogenicity of hexachlorobutadiene in mice by skin and oral administration (IARC, 1978).
3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The single oral LD₅₀ of hexachlorobutadiene in male and female mice and rats are 80, 65, 250 and 270 mg/kg bw, respectively; the i.p. LD₅₀ are 105, 76, 216 and 175 mg/kg bw, respectively (Gradiski et al., 1975). The oral LD₅₀ in neonatal rats is 1/4 that in adult animals. Female rats are more sensitive to hexachlorobutadiene than males (Schwetz et al., 1977).

Hexachlorobutadiene is toxic to experimental animals when inhaled, ingested, injected intraperitoneally or absorbed through the skin (Gage, 1970; Gradiski et al., 1975; Poteryaeva, 1972, 1973). It has a moderate acute toxicity but is more toxic after chronic exposure, indicating a cumulative effect. It affects the central nervous system and causes hepatic disorders (Gradiski et al., 1975). A major target organ appears to be the kidney (Gage, 1970; Gradiski et al., 1975; Kociba et al., 1977; Schwetz et al., 1977). Feeding of 30-100 mg/kg bw/day to rats for 30 days caused renal tubular degeneration, necrosis and regeneration (Schwetz et al., 1977). Renal necrosis also occurred after a single dose of 10 mg/kg bw (Shroit et al., 1972).

Male and female Sprague-Dawley rats were fed a diet providing an intake of 0, 0.2, 2 or 20 mg hexachlorobutadiene/kg bw/day for up to 2 years. Doses of 2 and 20 mg/kg bw/day caused renal tubular hyperplasia. Urinary excretion of coproporphyrin was increased in males and females receiving the highest dose and in females receiving 2 mg/kg bw/day (Kociba et al., 1977).

Embryotoxicity and teratogenicity

All newborn rats from mothers that received a single s.c. dose of 20 mg/kg bw hexachlorobutadiene before mating died during the next 3 months, compared with only 21.3% in a control group (Poteryaeva, 1966). Schwetz et al. (1977) observed no significantly deleterious effects on fertility or health of pups when adult male and female rats were maintained on a diet that contained up to 20 mg/kg bw/day hexachlorobutadiene for 90 days prior to mating.

Adult male and female Japanese quails were fed diets containing 0.3, 3, 10 or 30 mg/kg diet hexachlorobutadiene for 90 days. These dose levels had no effect on body weight, demeanour, food consumption, egg production, percent fertility and hatchability of eggs, survival of hatched chicks or eggshell thickness (Schwetz et al., 1974).
Absorption, distribution, excretion and metabolism

In rats, hexachlorobutadiene was found in lung, blood, liver, brain, kidney, spleen and mesentery after a single injection (unspecified) and was excreted with the urine for 7 days (Gul'ko & Dranovskaya, 1972). In the kidney, the highest concentration was observed in the proximal section of the nephron (Shroit et al., 1972).

Mutagenicity and other related short-term tests

Hexachlorobutadiene was reported to be mutagenic in spot tests with Salmonella typhimurium TA100 (Tardiff et al., 1976), but no data were given.

(b) Humans

A group of 205 vineyard workers who were exposed seasonally to hexachlorobutadiene and polychlorobutane-80 (0.8-30 mg/m³ and 0.12-6.7 mg/m³, respectively, in the air over the fumigated zones) showed multiple toxic effects contributing to the development of hypotension, cardiac disease, chronic bronchitis, disturbances of nervous function and chronic hepatitis (Krasniuk et al., 1969).

For the occurrence of hexachlorobutadiene in human tissues see section 2.2 (f).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Hexachlorobutadiene was tested in one experiment in rats by oral administration: it produced benign and malignant tumours in the kidneys of animals of both sexes. It was tested inadequately in one experiment in mice by intraperitoneal injection.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The occurrence of hexachlorobutadiene as a by-product in the production of various chlorinated hydrocarbons for over 50 years and its use in some areas as a pesticide indicate that widespread human exposure in both the occupational and general environment occurs. This is confirmed by reports of its occurrence in the environment.
4.3 Evaluation

There is limited evidence that hexachlorobutadiene is carcinogenic in rats.
5. References


Gorenshtein, R.S. (1973) Hexachlorobutadiene residues in wine and grape juice (Russ.). Zashch. Rast. (Moscow), 12, 27 [Chem. Abstr., 81, 48484k]


HEXACHLOROBUTADIENE


Poteryaeva, G.E. (1972) Data for substantiating the maximum permissible concentration of hexachlorobutadiene in the air of industrial premises (Russ.). Gig. Sanit., 37, 32-36

Poteryaeva, G.E. (1973) Toxicity of hexachlorobutadiene during entry into the organism through the gastrointestinal tract (Russ.). Gig. Tr., 9, 98-100


US Environmental Protection Agency (1975b) Preliminary Assessment of Suspected Carcinogens in Drinking Water, Washington DC, p. II-4


These substances were considered by a previous Working Group, in October 1973 (IARC, 1974). Since that time new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.

Two reviews on lindane are available (Mercier, 1975; Ulmann, 1972).

1. Chemical and Physical Data

1.1 Synonyms and trade names

Mixture of HCH isomers

Chem. Abstr. Services Reg. No.: 608-73-1
Chem. Abstr. Name: 1,2,3,4,5,6-Hexachlorocyclohexane
Synonyms: BHC; HCCH; hexachlor; hexachloran
Trade names: 666; Benzahex; Benzex; Dol; Dolmix; FBHC; Hexafor; Hexyclan; Kotol; Soprocide

α-isomer

Chem. Abstr. Services Reg. No.: 319-84-6
Chem. Abstr. Name: 1α,2α,3β,4α,5β,6β-Hexachlorocyclohexane
Synonyms: α-Benzene hexachloride; α-BHC; α-HCH; α-hexachlorlan; α-hexachlorane; α-hexachlorcyclohexane; α-1,2,3,4,5,6-hexachlorcyclohexane; α-hexachlorocyclohexane; α-1,2,3,4,5,6-hexachlorocyclohexane; α-lindane

β-isomer

Chem. Abstr. Services Reg. No.: 319-85-7
Chem. Abstr. Name: 1α,2β,3α,4β,5α,6β-Hexachlorocyclohexane
Synonyms: β-Benzene hexachloride; β-BHC; β-HCH; β-hexachlorobenzene; β-hexachlorocyclohexane; β-1,2,3,4,5,6-hexachlorocyclohexane; β-lindane
γ-isomer (lindane)
Chem. Abstr. Name: \(1\alpha, 2\alpha, 3\beta, 4\alpha, 5\alpha, 6\beta\)-Hexachlorocyclohexane
Synonyms: γ-Benzene hexachloride; BHC; γ-BHC; HCH; γ-HCH; γ-hexachlorobenzene; γ-1,2,3,4,5,6-hexachlorocyclohexane; γ-lindane
Trade names: 666; Aalindan; Aficide; Agrocide; Agrocide III; Agrocid WP; Ameisenmittel Merck; Ameisentod; Aparasin; Aphtiria; Aplidal; Arbitex; BBH; Ben-Hex; Bentox 10; Bexol; Celanex; Chloresene; Codechine; DBH; Detmol-Extrakt; Devoran; Dol Granule; Drill tox-Spezial Aglukon; ENT 7796; Entomoxan; Forlin; Gamacid; Gamaphex; Gammalin; Gammalin 20; Gammaterr; Gammexane; Gexane; Heclotox; Hexa; Hexachloran; γ-Hexachloran; Hexachlorane; γ-Hexachlorane; Hexatox; Hexaverm; Hexicide; Hexyclan; HGI; Hortex; Isotox; Jacutin; Kokotine; Kwell; Lendine; Lentox; Lidenal; Lindafor; Lindagam; Lindatox; Lindosep; Lintox; Lorexane; Milbol 49; Mszycol; Neo-Scabicidol; Nexen FB; Nexit; Nexit-Stark; Nexol-E; Nicocloran; Novigam; Onmitox; Ovadziak; Owadziak; Pedraczak; Pflanzol; Quellada; Sang-gamma; Silvanol; Spritz-Rapidin; Spruehpflanzol; Streunex; TAP 85; Tri-6; Viton

δ-isomer
Chem. Abstr. Services Reg. No.: 319-86-8
Chem. Abstr. Name: \(1\alpha, 2\alpha, 3\alpha, 4\beta, 5\alpha, 6\beta\)-Hexachlorocyclohexane
Synonyms: δ-Benzene hexachloride; δ-BHC; δ-HCH; δ-hexachlorocyclohexane; δ-1,2,3,4,5,6-hexachlorocyclohexane; δ-(aeaeae)-1,2,3,4,5,6-hexachlorocyclohexane; δ-lindane

ε-isomer
Chem. Abstr. Services Reg. No.: 6108-10-7
Chem. Abstr. Name: \(1\alpha, 2\alpha, 3\alpha, 4\beta, 5\beta, 6\beta\)-hexachlorocyclohexane
Synonyms: ε-Benzene hexachloride; ε-BHC; ε-HCH; ε-hexachlorocyclohexane; ε-1,2,3,4,5,6-hexachlorocyclohexane; ε-lindane
HEXACHLOROCYCLOHEXANE

ξ-isomer
Chem. Abstr. Services Reg. No.: 6108-11-8
Chem. Abstr. Name: 1α,2α,3α,4α,5α,6α-Hexachlorocyclohexane
Synonyms: ξ-Hexachlorocyclohexane; ξ-lindane

η-isomer
Chem. Abstr. Services Reg. No.: 6108-12-9
Chem. Abstr. Name: 1α,2α,3α,4α,5β,6β-Hexachlorocyclohexane
Synonyms: η-Hexachlorocyclohexane; η-lindane

θ-isomer
Chem. Abstr. Services Reg. No.: 6108-13-0
Chem. Abstr. Name: 1α,2α,3α,4α,5α,6β-Hexachlorocyclohexane
Synonyms: θ-Hexachlorocyclohexane; θ-lindane

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{C}_6\text{H}_6\text{Cl}_6 & \quad \text{Mol. wt: 290.9}
\end{align*}
\]

Isomers differ in the spatial positions of the chlorine atoms on the boat and chair forms.

1.3 Chemical and physical properties of the mixture and of the pure substances

Physical properties, except solubility, of the HCH isomers are given in Table 1.

(a) Solubility: The solubility of various HCH isomers in several organic solvents has been reported (Demozay & Marechal, 1972a).

(b) Stability: Fortified HCH is stable to light, air and heat (Hooker Chemical Corporation, 1969) (see section 1.4 for a definition of fortified HCH). Lindane is stable to light under atmospheric conditions and is heat stable to 165.5°C (Hooker Chemical Corporation, 1973).
<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>MIXTURE (FORTIFIED)</th>
<th>α-ISOMER</th>
<th>δ-ISOMER</th>
<th>γ-ISOMER (lindane)</th>
<th>δ-ISOMER</th>
<th>ε-ISOMER</th>
<th>ζ-ISOMER</th>
<th>η-ISOMER</th>
<th>θ-ISOMER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Brownish-to-white crystals</td>
<td>Monoclinic prisms</td>
<td>Cubic crystals</td>
<td>White, monoclinic crystals</td>
<td>Crystals or fine platelets</td>
<td>Monoclinic needles or hexagonal, monoclinic crystals</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Boiling-point (℃)</td>
<td>-</td>
<td>288</td>
<td>60 (0.58 mm)</td>
<td>323.4</td>
<td>60 (0.34 mm)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melting-point (℃)</td>
<td>-</td>
<td>157.5-158</td>
<td>309.8-310.7</td>
<td>112.5-113</td>
<td>138.0-138.4</td>
<td>219.3</td>
<td>68-88</td>
<td>89.8-90.6</td>
<td>124-125</td>
</tr>
<tr>
<td>Density</td>
<td>-</td>
<td>1.8720</td>
<td>1.8919</td>
<td>1.85</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Refractive index</td>
<td>-</td>
<td>1.60-1.626</td>
<td>1.630</td>
<td>1.60-1.635</td>
<td>1.576-1.674</td>
<td>1.00-1.635</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spectra b</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vapour pressure at 20℃ (mm Hg)</td>
<td>-</td>
<td>0.02</td>
<td>0.005</td>
<td>0.03</td>
<td>0.02</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a From Demozay & Marechal, 1972a; Grasselli & Ritchey, 1975; Hooker Chemical Corporation, 1969
b Spectral data tabulated by Grasselli & Ritchey, 1975 (ir - infra-red; nmr - nuclear magnetic resonance)
HEXACHLOROCYCLOHEXANE

(c) Reactivity: Fortified HCH and lindane do not react with strong acids; they decompose in the presence of alkali at ambient temperatures, forming trichlorobenzenes (Hooker Chemical Corporation, 1969a, 1973). Lindane decomposes in the presence of certain powdered metals such as iron, aluminium and zinc (Demozay & Marechal, 1972a).

1.4 Technical products and impurities

Two forms of hexachlorocyclohexane are available commercially in the US. One, a mixture of isomers, is called HCH; the other, which consists essentially of pure γ-isomer, is called lindane.

HCH

As produced initially by photochlorination of benzene, HCH contains only 14-77% of the γ-isomer. Technical grade HCH available commercially in the US is 'fortified' HCH (FHCH) containing a varying mixture of at least 5 isomers, with a minimum of 40% γ-isomer. Typical isomer distribution is as follows (% by wt): γ, 40-45; δ, 20-22; α, 18-22; β, 4; ε and inerts, 1; and heptachlorocyclohexane, 10 (Hooker Chemical Corporation, 1969).

HCH is available in the US as dusts, wettable powders, oil solutions and emulsifiable concentrates (Berg, 1978).

HCH available in Japan had a γ-isomer content of 12-15%.

Lindane

Commercial lindane available in the US contains a minimum of 99.9% (by weight) of the γ-isomer. The remaining 0.1% consists of other unspecified isomers of HCH (Hooker Chemical Corporation, 1973). It is available in the US as emulsifiable concentrates, wettable powders, oil-base sprays, dusts, aerosol sprays, granules and as a smoke generator (Berg, 1978).

Lindane is available generally in Europe, with a purity of 99-99.5%. Lindane available in Japan had a purity over 99% and a melting-point of 112-113°C.
2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

HCH

HCH was first prepared by Faraday in 1825 by the addition of chlorine to benzene in sunlight (Hardie, 1964). It is produced commercially in the US by the photochlorination of benzene, followed by fortification of the γ-isomer content by extraction (e.g., with methanol) and concentration of this isomer.

Commercial production of HCH in the US was first reported in 1945 (US Tariff Commission, 1946). US production reached a maximum in 1951 when 16 companies produced 53 million kg containing 7 million kg of the γ-isomer (US Tariff Commission, 1952). In 1963, the last year for which production data were reported, the number of US producers had dropped to 5 and total production of HCH amounted to 3.1 million kg, containing 0.8 million kg of the γ-isomer (US Tariff Commission, 1964). In 1976, only one US company reported production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977a).

The following western European countries were reported to be producing HCH (technical grades) in 1973 (number of producing companies is given in parentheses): Federal Republic of Germany (1), France (1) and Italy (2) (Economie Documentation Office, 1973). One company in the UK may also be producing it. France, the Federal Republic of Germany and Spain produce 30, 16 and 8.5 million kg/year, respectively. HCH (technical grades) is also believed to be produced in the German Democratic Republic and to a lesser extent in Poland, Yugoslavia and Roumania. Production of 18 million kg/year has been reported for the USSR.

Imports of this material by European countries in 1975 were as follows (thousands of kg): Belgium and Luxembourg (42); Federal Republic of Germany (580); Italy (39); The Netherlands (22); and the UK (42). Exports in 1975 were: Belgium and Luxembourg (30); Federal Republic of Germany (2); Italy (304); The Netherlands (42) and the UK (5) (EUROSTAT, 1975).

HCH was first produced commercially in Japan in 1949; however, it has not been produced there since 1971. In 1974, exports amounted to an estimated 922 thousand kg (from inventory disposal), and none was imported.

Lindane

A review on lindane has been published (Blaquiere, 1972).
In 1944, the insecticidal properties of HCH were found to be due to the $\gamma$-isomer (lindane) (Hardie, 1964). Lindane is extracted from HCH by the use of selected solvents, the most common of which is methanol. The $\gamma$-isomer so obtained is treated with nitric acid to remove odour (Demozay & Marechal, 1972b).

Commercial production of lindane in the US was first reported in 1950 (US Tariff Commission, 1951). The quantity produced in the US reached a maximum in the early 1950's and has declined since due to increased use of organophosphate insecticides. One US company, the only one to have reported lindane production since 1956, is estimated to have produced 227 thousand kg in 1972 (US Environmental Protection Agency, 1976a). US imports in 1976 through the principal US customs districts were 10,851 kg (US International Trade Commission, 1977b).

In Europe, 3.5, 1.7 and 1 million kg/year lindane are produced in France, the Federal Republic of Germany and Spain, respectively. It is produced in the German Democratic Republic and to a lesser extent in Poland, Yugoslavia and Roumania. In the USSR, 2 million kg lindane are produced annually.

Lindane was first produced commercially in Japan in 1949; however, it has not been produced there since 1971, although one company produces minor quantities for industrial use. In 1974, exports amounted to an estimated 153 thousand kg (from inventory disposal); none was imported.

(b) Use

HCH

The only known use of HCH is as an insecticide. It is registered for use in the US on a wide variety of fruits, vegetables, field crops, uncultivated land for general outdoor use and on breeding stock (US Environmental Protection Agency, 1970).

An estimated 450 thousand kg were used in the US in 1974, as follows: forests, 60%; livestock and poultry, 20%; and commercial, household and industrial establishments, 20%.

Tolerances in the US for residues of HCH in or on raw agricultural commodities are established at 1 mg/kg for a variety of 32 fruits and vegetables and at 0.01 mg/kg in or on pecan nuts (US Environmental Protection Agency, 1976b).

A notice of rebuttable presumption against registration and continued registration (RPAR) (see General Remarks on the Substances Considered, p. 31) of pesticide products containing HCH was issued by the US Environmental Protection Agency on 19 October, 1976 (US Environmental Protection Agency, 1976c) on the basis of carcinogenic effects.
The future use of HCH in the US depends largely on the outcome of these actions.

No data on its use in Europe were available.

HCH was used as an insecticide in Japan until 1971, when its use was discontinued.

Lindane

Lindane is used primarily as an insecticide (Demozay & Marechal, 1972c) and as a therapeutic agent in human and veterinary medicine.

It is registered in the US for insecticidal use on a wide variety of vegetable, fruit and field crops, as well as for use on animals, agricultural premises, general outdoor use and on uncultivated land (US Environmental Protection Agency, 1970). An estimated 270 thousand kg lindane were used in the US for insecticidal purposes in 1974, with 67% on livestock and poultry and 33% on field crops.

Lindane is used in human medicine as a scabicide and pediculocide. Less than 1000 kg were used in the US for this purpose in 1971. It is available for human use in preparations as a lotion (1%), cream (1%) and shampoo (1%) (Kastrup, 1976).

In Europe, it is used as an insecticide on various vegetables, fruits and crops and on animals and animal premises. For specific uses in different countries, see Blaquière (1976a).

Domestic use of lindane in aerosol form has been prohibited in Sweden and Finland and restricted in Canada (Blaquière, 1976b).

Lindane was used as an insecticide in Japan until 1971 when its use was discontinued.

In November 1975, the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues recommended maximum residue limits for 20 commodities ranging from 0.05 mg/kg on potatoes to 2 mg/kg on lettuce; 0.5 mg/kg was recommended for most fruit and vegetables (WHO, 1976). Residue tolerances in the US range from 0.01 mg/kg for pecans to 7 mg/kg for the fat of meat, with most fruit and vegetables falling in the range of 1-3 mg/kg (US Environmental Protection Agency, 1976b).

A notice of rebuttable presumption against registration and continued registration (RPAR) (see General Remarks on the Substances Considered, p. 31) of pesticide products containing lindane was issued by the US Environmental Protection Agency on 17 February 1977 (US Environmental Protection Agency, 1977) on the basis of carcinogenic and delayed toxic
effects and acute toxicity risk related to hazards in aquatic wildlife. The future use of lindane in the US depends largely on the outcome of these actions.

A maximum acceptable daily intake of lindane for humans was established at 0-0.01 mg/kg bw by the 1975 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues (WHO, 1976). This level was re-established in 1977 (FAO/WHO, 1978).

The US Occupational Safety and Health Administration's standards for air contaminants require that an employee's exposure to lindane not exceed an 8-hr time-weighted average of 0.5 mg/m³ in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1976).

The corresponding standard in the Federal Republic of Germany is 0.5 mg/m³, and that in the German Democratic Republic, 0.2 mg/m³; the ceiling concentration in the USSR is 0.05 mg/m³ (Winell, 1975).

2.2 Occurrence

HCH and lindane are not known to occur as natural products.

(a) Air

The occurrence of residues of lindane in air has been reviewed by Sieper (1972).

In weekly air samples taken in the Mississippi Delta, maximum levels of lindane were 9.3 ng/m³ and maximum levels of β-HCH were 49.4 ng/m³ (Arthur et al., 1976). Lindane was also detected in the air of a plant producing hexachlorobenzene (Melnikova et al., 1975).

(b) Water and sediments

The presence of HCH and lindane in surface waters, drinking-water, and industrial and sewage effluents in the US and Europe has been reviewed and tabulated (Eurocop-Cost, 1976; Shackelford & Keith, 1976; Sieper, 1972).

The concentrations of α-HCH and lindane in rainwater in Tokyo were in the range of 45-830 ng/l and 29-398 ng/l, respectively (Masahiro & Takahisa, 1975).

HCH and lindane residues in ground-water used for drinking purposes were: (1) ≤ 15 ng/l lindane and 4 ng/l α-HCH in wells in Israel (Lahav & Kahanovitch, 1974); 10-340 ng/l lindane and 0-220 ng/l β-HCH in Czechoslovakia (Rosival & Szokolay, 1975); and < 10-319 ng/l lindane
in 3 US rural areas (Achari et al., 1975; Sandhu et al., 1978). In a survey of finished US drinking-water, the highest reported level of HCH was 100 ng/l (US Environmental Protection Agency, 1975).

Levels of lindane in a US river during 1974 ranged from 1.25–2.9 ng/l (Brodtmann, 1976); lindane concentrations in two rivers in Canada ranged from 0.4–1.6 ng/l (Mamarbachi & St-Jean, 1976). HCH and lindane have been reported in rivers in the Federal Republic of Germany, at concentrations ranging from 5–2500 ng/l α-HCH and 5–7100 ng/l lindane (Herzel, 1972); at a river mouth in Italy, 9.5 ng/l lindane (Andryushchenko et al., 1975); in Spain, 25 ng/l α-HCH and 47 ng/l lindane (Simal et al., 1975); and in the UK, 15–55 ng/l lindane and 3–8 ng/l α-HCH (Musty & Nickless, 1976).

Lindane concentrations in a lake in Europe were 5 ng/l at the surface and 1.5–3 ng/l at a depth of 60 m (Maier & Wendlandt, 1976).

Rivers in Japan have been found to contain levels of HCH isomers ranging from traces to 860 ng/l (α-HCH), 10–30 ng/l (β-HCH), 5–410 ng/l (lindane) and 0–10 ng/l (δ-HCH) (Hirano & Katada, 1975; Kitayama et al., 1976; Ochiai & Hanya, 1976; Saito & Kitayama, 1974); a maximum level of 10,000 ng/l total HCH has been found (Yamato et al., 1975).

In a controlled study in a flooded limestone quarry, 41.1% of added lindane remained after 240 days: 40.6% in the water and 0.5% in the bottom sediments (Hamelink & Waybrant, 1973).

(c) Soil

A review on the degradation and persistence of lindane in soils has been published (Sieper, 1972).

In Japan after prohibition of the use of HCH on arable land, total HCH residues in soils declined from 7.9 mg/kg in 1970 to 0.4 μg/kg in 1973 in one area (Yamada & Sakamoto, 1975); in another area, lindane concentrations in soils declined from 0.06–1.12 mg/kg in 1970 to 0.013–0.848 mg/kg in 1972 (Saito & Kitayama, 1973).

Soil in southern Bohemia was reported to contain 1 μg/kg lindane (Hruska & Kociánova, 1975).

In a radioactive tracer study of lindane degradation in soils, approximately 89% and 86% of added lindane was recovered from moist and submerged organic soils, respectively, after 8 weeks, and 84% and 70% was recovered from moist and submerged mineral soils, respectively (Mathur & Saha, 1977).
(d) Food and drink

A review has been published on lindane residues on vegetables in supervised trials (WHO, 1976). The occurrence of lindane in foods has been reviewed (Sieper, 1972).

In a programme still in progress involving the monitoring of pesticide residues in food, the US Department of Health, Education, and Welfare monitored levels of lindane in foods during the period 1965-1974 and calculated the average daily intake. For the period 1965-1970, the average daily intake of lindane was 3 µg/day; in 1973, this dropped to 0.2223 µg/day, and it rose slightly in 1974 to 0.5856 µg/day (US Food & Drug Administration, 1975, 1977).

In total diet studies in Spain in 1971-1972, the estimated per capita intake of α-HCH was 11.52 µg/day; that of lindane was 13.78 µg/day (Carrasco et al., 1976). In the German Democratic Republic, the estimated average daily intake of lindane of an adult male in 1971 was 10 µg, and that of nursery school children was 7 µg (Engst et al., 1976a). In Yugoslavia, the average daily intake of total HCH in 1970-1971 was 494 µg (Adamovic et al., 1975). A model daily diet for adult Japanese contained an average of 3.5 µg lindane (Ushio et al., 1974).

In a 4-year study (1971-1974) in Japan, average levels of HCH in vegetables gradually decreased following prohibition of its use on arable land in 1970. The proportion of isomers in total HCH residues was very different from that in the technical product: the β-isomer, in particular, was present in a much higher proportion in the residues than in the commercial product, due to its greater persistence (Suzuki et al., 1976).

Apple and pear samples in Italy contained mean levels of 0.5 µg/kg α-HCH and 2.5 µg/kg lindane (Avancini & Stringari, 1974).

Honey and beeswax samples in the US contained α-HCH in ranges of 0.01-0.08 µg/kg and 0.21-3.5 µg/kg, respectively; β-HCH in ranges of 0.03-0.3 µg/kg and 0.68-5.26 µg/kg; and lindane in ranges of 0.01-0.38 µg/kg and 0.3-6 µg/kg (Estep et al., 1977).

The lindane content of raw and processed vegetable oils in Iran was 29 µg/kg and 2 µg/kg, respectively (Hashemy-Tonkabony & Soleimani-Amiri, 1976).

Maximum residues of lindane in cultured fish and shellfish in Taiwan were 0.16 mg/kg (Jeng & Sun, 1974).

Lindane was present in 8/10 samples of cow's milk in Italy at concentrations ranging from 3-18 µg/l (Cerutti et al., 1975). Milk and milk products in the Federal Republic of Germany contained mean levels
of 40 μg/l α-HCH and 72 μg/l lindane (Heeschen et al., 1976). Samples of cow's milk in Roumania had concentrations of 124 μg/l and 255 μg/l lindane (Cocisiu et al., 1975a). In Japan, after prohibition of use of HCH on arable land, lindane concentrations in cow's milk decreased from 244 μg/l in 1970 to 1 μg/l in 1973 (Yamada & Sakamoto, 1975).

Lindane concentrations in the fat of cattle given controlled feed for 112 days prior to slaughter (0.026 mg/kg) were higher than the original concentration in the feed (0.002 mg/kg) (Clark et al., 1974).

In feeding experiments with broiler breeder hens, the ratio of the level of HCH in the animal fat to the level in the feed was 1.8 for α-HCH, 18 for β-HCH and 1.8 for lindane. The ratio of the level of HCH in eggs to the level in the feed was 0.10 for α-HCH, 1.5 for β-HCH and 0.13 for lindane on a whole egg basis (Kan & Tuinstra, 1976).

(e) Animals

The occurrence of lindane in animals has been reviewed (Sieper, 1972).

In Japan, crows were found to contain 8.2 mg/kg total HCH (Kaneshima et al., 1976), and wild ducks contained 0–0.19 mg/kg total HCH (Ushio et al., 1976). Levels of lindane in eggs of birds in France were 0.03–0.5 mg/kg (Mendola et al., 1977). In the US, residues of HCH in starlings ranged from traces to 0.036 mg/kg in 1972 and from traces to 0.094 mg/kg in 1974 (Nickerson & Barbehenn, 1975; White, 1976).

Fat samples taken from 20 raccoons in the US contained 0.17 mg/kg α-HCH (in one animal), 0.1–2.3 mg/kg β-HCH (in 15 animals) and 0.02–0.12 mg/kg lindane (in 5 animals) (Nalley et al., 1975). Wild rabbits in Roumania had α-HCH and lindane in all tissues, with the highest concentration found in adipose tissue (Floru et al., 1975).

Lindane was found in lake trout in the US at a mean concentration of 1.19 mg/kg (Parejko et al., 1975). Molluscs in Spain contained maximum levels of 1.54 μg/kg α-HCH and 2.30 μg/kg lindane (Boado et al., 1975). Fish in Iran contained residues of lindane ranging from 0–0.054 mg/kg (Hashemy-Tonkabony & Asadi Langaroodi, 1976); and fish in Lake Tanganyika contained 0.22–1.4 mg/kg lindane (Deelstra, 1974).

(f) Humans

The occurrence of lindane in humans has been reviewed (Sieper, 1972).

Milk samples taken from Italian women contained 0.06–0.52 mg/l β-HCH and 0.08–0.88 mg/l lindane (fat basis) (Cerutti et al., 1976). Median values of HCH in mother's milk in The Netherlands were 0.01 mg/l α-HCH, 0.28 mg/l β-HCH and 0.02 mg/l lindane (fat basis) (Wegman & Greve, 1974). Milk fat from Austrian women contained mean concentrations of 0.2 mg/l
β-HCH and 0.048 mg/l lindane (Pesendorfer, 1975). In Japan, mother's milk contained 0.220 mg/l β-HCH in 1970; this declined to 0.013 mg/l in 1973 after use of HCH had been prohibited (Yamada & Sakamoto, 1975).

In the US, β-HCH levels in the serum of new mothers in a rural area ranged from 0-19 μg/l (mean, 1.9 μg/l) in blacks and 0-9 μg/l (mean, 3 μg/l) in whites; serum levels of β-HCH in the newborns ranged from 0-9 μg/l (means, 0.75 μg/l in black babies and 1 μg/l in white babies) (D’Ercole et al., 1976). In a study of post-mortem human blood from 497 Virginia residents, 8.3% of samples contained lindane, in concentrations ranging from 1-17 μg/l, with a mean of 3.5 μg/l (Griffith & Blanke, 1975).

In Spain, lindane was detected in 94% of 199 samples of human serum tested, with an average concentration of 0.066 mg/l (Santiago Laguna et al., 1975).

In 51 human fat samples analysed at autopsy in New Zealand in 1973, measurable amounts of β-HCH were found in 37% and lindane in 22% (Solly & Shanks, 1974). HCH was present in 49/52 fat samples from autopsied children in Argentina, at levels of 0.22 mg/kg α-HCH, 0.86 mg/kg β-HCH and 0.09 mg/kg lindane (Astolfi et al., 1973).

In a 1970 survey of pesticide residues in the adipose tissue of the general population of the US, mean levels of α-HCH were 0.01 mg/kg, β-HCH levels were 0.6 mg/kg, lindane levels were 0.01 mg/kg and δ-HCH levels were 0.01 mg/kg (Kutz et al., 1974). Adipose tissue levels of β-HCH in Spain averaged 2.55 mg/kg (Vioque & Sáez, 1976). Lindane levels in adipose tissue in Roumania averaged 4.76 mg/kg (Cocisiu et al., 1975b). In Japan, total HCH averaged 4.26 mg/kg in subjects less than 1 year old, 4.95 mg/kg in subjects from 1-19 years old, 8.45 mg/kg in subjects from 20-49 years old, and 7.46 mg/kg in subjects over 50 years of age (Yamada et al., 1976).

The storage levels of total HCH isomers in adipose tissue in the general populations of different countries varied from 0.02-1.43 mg/kg, and the concentration in human blood was 0.003 mg/l (Durham, 1969). Sieper (1972) listed adipose tissue levels of lindane in the general population: the lowest concentration was 0.015 mg/kg in the UK, and the highest was 1.19 mg/kg in France. In 241 human adipose tissue samples from Japan, the mean concentration of α-HCH was 0.14 mg/kg, that of β-HCH 1.28 mg/kg, and that of lindane 0.12 mg/kg (Curley et al., 1973). The total HCH concentration in human adipose tissue samples taken in Budapest averaged 0.76 mg/kg (Soós et al., 1972); and in Australia, the value of total HCH varied from 0-2.6 mg/kg in 8/75 human adipose tissue samples (Brady & Siyali, 1972).
2.3 Analysis

Methods used for the analysis of HCH and lindane in environmental samples are listed in Table 2.

The separation of 6 isomers of HCH by thin-layer chromatography alone (Thielemann, 1976) and in combination with gas chromatography (Szokolay et al., 1975) has been investigated. The use of gel-permeation chromatography in an automated system has been proposed (Stalling, 1976).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Three groups of 20 male dd mice were fed diets containing either 6.6, 66 or 660 mg/kg diet technical HCH, comprising 66.5% α-isomer, 11.4% β-isomer, 15.2% lindane, 6.4% δ-isomer and 0.5% other isomers, for 24 weeks, at which time all animals were killed. Hepatomas were found in 20/20 animals fed 660 mg/kg diet technical HCH, but no such tumours were observed in mice receiving the lower doses. No liver tumours occurred in 14 male controls (Nagasaki et al., 1971, 1972).

In a study reported while the experiment was still in progress, groups of 20 male ICR-JCL mice, aged 5 weeks, were fed 600 mg/kg diet technical HCH, pure α- or β-isomers or lindane or a mixture of δ- and ε-HCH. Further groups of 20 mice received 300 mg/kg diet lindane or a control diet. Gross examination of 10 animals of each group after 26 weeks showed the presence of liver nodules in those receiving 600 mg/kg diet technical HCH, α-HCH, lindane and the δ + ε mixture. Histologically benign liver tumours were observed in all treated groups, except in

1The Working Group was aware of studies in progress in mice in which α- and β-HCH are given in the diet, and of studies completed, but not published, in mice and rats given lindane in the diet (IARC, 1978).
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td>Dissolve (carbon disulphide)</td>
<td>IR</td>
<td>-</td>
<td>US Environmental Protection Agency (1976d)</td>
</tr>
<tr>
<td></td>
<td>Dissolve (chloroform), centrifuge, filter</td>
<td>IR</td>
<td>-</td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Powders (&gt; 10% lindane)</td>
<td>Extract (nitromethane-hexane), filter, CC, evaporate solvent</td>
<td>Weigh residue</td>
<td>-</td>
<td>Goza (1972)</td>
</tr>
<tr>
<td>Air</td>
<td>Trap in iso-octane</td>
<td>GC/Electrolytic conductivity detection</td>
<td>50 μg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977)</td>
</tr>
<tr>
<td>Workplace</td>
<td>Trap on Chromosorb 102, extract (hexane-acetone) in Soxhlet</td>
<td>GC/ECD or thermionic detection</td>
<td>&lt; 1 ng/m³</td>
<td>Thomas &amp; Seiber (1974)</td>
</tr>
<tr>
<td>Atmosphere during field spraying</td>
<td>Trap in iso-octane</td>
<td>GC/ECD or thermionic detection</td>
<td>&lt; 1 ng/m³</td>
<td>Thomas &amp; Seiber (1974)</td>
</tr>
<tr>
<td>Water</td>
<td>Filter, CC (reversed phase), elute (petroleum ether)</td>
<td>TLC</td>
<td>-</td>
<td>Musty &amp; Nickless (1976)</td>
</tr>
<tr>
<td>Soil</td>
<td>Extract (acetone), double CC</td>
<td>TLC (revelation: silver nitrate/ultraviolet)</td>
<td>25 μg/kg</td>
<td>Taylor et al. (1975)</td>
</tr>
<tr>
<td>Sediments</td>
<td>Centrifuge, extract solid (acetone), liquid/liquid partition, transfer into trimethylpentane, treat to remove sulphur, isolate in trimethylpentane</td>
<td>GC/ECD</td>
<td>1-10 μg/kg</td>
<td>Jensen et al. (1977)</td>
</tr>
</tbody>
</table>
**TABLE 2. METHODS FOR THE ANALYSIS OF HEXACHLOROCYCLOHEXANE (TECHNICAL lCH AND LINDANE)**

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>Extract (carbon tetrachloride), remove solvent, dechlorinate, nitrate, extract (ether), remove solvent, dissolve (methyl ethyl ketone), add potassium hydroxide</td>
<td>Spectrophotometry (565 nm)</td>
<td>-</td>
<td>Horwitz (1965)</td>
</tr>
<tr>
<td>Food</td>
<td>Macerate with sulphuric acid, steam-distill with carbon tetrachloride, evacuate carbon tetrachloride phase, dissolve residue (acetone)</td>
<td>PC (revelation: fluorescein/ultra-violet)</td>
<td>20 µg/kg</td>
<td>Belonosov (1973)</td>
</tr>
<tr>
<td>Food</td>
<td>Extract (petroleum ether), wash (acid), transfer to hexane</td>
<td>TLC (revelation: ultra-violet)</td>
<td>-</td>
<td>Tikhomirova et al. (1975)</td>
</tr>
<tr>
<td>Food</td>
<td>Extract (petroleum ether-dichloromethane), CC</td>
<td>TLC</td>
<td>-</td>
<td>Piechocka (1975)</td>
</tr>
<tr>
<td>Food</td>
<td>Extract (acetonitrile), liquid/liquid partition, CC</td>
<td>GC/Thermionic detection, TLC, PC</td>
<td>-</td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Food</td>
<td>Extract (acetonitrile), liquid/liquid partition, CC</td>
<td>GC/Thermionic detection</td>
<td>-</td>
<td>Finsterwalder (1976)</td>
</tr>
<tr>
<td>Biological</td>
<td>Extract (hexane or acetone), liquid/liquid partition</td>
<td>TLC</td>
<td>-</td>
<td>Rao et al. (1975)</td>
</tr>
<tr>
<td>Biological</td>
<td>Extract (hexane) in vortex mixer, centrifuge, separate hexane layer</td>
<td>GC/ECD</td>
<td>15 ng/l</td>
<td>Franken &amp; Luyten (1976)</td>
</tr>
<tr>
<td>Biological</td>
<td>Homogenize with acetonitrile, liquid/liquid partition, CC</td>
<td>TLC (revelation: silver nitrate/ultra-violet)</td>
<td>0.1 µg (on the plate)</td>
<td>Stute &amp; Kaufmann (1971)</td>
</tr>
</tbody>
</table>

**Abbreviations:** IR - infra-red spectrometry; CC - column chromatography; GC - gas chromatography; ECD - electron capture detection; PC - paper chromatography; TLC - thin-layer chromatography
those receiving 300 mg/kg diet lindane. In animals administered diets containing α-HCH and the δ + ε mixture, the histological appearance of tumours was frequently malignant (Goto et al., 1972) [The Working Group noted that this study was inadequately reported].

Twelve groups of 10-11 dd mice of each sex, aged 6 weeks, were fed diets containing 100, 300 or 600 mg/kg diet of either α-, β- or technical HCH or lindane for 32 weeks. A control group of 21 male and 20 female mice were fed the basal diet. At 26 weeks, 104 experimental and 35 control mice were still alive; 26 male and 27 female experimental animals were laparotomized at this time to observe the condition of the liver. All survivors were killed 5-6 weeks after the end of exposure. Proportions of mice found to have hepatomas at the end of the study are shown in Table 3.

Table 3. Proportions of mice fed various levels of HCH isomers that developed hepatomas

<table>
<thead>
<tr>
<th>HCH isomer</th>
<th>Sex</th>
<th>mg/kg diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>α-HCH</td>
<td>males</td>
<td>1/8</td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>0/8</td>
</tr>
<tr>
<td>β-HCH</td>
<td>males</td>
<td>0/9</td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>0/9</td>
</tr>
<tr>
<td>Lindane</td>
<td>males</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>0/8</td>
</tr>
<tr>
<td>Technical HCH</td>
<td>males</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>0/8</td>
</tr>
</tbody>
</table>

In mice receiving α-HCH and technical HCH, the average size of the liver tumours was dose-related and ranged from 2 to 11 mm. No liver tumours were observed in 14 male and 15 female effective control mice (Hanada et al., 1973) [The Working Group noted the short duration of the experiment and the small size of the experimental groups].

In a series of experiments in 8-week-old male dd mice, either α-, β- or δ-HCH or lindane (99% pure by gas chromatography) was added to the diet at concentrations of 100, 250 and 500 mg/kg diet. Each group included 20 mice, except for the group that received 250 mg/kg diet α-HCH, which consisted of 38 mice. Treatment lasted for 24 weeks, at which time all survivors were killed. Hepatocellular carcinomas up to 2 cm in diameter were found in 10/38 mice that received 250 mg/kg diet α-HCH and in 17/20 mice that received 500 mg/kg diet α-HCH; in the same groups, 30/38 and 20/20 mice, respectively, also had liver...
nodular hyperplasia. Nine additional groups of 26-30 mice were fed diets containing 50, 100 or 250 mg/kg diet of either α- or β-HCH or lindane for 24 weeks. Hepatocellular carcinomas and/or nodular hyperplasia were found only in the group that received 250 mg/kg diet α-HCH (23/30 with nodular hyperplasia and 8/30 with hepatocellular carcinoma) (Ito et al., 1973a) [The Working Group noted the short duration of the experiment].

In an experiment lasting 110 weeks, a group of 30 male and 30 female CFl mice were fed 200 mg/kg diet β-HCH (purity > 99%), and a group of 29 males and 29 females received 400 mg/kg diet lindane (purity, 99.5%). A group of controls comprising 45 male and 44 female mice were fed a standard diet. Benign and malignant liver tumours were found in the following numbers of animals receiving 0, 200 mg/kg β-HCH or 400 mg/kg diet lindane: in males, 11 (24%), 22 (73%) and 27 (93%), respectively; and in females, 10 (23%), 13 (43%) and 20 (69%), respectively. Lung metastases were found in 4 (13%) and 3 (10%) male animals receiving β-HCH and lindane and in 9 (3%) females receiving lindane. The incidence of other tumours was not increased by exposure to either isomer (Thorpe & Walker, 1973).

The combined effect of the different HCH isomers was investigated in another study lasting 24 weeks. Groups of 8-week-old male dd mice were given 250 mg/kg diet α-HCH only, or this concentration of the α-isomer plus the same concentration of either β- or δ-HCH or lindane (each isomer being > 99.0% pure). Proportions of mice that developed hepatocellular carcinomas with no metastases were 10/38 in animals given only the α-isomer and 14/28, 12/28 and 7/28 in those receiving, respectively, α + β, α + lindane and α + δ; 75-93% of the animals also had nodular hyperplasia. These observations were considered to indicate a lack of combined effects of the four HCH isomers. Combined exposures of groups of 29 mice to the β-isomer + lindane, to the β- + δ-isomers and to lindane + the δ-isomer produced no hepatocellular carcinomas. Only 1 nodular hyperplasia was seen among mice fed the β- + δ-HCH mixture (Ito et al., 1973b) [The Working Group noted the short duration of the experiment].

Twenty male DDY mice, aged 5-6 weeks, were fed a diet containing 500 mg/kg diet α-HCH for 24 weeks, at which time they were killed; 16 controls were fed the basal diet. Average liver weight in treated animals was 12.6% of body weight (versus 3.7% in controls); 6 treated mice had well-differentiated hepatocellular carcinomas, and nodular hyperplasia was found in all treated animals. No liver lesions were found in control mice. In the same series of studies, groups including 13-29 mice of each sex, of the DDY, ICR, DBA/2, C57BL/6 and C3H/He strains, were fed 500 mg/kg diet α-HCH for 24 weeks, at which time they were killed; controls were fed the basal diet. Hepatocellular carcinomas were observed in mice of the DDY strain (13/20 males and 5/20 females), the ICR strain (8/23 males and 6/29 females), the DBA/2
strain (1/16 males and 1/15 females) and the C3H/He strain (0/20 males and 2/20 females), but not among 21 male and 18 female C57BL/6 mice. Nodular hyperplasia was observed in mice of all strains, the incidence being the lowest in C57BL/6 mice (4/21 males and 3/18 females) and the highest in DDY mice (20/20 males and 16/20 females). No hepatocellular carcinomas or hyperplasia were found in control mice of any strain (Nagasaki et al., 1975).

Sixteen groups of 12-21 male DDY mice, 8 weeks old, were fed a diet containing 500 mg/kg diet α-HCH (> 99.0% pure) for periods of 16, 20, 24 or 36 weeks and were killed at intervals 0-36 weeks later. All mice treated for 16 weeks were killed at the end of treatment, and 5/21 had liver tumours up to 1 cm in diameter. Among mice treated for 20 weeks, proportions with liver tumours were 14/20, 8/20, 5/20 and 2/19 in those killed 0, 4, 8 and 12 weeks after the end of treatment, respectively. Among mice treated for 24 weeks, proportions with liver tumours were 20/20, 18/19, 9/16, 7/17, 8/16, 12/15 and 14/14 among those killed 0, 4, 8, 12, 16, 24 and 32 weeks after the end of treatment. Among mice treated for 36 weeks, proportions with liver tumours were 14/14, 11/13, 12/12 and 13/13 in those killed 0, 12, 24 and 36 weeks after the end of treatment. No liver tumours were found among 18 control mice observed for 72 weeks (Ito et al., 1976).

Groups of 50 NMRI mice of each sex received diets containing 12.5, 25 or 50 mg/kg diet lindane (purity not specified), starting at 34 days of age. Untreated controls included 100 mice of each sex. Treatment lasted 80 weeks, at which time all survivors were killed; a total of 79 control and treated mice died during the experiment, with no effects related to treatment. Liver tumours were found in 4 control males and 1 control female, in 2 males and 1 female fed 12.5 mg/kg diet and in 2 males fed 50 mg/kg diet; all were liver-cell adenomas, except 1 malignant haemangioendothelioma in a male fed 12.5 mg/kg diet. A total of 35 animals developed lymphocytic leukaemia or lymphosarcoma (17 controls and 7, 4 and 7 mice fed 12.5, 25 and 50 mg/kg diet, respectively); and 50 mice developed lung tumours (21 controls and 11, 8 and 10 mice fed 12.5, 25 and 50 mg/kg diet, respectively). Other tumours included 8 reticulum-cell neoplasms (1 in controls), and 3 cutaneous or subcutaneous sarcomas (Weisse & Herbst, 1977) [The Working Group noted the relatively low dose administered, in comparison with other experiments with lindane in mice].

Groups of 50 male and 50 female B6C3F1 hybrid mice, 5 weeks of age, were fed diets containing 80 or 160 mg/kg diet lindane (100% pure) for 80 weeks, and then observed for an additional 10-11 weeks. Groups of 50 mice of each sex were used as controls; of these only 10 were fully contemporary to the treated animals, whereas the other 40 overlapped the study with lindane by at least a year. Survival rates were similar for treated and control groups: at least 88% of the males and 80% of the females lived to the end of the study. In males, hepato-
cellular carcinomas were found in 5/49 pooled controls (2/10 matched controls), in 19/49 mice fed 80 mg/kg diet and in 9/46 mice fed 160 mg/kg diet. The corresponding proportions in females were 2/47 (0/10), 2/47 and 3/46. In addition, 1 mouse of each sex in matched controls, 3 male and 1 female pooled controls, 2 females fed the low dose and 1 male fed the high dose had neoplastic nodules of the liver in the absence of hepatocellular carcinoma. Four hepatocellular carcinomas in males given the low dose produced metastases. Examination of data on historical controls at this laboratory indicated that hepatocellular carcinomas and neoplastic nodules of the liver occurred in 75/360 (20.8%) male B6C3Fl mice. In males, the first liver tumour was observed at 60 weeks in those given the low dose, at 77 weeks in controls and at 79 weeks in the high-dose group. Tumours at other sites occurred sporadically in all groups (National Cancer Institute, 1977) (The Working Group noted the relatively low dose used and the small number of controls contemporary to the experimental groups).

Rat: Groups of 10 male and 10 female weanling Wistar rats were fed for lifespan on diets containing 10, 50, 100 or 800 mg/kg diet technical HCH; 10, 50, 100 or 800 mg/kg diet α-HCH; 10, 100 or 800 mg/kg diet β-HCH; 5, 10, 50, 100, 400, 800 or 1600 mg/kg diet lindane as a solution in corn oil; or 10, 100 or 800 mg/kg diet powdered lindane. The technical HCH contained 64% α-, 10% β-, 9% δ- and 1.3% ε-isomers and 13% lindane; the individual isomers were > 98% pure. Average lifespan was significantly reduced in all groups given the 800 mg/kg diet levels, except for those given powdered lindane; the mean age at death was 58 weeks in a group of 40 control animals and 33-70 weeks in experimental groups (4 weeks in the group given 800 mg/kg diet β-HCH). No increase in tumour incidence was reported in treated animals; however, organs were examined microscopically in only 238 animals, with detailed sectioning of 86 animals (Fitzhugh et al., 1950) (The Working Group noted the early mortality and the relatively small proportions of rats submitted to pathological study).

Male W rats, 5-8 weeks old, were fed diets containing either α-HCH (500 or 1000 mg/kg diet for 24 or 48 weeks or 1000 or 1500 mg/kg diet for 72 weeks), β-HCH (500 mg/kg diet for 24 or 48 weeks or 1000 mg/kg diet for 24 weeks), lindane (500 mg/kg diet for 24 or 48 weeks) or δ-HCH (500 or 1000 mg/kg diet for 24 or 48 weeks). Each isomer was more than 99% pure. The original sizes of the groups and survival rates were not reported. Survivors (5-16 per group) were killed at the end of the feeding period. Hepatocellular carcinomas were found in 3/13 and 1/16 rats fed 1500 and 1000 mg/kg diet α-HCH for 72 weeks. No liver tumours were found in 31 rats fed 500 or 1000 mg/kg diet α-HCH for 24 or 48 weeks, or in 59 rats fed the β- or δ-isomers or lindane at concentrations of 500 or 1000 mg/kg diet for 24 or 48 weeks, or in 8 control rats observed for 72 weeks. Liver nodular hyperplasia was found in a total of 27/41 rats fed α-HCH at concentrations of 1000 or 1500 mg/kg diet for at least 48 weeks (Ito et al., 1975) (The Working
HEXACHLOROCYCLOHEXANE

Group noted the relatively short duration of the study and the small sizes of the control and experimental groups.

Groups of 50 male and 50 female 5-week-old Osborne-Mendel rats were fed diets containing lindane (100% pure) at two dose levels for 80 weeks and kept under observation for a further 29-30 weeks. Preliminary experiments had indicated that a dietary concentration of 640 mg/kg diet caused a reversible early decrease in weight gain but no deaths; therefore, initial dietary concentrations of lindane were set at 640 and 320 mg/kg diet. Because of intercurrent deaths, however, these concentrations were reduced to half after 2 and 38 weeks of treatment in females and males, respectively; in females, a further reduction to one-fourth of the original dietary concentration was introduced 49 weeks after the beginning of treatment. Time-weighted average dietary concentrations were 236 and 472 mg/kg diet for males and 135 and 270 mg/kg diet for females. Groups of 55 rats of each sex were used as controls; of these only 10 were fully contemporary to the treated animals, whereas the other 45 overlapped the study with lindane by at least a year. Over 80% of rats lived for longer than 52 weeks. Among male rats, 60%, 50% and 48% were still alive at the end of the study in the control, low- and high-dose groups; in females, only 40% of the controls survived to the end of the study, while at least 60% of the low- and high-dose groups survived. Liver lesions were classified according to Squire & Levitt (1975). The proportions of animals that developed neoplastic nodules in the liver and thyroid tumours are shown in Table 4. Tumours occurred sporadically at other sites, but their incidence did not differ between control and treated animals (National Cancer Institute, 1977) [The Working Group noted the small number of contemporary controls and the poor survival rates in all groups. In

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Sex</th>
<th>Group</th>
<th>Matched controls</th>
<th>Pooled controls</th>
<th>Low-dose</th>
<th>High-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplastic liver nodules</td>
<td>males</td>
<td>0/10</td>
<td>0/49</td>
<td>3/45</td>
<td>2/45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>0/10</td>
<td>1/49</td>
<td>4/48</td>
<td>2/45</td>
<td></td>
</tr>
<tr>
<td>Thyroid follicular-cell adenomas or carcinomas</td>
<td>males</td>
<td>1/6</td>
<td>3/42</td>
<td>6/37</td>
<td>4/37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>0/8</td>
<td>0/48</td>
<td>2/44</td>
<td>1/42</td>
<td></td>
</tr>
<tr>
<td>Thyroid C-cell adenomas</td>
<td>males</td>
<td>1/6</td>
<td>2/42</td>
<td>3/37</td>
<td>1/37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>females</td>
<td>0/8</td>
<td>0/48</td>
<td>4/44</td>
<td>3/42</td>
<td></td>
</tr>
</tbody>
</table>

α P < 0.05
addition, there was no adequate evidence that the dose given to male rats corresponded to the maximum tolerated dose).

(b) **Skin application**

**Mouse:** In a study reported while still in progress, a group of 30 stock mice were given twice-weekly applications of a 0.5% solution of lindane in acetone to the skin for 15 months. Twenty-one mice were alive at the time of reporting (at least 15 months), and no skin tumours had occurred (Orr, 1948) [The Working Group noted the inadequacy of the report].

(c) **Subcutaneous and/or intramuscular administration**

**Mouse:** In an experiment reported while still in progress, no treatment-related tumours were observed in 12/20 stock mice still alive 10 months after s.c. implantation of a paraffin wax pellet containing 3% lindane (Orr, 1948) [The Working Group noted the inadequacy of the report].

(d) **Intraperitoneal administration**

**Mouse:** Three groups of 20 male A/St mice, 6-8 weeks of age, were given thrice weekly i.p. injections of 8, 20 or 40 mg/kg bw lindane in tricaprylin for 8 weeks. All survivors were killed 24 weeks after the first injection. The number of lung tumours per mouse was not increased in comparison with that in controls injected with tricaprylin (Theiss et al., 1977) [The Working Group noted the limitations of a negative result obtained with this test system; see General Remarks on the Substances Considered, p. 34].

(e) **Carcinogenicity of metabolites**

**Mouse:** Three metabolites of HCH, 1,2,4-trichlorobenzene, 2,3,5-trichlorophenol and 2,4,5-trichlorophenol, were administered at concentrations of 600 mg/kg diet to groups of 20 ICR-JCL male mice for 6 months, at which time 10 animals from each group were examined. No liver tumours were observed in these animals, in contrast to parallel experiments in which the same dose levels of HCH isomers (α, β, lindane or a δ + ε mixture) gave rise to benign and/or malignant liver tumours (Goto et al., 1972) (See also monograph on 2,4,5- and 2,4,6-trichlorophenols, p. 349) [The Working Group noted the short duration of the experiment].

3.2 **Other relevant biological data**

A review on lindane is available (WHO, 1972).
(a) Experimental systems

Toxic effects

The oral LD$_{50}$ of α-HCH is 1000 mg/kg bw in mice and 500-1700 mg/kg bw in rats; that of β-HCH is 1500 mg/kg bw in mice and 2000 mg/kg bw in rats; that of δ-HCH is 750-1000 mg/kg bw in rats; and that of a mixture of HCH isomers is 700 mg/kg bw in mice and 600-1250 mg/kg bw in rats (WHO, 1969).

The oral LD$_{50}$ of lindane is 86 mg/kg bw in mice, 125-230 mg/kg bw in rats, 100-127 mg/kg bw in guinea-pigs and 60-200 mg/kg bw in rabbits (WHO, 1967). The LD$_{50}$ of lindane by topical application in xylene to rats is 900-1000 mg/kg bw (Gaines, 1969).

Signs of acute lindane poisoning in rats include diarrhoea, hypothermia, epistaxis and convulsions; death is due to respiratory failure (Chen & Boyd, 1968).

Liver-cell hypertrophy was observed in rats and hamsters fed 500 mg/kg diet α-HCH for 24 weeks (Nagasaki et al., 1975).

Groups of 10 male and 10 female Wistar rats were administered diets containing 10-1600 mg/kg diet of α- or β-HCH isomers, lindane, technical HCH or powdered lindane for lifespan. Weight gain was reduced in females receiving 100 mg/kg diet β-HCH and in animals of both sexes receiving 800 mg/kg diet α-HCH or technical HCH. Mortality was increased significantly in all groups receiving 800 mg/kg diet of the test compounds, except in those receiving powdered lindane. Fatty degeneration and focal necrosis of the liver were observed in the higher dose groups. Chronic nephritis with glomerular fibrosis and hyaline deposits was seen in rats fed 800 mg/kg diet α-HCH, powdered lindane or technical HCH (Fitzhugh et al., 1950).

Embryotoxicity and teratogenicity

Daily doses of 0.5 mg/kg bw lindane given orally for 4 months to female rats produced disturbances of the oestrous cycle, inhibited the animals' capacity for conception and fertility, lowered the viability of embryos and delayed their physical development (Naishtein & Leibovich, 1971). Treatment of rats with 0.05 mg/kg bw did not produce such effects (Shtenberg & Mametkuliev, 1976).

No significant teratogenic effect was produced by administration of oral doses of 5, 10 or 20 mg/kg bw lindane on days 6-18 of gestation to rabbits or on days 6-15 of gestation to rats (Palmer et al., 1978).

An increased incidence of stillborn pups was observed in litters of beagle bitches given 7.5 or 15 mg/kg bw/day lindane from day 5 throughout gestation (Earl et al., 1973).
Inj ection of 2 mg/egg lindane did not decrease the hatchability of hens' eggs (Smith et al., 1970). When Japanese quail eggs were sprayed with 0.15, 0.3 or 0.6% solutions of commercial lindane over 4 generations, reduced fertility, increased embryonic mortality and decreased egg hatchability, production and weight of eggs and chicks were observed (Lutz-Ostertag, 1974).

Absorption, distribution, excretion and metabolism

When single doses of $^{36}$Cl-labelled α-HCH and lindane were given intraperitoneally to rats at levels of 200 mg/kg bw and 40 mg/kg bw, respectively, approximately 80% of the total radioactivity was excreted in the urine and 20% in the faeces (Koransky et al., 1964). When labelled β-HCH was administered orally to female Sprague-Dawley rats, 80% was found to have been absorbed (Oshiba, 1972).

In rats fed 800 mg/kg diet α- and δ-HCH and lindane for 20 months, 3.5 mg/g α-isomer, 0.55 mg/g δ-isomer and 0.44 mg/g lindane were found in the adipose tissue; the levels in other tissues were lower by a factor of 5–10. β-HCH fed at 100 mg/kg diet for 20 months was stored to a greater extent, the concentration in adipose tissue being 1.9 mg/g; brain contained 130 μg/g and liver only 20 μg/g. Upon cessation of dietary exposure to HCH isomers, α- and δ-isomers and lindane disappeared from fat depots within 3 weeks, while the β-isomer persisted in the adipose tissue in small amounts after 14 weeks. The α-, β- and δ-isomers of HCH and lindane are stored in the adipose tissue of dogs; the α- and β-isomers are also stored to a lesser degree in the liver, kidneys and adrenals (Davidow & Frawley, 1951). Similar studies have been carried out by Kamada (1971), Koransky & Ullberg (1964), Oshiba (1972) and Oshiba & Kawakita (1972).

Pretreatment of rats with phenobarbital accelerated the rate of excretion of α-HCH and lindane (Koransky et al., 1964).

In mice, urinary metabolites of a single i.p. injection of lindane accounted for 57% of the dose; these consisted mostly of glucuronide and sulphate conjugates of 2,4,6-trichlorophenol and 2,4-dichlorophenol. No mercapturic acid conjugates were detected (Kurihara & Nakajima, 1974).

When lindane was administered intraperitoneally to rats, 2,3,5- and 2,4,5-trichlorophenol were identified in their urine, either free or as conjugates with glucuronic and/or sulphuric acid (Grover & Sims, 1965). When weanling Sprague-Dawley rats were fed 400 mg/kg diet lindane, 3,4-dichlorophenol, 2,4,6-trichlorophenol, 2,3,4,5- and 2,3,4, 6-tetrachlorophenol and 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol were identified in the urine (Chadwick & Freal, 1972). Pentachlorobenzene, 2,3,4,6- and 2,3,5,6-tetrachlorophenol and 2,4,6-trichlorophenol were excreted in the urine of rats given oral doses of lindane (Engst et al., 1976b).
In vitro studies indicate that at least three mechanisms may lead to the formation of trichlorophenols: (1) as a major pathway, a direct hydroxylation of lindane and subsequent decomposition of the labile intermediate to yield 2,4,6-trichlorophenol; (2) dehydrochlorination to pentachlorocyclohexene or dehydrogenation to hexachlorocyclohexene, subsequent addition of oxygen and, following dehydrochlorination, formation of 2,4,5-trichlorophenol and 2,3,4,6-tetrachlorophenol (Freal & Chadwick, 1973); and (3) hydroxylation of the intermediate trichlorobenzene (Tanaka et al., 1977). Pretreatment of rats with other organochlorine pesticides modified lindane metabolism (Chadwick et al., 1977a,b; Freal & Chadwick, 1973).

In rats, 65% of an i.p. dose of \( ^{14} \text{C}-\alpha\)-HCH was excreted in the urine and 16% in the faeces within 4 weeks. Conjugated 2,4,6-trichlorophenol was the major urinary metabolite; chlorothiophenols were also detected in the urine, and the proportion increased when animals were pretreated with \( \alpha \)-HCH (Koransky et al., 1975).

Mutagenicity and other related short-term tests

Lindane was not mutagenic in the host-mediated assay when Salmonella typhimurium (strain G46) and Serratia marcescens (strain a21) were used for reversion studies (Buselmaier et al., 1972). HCH (a mixture of \( \alpha \)- and \( \beta \)-isomers and lindane) was negative in the rec assay with Bacillus subtilis (Shirasu et al., 1976). Exposure to lindane was not accompanied by an increase in respiration-deficient yeast mutants (Schubert, 1969). Reversion studies using Saccharomyces cerevisiae (strain XV185-14C) were also negative with \( \alpha \)-HCH, both in the presence and absence of a mouse liver microsomal activation system (Shahin & von Borstel, 1977). No sex-linked recessive mutants were found in Drosophila melanogaster injected with a 0.001% solution of lindane (Benes & Sram, 1969).

Although it does not induce mutations, lindane is potent in inducing complete c-mitosis (colchicine-like effect; mitotic arrest at metaphase) in Allium cepa roots. The \( \alpha \)-isomer, on the other hand, induced only partial c-mitosis, and the \( \beta \)-isomer was ineffective (Nybom & Knutsson, 1947). Induction of mitotic arrest, as well as polyploidy, by lindane have also been recorded in root tips of 8 varieties of common pulses, including Pisum sativum (Baquar & Khan, 1971; Sharma & Gosh, 1969). Commercially available powder and liquid insecticide preparations containing lindane (10 or 20%) and lindane crystals (100% pure) induced chromosome aberrations in Allium cepa roots (Sax & Sax, 1968).

In rats given 0.06% \( \alpha \)-HCH in their diet for 3 weeks, there was a marked increase in mitotic rate in the liver parenchymal cells. Nearly one-third of the cells were tetraploid, and several cells had marker chromosomes. The cytogenetic changes observed were qualitatively similar to those seen in regenerating liver after partial hepatectomy (Hitachi et al., 1975). Chromosome breaks and gaps were observed in
metaphase preparations of bone-marrow cells from rats injected with 0.01-10 mM/kg bw β-HCH solution (Shimazu et al., 1976).

Lindane caused a slight increase in the frequencies of chromatid gaps and breaks in Chinese hamster fibroblasts in vitro (Ishidate & Odashima, 1977).

Concentrations of 5-10 μg/ml lindane inhibited cell division in human peripheral blood lymphocytes in vitro and caused a concentration-related increase in the frequency of chromatid breaks (Tzoneva-Maneva et al., 1971). In SV40-transformed human fibroblasts (VA-4), 1 or 1000 μM lindane failed to induce unscheduled DNA synthesis either in the presence or absence of a rat liver microsomal activation system (Ahmed et al., 1977).

(b) Humans

The toxicity of lindane to humans has been reviewed; therapeutic doses used in the treatment of scabies have been found to have neurotoxic and other effects (e.g., nausea, convulsions, cyanosis) (Solomon et al., 1977). Ingestion of large (unspecified) doses has led to muscle and kidney necrosis and, in one case, to pancreatitis (Munk & Nantel, 1977). Digestive tract inflammation, haemorrhage, coma and death have been reported after lindane poisoning (Herbst & Bodenstein, 1972).

Cirrhosis and chronic hepatitis were observed in liver biopsies from 8 workers heavily exposed to lindane, DDT or both for periods ranging from 5-13 years (Schüttmann, 1968).

The occurrence of HCH isomers in human tissues is discussed in section 2.2 (f). Trace amounts of HCH have been detected in human milk and blood (Curley & Kimbrough, 1969; D'Ercole et al., 1976; Grasso et al., 1973), and transplacental passage of HCH has been established (Curley et al., 1969; D'Ercole et al., 1976; Grasso et al., 1973).

In an 18-month-old infant fatally poisoned with lindane, about 350 mg/kg were found in the adipose tissue and 88 mg/kg in the liver (Joslin et al., 1958). Following the accidental ingestion of lindane by a 2½-year-old girl, 0.84 and 0.49 mg/l lindane were found in the serum after 2 and 4 hrs, respectively. Unchanged compound was found in the faeces; and several urinary metabolites, 2,4-dichloro-, 2,4,6-trichloro-, 2,3,5-trichloro-, 2,4,5-trichloro- and 2,3,4,6-tetrachlorophenols and 2,4-dichloromercapturic acid, were identified (Starr & Clifford, 1972).
3.3 Case reports and epidemiological studies

Approximately 30 cases of aplastic anaemia associated with exposure to HCH or lindane have been reported (Hans, 1976; Loge, 1965; West, 1967; Woodliff et al., 1966). At least 10 further cases were associated with exposure to HCH or lindane in combination with other compounds, mainly DDT (Hans, 1976; Woodliff et al., 1966).

Aplastic anaemia has also been reported in people exposed to HCH or lindane in consumer products: 2 were exposed to lindane by frequent treatment of dogs with products containing the compound, and at least 3 were exposed to lindane as a result of vaporization in their houses (Hans, 1976; Loge, 1965; West, 1967; Woodliff et al., 1966).

A case of acute myelomonocytic leukaemia, secondary to aplastic anaemia, was associated with dermal exposure to a lindane/toxaphene mixture (US Environmental Protection Agency, 1978).

The simultaneous development of acute paramyeloblastic leukaemia in two cousins, both aged 20, exposed at the same time to lindane while unloading sacks of insecticide, has also been reported (Jedlicka et al., 1958) [The Working Group noted that constitutional, hereditary, familial and other common exposure factors may, or may not, have played a role in the etiology of these two cases of leukaemia].

An increased incidence of lung cancer was reported between 1970 and 1975 in 285 workers who had applied various pesticides, including HCH, in agricultural settings; their ages ranged from 36–74 years (Barthel, 1976) [The Working Group noted that since exposure may have been to compounds other than HCH or in addition to HCH, no evaluation of the carcinogenicity of HCH could be made on the basis of this study. However, the increased incidence was too high to be accounted for by smoking alone].

4. Summary of Data Reported and Evaluation

4.1 Experimental data

α-HCH was tested in several experiments in mice by oral administration: it produced benign and malignant liver tumours in animals of both sexes; a treatment of 16 weeks was sufficient to produce tumours. Two feeding experiments in rats, one of which suggested a carcinogenic effect on the liver, were considered to be inadequate.

β-HCH was tested in four experiments in mice by oral administration: two were inadequate, and another was inadequately reported but suggested hepatocarcinogenicity; in the fourth study, β-HCH induced benign and malignant liver tumours in animals of both sexes. Two feeding experiments
in rats were considered to be inadequate.

Lindane was tested in six experiments in mice by oral administration: it produced benign and malignant liver tumours in animals of both sexes in two experiments, one of which involved only small groups of animals. The results of a third experiment suggested hepatocarcinogenicity but were inadequately reported. The results of a fourth experiment also suggested hepatocarcinogenicity but were considered inadequate because of the low number of control animals used. The other experiments were considered inadequate for an evaluation of carcinogenicity. Lindane was also tested in three feeding studies in rats: two were considered inadequate; in the other a slight excess of thyroid tumours was observed in females. Lindane was tested inadequately in mice by skin application and by subcutaneous and intraperitoneal administration.

Experimental data on the long-term effects of the δ- and ε-isomers were considered to be inadequate.

Technical HCH was tested in three experiments in mice by oral administration, producing liver tumours. A feeding experiment in rats was considered to be inadequate.

Lindane is embryotoxic. α- and β-HCH and lindane, when tested individually and/or as a mixture, were not mutagenic in bacteria, yeast or Drosophila. Lindane induces chromosome aberrations, polyploidy and mitotic arrest in a number of plant systems. It also induced chromatid breaks in human lymphocytes in vitro.

4.2 Human data

Several case reports indicate a relationship between exposure to HCH or lindane and the occurrence of aplastic anaemia. Two cases of acute myeloid-type leukaemia in cousins exposed to lindane and one case of acute myelomonocytic leukaemia, secondary to aplastic anaemia, that was associated with dermal exposure to a lindane/toxaphene mixture have also been reported.

The only epidemiological study related to possible carcinogenic effects of HCH or lindane in humans involved exposure to many pesticides; the Working Group was thus unable to draw any conclusion specific to HCH or lindane.

The extensive production of HCH and lindane and their use in veterinary, agricultural and consumer products since the early 1950s indicate that widespread human exposure occurs. This is confirmed by many reports of their occurrence in the general environment and by reports of their presence in body fluids and tissues, both in the general population and in exposed workers.
4.3 Evaluation

There is sufficient evidence that α-HCH, lindane and technical HCH are carcinogenic in mice; there is limited evidence that β-HCH is carcinogenic in mice.
5. References


HEXACHLOROCYCLOHEXANE


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HEXACHLOROPHENE

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 70-30-4
Chem. Abstr. Name: 2,2'-Methylenebis(3,4,6-trichlorophenol)
Synonyms: Bis(2-hydroxy-3,5,6-trichlorophenyl)methane; bis(3,5,6-trichloro-2-hydroxyphenyl)methane; 2,2'-dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane; 2,2'-dihydroxy-3,5,6,3',5',6'-hexachlorodiphenylmethane; 2,2',3,3',5,5'-hexachloro-6,6'-dihydroxydiphenylmethane; hexachloroefen; hexachlorophane; hexachlorophen; hexophene; trichlorophene

Trade names: Acigena; Almederm; AT 7; AT-17; B32; Bilevon; Compound G-11; Cotofilm; Dermadex; Exofene; Fostril; G 11; G-11, Gamophen; Gamophe; G-Eleven; Germa-Medica; Hexabalm; Hexafen; Hexide; Hexosan; Isobac 20; Nabac; Neosept V; Phisodan; pHisoHex; Ritosept; Septisol; Septofen; Steral; Steraskin; Surgi-Cen; Surgi-Cin; Surofene; Tersaseptic; Turgex

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{Cl} & \quad \text{OH} & \quad \text{HO} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]

C\text{C}_{13}\text{H}_{6}\text{O}_{2}\text{Cl}_{6} \quad \text{Mol. wt: 406.9}

1.3 Chemical and physical properties of the pure substance

(a) Description: White, free-flowing powder (Hawley, 1977)

(b) Melting-point: 166-167°C (Grasselli & Ritchey, 1975)

(c) Spectroscopy data: Infra-red and nuclear magnetic resonance spectral data have been tabulated (Grasselli & Ritchey, 1975).
(d) **Solubility:** Practically insoluble in water; soluble in ethanol, acetone, diethyl ether, chloroform, polypropylene glycol, polyethylene glycol, olive oil, cottonseed oil and dilute alkali (Windholz, 1976)

(e) **Reactivity:** Forms salts with alkali (Windholz, 1976)

1.4 **Technical products and impurities**

Hexachlorophene available in the US contains 98.0-100.5% of the pure chemical, calculated on a dry basis. Hexachlorophene produced from 2,4,5-trichlorophenol contains less than 15 μg/kg 2,3,7,8-tetrachlorodibenzo-para-dioxin (see IARC, 1977).

Hexachlorophene is available in the US as a detergent lotion containing 3% active ingredient and as a liquid soap containing 0.25% of the chemical (US Pharmacopeial Convention, Inc., 1975). The monosodium salt of hexachlorophene is available as a liquid soil fungicide containing 20% of the salt.

2. **Production, Use, Occurrence and Analysis**

2.1 **Production and use**

(a) **Production**

The preparation of hexachlorophene was first reported in 1941, by the reaction of 2,4,5-trichlorophenol with formaldehyde (Gump, 1941); this is the method used currently for its production (Gump et al., 1957).

Commercial production of this chemical in the US was first reported in 1951 (US Tariff Commission, 1952). Only one company reported production of an undisclosed amount in 1976 (see preamble, p. 16) (US International Trade Commission, 1977).

It is produced in western Europe, but there has been no production of hexachlorophene in Japan since 1972. Minor quantities of a product containing 3% hexachlorophene are imported to Japan from the US.

(b) **Use**

The principal use of hexachlorophene has been in the manufacture of germicidal soaps; it is also used as a topical anti-infective agent for humans and as an anthelminthic in veterinary medicine (Windholz, 1976). The monosodium salt is used as a broad-spectrum soil fungicide (Berg, 1978); it is also used widely as a disinfectant, particularly for hospital equipment.
Hexachlorophene has been used extensively as a soap additive, particularly for deodorant soaps, because trace quantities are retained on the skin after washing with a soap or detergent containing it, imparting a bacteriostatic effect (Klarmann, 1963; Ryer, 1969).

On 27 September 1972, the US Food and Drug Administration (FDA) issued revised rules and regulations for the production, sale and use of drug and cosmetic products containing hexachlorophene. Under this order, infant powders containing more than 0.75% of the chemical were recalled by the manufacturers. All other products for infant use containing more than 0.75% hexachlorophene were made available only by prescription. Nonprescription drugs and cosmetic products containing 0.75% or less of the chemical were not recalled, but future production and shipment were banned. New labels for hexachlorophene-containing products were required to warn against its use on burned or denuded skin, or on any mucous membranes (Anon., 1972; US Food & Drug Administration, 1972). Drug products formerly sold on a nonprescription (over-the-counter) basis are permitted to be sold as prescription drugs only after approval by the FDA of new drug applications proving safety and efficacy. These are approved only for surgical scrubbing and handwashing for controlled outbreaks of certain infections. Of 20 such new drug applications filed in 1972, 7 were reported to be still under evaluation by the FDA in February 1978 (Anon., 1978a). Hexachlorophene is permitted to be used as a preservative in drug and cosmetic products only at levels up to 0.1% (US Food & Drug Administration, 1972).

In April 1977, there were 54 registrants of 110 products containing hexachlorophene which are regulated by the US Environmental Protection Agency (1977); most are believed to be disinfectant products.

The sodium salt is used as a seed-treatment fungicide; an estimated 45 thousand kg of hexachlorophene were used for this purpose in 1975. In 1977, 3.2 thousand kg were used to treat cottonseed in California (California Department of Food & Agriculture, 1978).

A tolerance of 0.05 mg/kg is established for hexachlorophene in or on cottonseed, resulting from use of the monosodium salt. The technical-grade hexachlorophene used in the formulation must not contain more than 0.1 mg/kg 2,3,7,8-tetrachlorodibenzo-para-dioxin (US Environmental Protection Agency, 1976).

No data on use patterns in Europe or Japan were available.
2.2 Occurrence

Hexachlorophene is not known to occur as a natural product.

(a) Water and sediments

Hexachlorophene has been found in two samples of finished drinking-water (Shackelford & Keith, 1976); in upstream and downstream water from 2 sewage treatment plants, at levels of 3.2-24 µg/l and 16.4-44.3 µg/l, respectively (Sims & Pfaender, 1975); in the influent and effluent water of 3 sewage plants at levels of 20-31 and 6-12 µg/l, respectively; and in a river, at levels of 0.01-0.1 µg/l (Buhler et al., 1973).

Hexachlorophene has been detected in the sediment of a creek at levels of 9.3-377 µg/kg and in marine organisms, at levels of 333-27,800 µg/kg (Sims & Pfaender, 1975).

(b) Humans

Hexachlorophene has been detected in human milk at levels of 0-9 µg/l (West et al., 1975).

In a study of the use of a 3% hexachlorophene solution as a body and hand soap, blood levels ranged from < 0.005-0.38 mg/l blood, compared with a mean baseline concentration in 30 control people of 0.02 mg/l blood. After prolonged use of a soap containing 0.75% hexachlorophene, levels ranged from 0.02-0.14 mg/l blood; and use of a mouthwash containing 0.5% hexachlorophene for 3 weeks produced levels of 0.02-0.12 mg/l blood. In a study of randomly selected hospital patients, hexachlorophene blood levels ranged from 0-0.12 mg/l, with a mean level of 0.03 mg/l (Butcher et al., 1973).

Samples of adipose tissue obtained from the neck during routine surgery contained a mean concentration of 0.01 mg/kg tissue; abdominal fat obtained at autopsy contained 0.04 mg/kg tissue (Ulsamer et al., 1973). In another study, hexachlorophene was detected at levels of 0-80 µg/kg adipose tissue (Shafik, 1973).

(c) Occupational exposure

In a controlled study of hospital operating-room personnel who scrubbed with hexachlorophene soaps or detergents, the mean hexachlorophene levels in the blood were 0.07 or 0.22 mg/l, respectively. Follow-up samples, taken 2-3 weeks after termination of hexachlorophene exposure, indicated a rapid return to the initial background level (Butcher et al., 1973).
A 1974 National Occupational Hazard Survey estimated that exposure to hexachlorophene was primarily in hospitals, sanitariums, convalescent homes and rest homes (National Institute for Occupational Safety & Health, 1977).

2.3 Analysis

Schwedt (1973) has reviewed methods for extracting hexachlorophene from soaps, powders, creams and cosmetic sprays and its detection and determination at levels of 0.05-1.3% (with a precision of 0.01-0.05%) by thin-layer and gas chromatography and ultra-violet spectrometry.

Methods used for the analysis of hexachlorophene in environmental samples are listed in Table 1.

Collaborative studies have been carried out with the method of the Association of Official Analytical Chemists (Sheppard & Wilson, 1975; Wilson, 1974). Tentative methods using high-performance liquid chromatography of hexachlorophene or its derivatives have been described (Carr, 1974; Porcaro & Shubiak, 1972); and thin-layer chromatography can also be used to determine hexachlorophene in formulations (Amin & Jakobs, 1977).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Rat: Groups of 24 male and 24 female Fischer 344 rats, 52 days old, were fed diets containing 0, 17, 50 or 150 mg/kg diet hexachlorophene (98% minimum purity) for 105-106 weeks. Of male rats, 79% of the high-dose group, 88% of the mid-dose group, 67% of the low-dose group and 88% of controls were still alive at the end of the study. In females, the respective percentages were 75%, 79%, 50% and 63%. No increased incidence of tumours was observed compared with that in controls (National Cancer Institute, 1978).

1The Working Group was aware of a study in progress in rats to assess the carcinogenicity of hexachlorophene by oral administration (IARC, 1978).
### Table 1. Methods for the Analysis of Hexachlorophene

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Extraction/Clean-up</th>
<th>Detection</th>
<th>Limit of Detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban drainage</td>
<td>Extract (ether), dry, concentrate, take up into benzene, acetylate</td>
<td>GC/ECD</td>
<td></td>
<td>Sims &amp; Pfaender (1975)</td>
</tr>
<tr>
<td>Sediments</td>
<td>Dry, extract (ether) in Soxhlet, acetylate</td>
<td>GC/ECD</td>
<td></td>
<td>Sims &amp; Pfaender (1975)</td>
</tr>
<tr>
<td>Food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peanuts and soya beans</td>
<td>Homogenize, extract (ether), centrifuge, recover ether, concentrate, add benzene-hexane, CC, methylate</td>
<td>GC/ECD</td>
<td>1 µg/kg</td>
<td>Van Auken &amp; Hulse (1977); Van Auken et al. (1977)</td>
</tr>
<tr>
<td>Biological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Extract (ether-absolute ethanol), add water, evaporate to dryness, acetylate, evaporate, take up into benzene</td>
<td>GC/ECD</td>
<td></td>
<td>Ulsamer (1972)</td>
</tr>
<tr>
<td>Organs</td>
<td>Homogenize (water), extract (chloroform-methanol), liquid/liquid partition, methylate</td>
<td>GC/ECD</td>
<td></td>
<td>Ulsamer (1972)</td>
</tr>
<tr>
<td>Human adipose tissue</td>
<td>Grind, extract (hexane), add caustic soda, mix, discard hexane layer, re-extract (hexane), discard, acidify, extract (ether), ethylate, transfer to hexane</td>
<td>GC/ECD</td>
<td>10 µg/kg</td>
<td>Shafik (1973)</td>
</tr>
<tr>
<td>Blood</td>
<td>Add citrate buffer pH5, extract (ether), concentrate to 1 ml, methylate, evaporate to dryness, take up into hexane, wash hexane with acid, dry hexane phase</td>
<td>GC/ECD</td>
<td></td>
<td>Ferry &amp; McQueen (1973)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
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<td>-------------</td>
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</tr>
<tr>
<td>Miscellaneous</td>
<td>Reflux sample (ethanol-hydrochloric acid), cool, add water, extract (chloroform), wash extracts (water), concentrate, CC</td>
<td>Spectrophotometry</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>Mix with ethanol, filtrate</td>
<td>TLC (many revelations)</td>
<td></td>
<td>Wilson (1975)</td>
</tr>
</tbody>
</table>

Abbreviations: CC - column chromatography; GC/ECD - gas chromatography/electron capture detection; TLC - thin-layer chromatography
(b) Skin application

Mouse: Hexachlorophene was applied to the dorsal skin of groups of 50 random-bred female Swiss mice twice a week for life, starting at 8 weeks of age, in doses of 0.02 ml of concentrations of 50, 25 and 5% in acetone, corresponding to 10, 5 and 1 mg hexachlorophene per application. A further group of 50 mice was used as controls [It was not specified whether they were untreated or given the solvent]. The treatment caused skin ulceration, necrosis and inflammation, as well as neurological symptoms. About 25% of treated animals at all dose levels died within 40 weeks of treatment, versus 5% of controls; 60 weeks after the start of treatment, 50-65% of treated animals had died, compared with 10% of controls. In the treated groups, tumours developed in 10/50 (15 tumours), 14/50 (17 tumours) and 15/50 (19 tumours) animals, respectively; 20/50 controls developed a total of 29 tumours. Among treated animals, only one benign skin papilloma developed. Lymphomas, lung adenomas, liver haemangiomas and other tumours occurred sporadically with similar frequencies in treated and experimental groups (Stenbäck, 1975) [The Working Group noted that lifespan was greatly reduced in all experimental groups].

3.2 Other relevant biological data

The toxicity of hexachlorophene in both experimental animals and humans has been reviewed recently (Kimbrough, 1976).

(a) Experimental systems

Toxic effects

The oral LD₅₀ of hexachlorophene in male rats is 66 mg/kg bw, in females 56 mg/kg bw and in weanling rats 120 mg/kg bw (Gaines et al., 1973); in suckling rats (10-days old), it is 9 mg/kg bw (Nieminen et al., 1973).

When rats were maintained on diets containing 400 mg/kg diet hexachlorophene, or given large dermal or oral doses, they exhibited neurotoxic symptoms which were characterized initially by a weakness in the hind legs; this has also been reported in mice, dogs, rabbits and monkeys (Kimbrough, 1974, 1976). The effect is at least partly reversible if the hexachlorophene-containing diet is replaced (Nakaue et al., 1973; de Jesus & Pleasure, 1973). Hexachlorophene induces a lesion in the white matter of brain and sciatic nerves, called status spongiosus, characterized by oedema and intramyelinic vacuolization at the interperiod line (Gaines et al., 1973; Kimbrough & Gaines, 1971; Pleasure et al., 1974).

Hexachlorophene inhibits rat liver mitochondrial oxidative phosphorylation (Caldwell et al., 1972).
Topical exposure of neonatal rats to 3% hexachlorophene solution caused reduced fertility in 7-month-old males, due to inability to ejaculate (Geller et al., 1978).

Embryotoxicity and teratogenicity

Placental transfer of hexachlorophene has been demonstrated in rats (Kennedy et al., 1977).

Administration of 500 mg/kg diet or 20-30 mg/kg bw/day by gavage to rats caused some malformations (angulated ribs, cleft palate, micro- and anophthalmia) and reduction in litter size (Gaines et al., 1973; Kennedy et al., 1975a, 1976; Oakley & Shepard, 1972). These dosages approached those that resulted in maternal death. A 45% suspension of hexachlorophene applied into the vagina of pregnant rats caused maternal toxicity and malformations in some offspring (hydrocephaly, micro- and anophthalmia, wavy ribs, urogenital defects) (Kimmel et al., 1974). In rabbits, an oral dose of 6 mg/kg bw/day caused a low frequency of rib malformations (Kennedy et al., 1975a). S.c. injection of 12.5 or 25 mg/kg bw/day hexachlorophene to mice on days 3-8, 7-12 or 11-17 of gestation caused foetal resorptions but no malformations (Majumdar et al., 1975).

A dose of 100 mg/kg diet hexachlorophene caused reduced survival in the F1 generation offspring of rats (Gaines et al., 1973). In another study, doses of up to 50 mg/kg diet failed to produce any effects in 3 generations of rats (Kennedy et al., 1975b). Hexachlorophene did not interfere with reproduction in hamsters (Alleva, 1973).

Absorption, distribution, excretion and metabolism

Hexachlorophene can be absorbed through the skin in rats (Nakaue & Buhler, 1976), especially when applied to skin lesions (Carroll et al., 1967).

Hexachlorophene administered orally to rats was recovered (80-90%) unchanged in the faeces within 10 days (Bjondahl & Isomaa, 1976); however, after i.p. administration, extensive biliary excretion (31-47% of the dose within 24 hrs) and enterohepatic circulation occurred (Edelson & McMullen, 1976; Gandolfi & Buhler, 1974). The principal metabolite in bile was the monoglucuronide. Much of the unchanged hexachlorophene in the faeces is probably a result of intestinal bacterial hydrolysis of the conjugate: when the bile duct was ligated, 55% of the dose was excreted as the monoglucuronide in the urine (Gandolfi & Buhler, 1974). It does not accumulate extensively in the brain at doses which induce lesions (Ulsamer et al., 1975).

Hexachlorophene is excreted in the milk of rats (Kennedy et al., 1977).
Mutagenicity and other related short-term tests

Hexachlorophene did not induce reverse mutations in *Salmonella typhimurium* G46 in a host-mediated assay using male albino rats that received 100 or 200 mg/kg diet for 90 days (Arnold et al., 1975). Dominant lethal tests with male mice treated with single i.p. injections of 2.5 or 5.0 mg/kg bw hexachlorophene were negative (Kennedy et al., 1975c).

In human peripheral blood lymphocytes treated with hexachlorophene in vitro at concentrations ranging from 1-200 mg/l and with treatment times extending from 6-21 hrs, there was no evidence of increased chromosome aberrations; however, mitosis was suppressed with concentrations as low as 40 mg/l applied for 6 hrs, and this effect was found to be both concentration- and treatment time-dependent (Vig, 1972).

(b) Humans

Poisoning by hexachlorophene, for example, by its liberal application to patients with burns or to infants, leads to circulatory failure, body temperature fluctuations and central nervous symptoms, including headache, twitching, convulsions and death (Kimbrough, 1976). Some infants treated with high doses of hexachlorophene have died; premature infants and newborns appear to be most susceptible. The spongiform brain changes seen in animals were also observed in infants who died from overexposure to hexachlorophene (Powell et al., 1973).

In newborn infants exposed to soap containing hexachlorophene, its half-life ranged from 6-44 hrs; the time of peak blood concentrations following a bath ranged from 6-10 hrs. One infant has a blood concentration of 4.3 µg/ml and developed symptoms comparable with hexachlorophene-induced toxicity (Tyrala et al., 1977).

Halling (1977, 1979) reported severe malformations in children of hospital personnel who had been exposed to hexachlorophene soap during pregnancy as compared with children of a group of unexposed personnel: 4 severe and 6 slight malformations were observed in 82 babies born to the exposed group versus 1 slight malformation in 46 babies born to mothers not exposed to hexachlorophene. The occurrence of chlorinated, so-called 'predioxins' in the soap was discussed. In a more recent report, 25 severe malformations, such as eye and central nervous system defects, were reported among 460 live births to these women, compared with no severe malformations seen in a control group of 233 live births from unexposed mothers. Minor malformations were also more frequent in the hexachlorophene exposed group (Anon., 1978b; Hay, 1978).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.
4. Summary of Data Reported and Evaluation

4.1 Experimental data

Hexachlorophene was tested in one experiment in rats by oral administration; it had no carcinogenic effect. It was inadequately tested in one experiment in mice by skin application.

Hexachlorophene is embryotoxic and produces some teratogenic effects. It was not mutagenic in Salmonella typhimurium and was negative in a dominant lethal assay in male mice. Cytogenetic tests with cultured human lymphocytes were also negative.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

Malformations have been reported in children born to mothers repeatedly exposed to hexachlorophene.

The extensive production and use, particularly in germicidal soap, of hexachlorophene over the past several decades indicate that widespread human exposure occurs in both the general and the working environment. This is confirmed by its presence in human body fluids. Episodes of intoxication have also been reported.

4.3 Evaluation

The available data do not allow an evaluation of the carcinogenicity of hexachlorophene to be made.

Subsequent to the meeting of the Working Group, the Secretariat became aware of completed studies on the carcinogenicity of hexachlorophene in which no carcinogenic effects were observed in mice or rats following its oral administration or in mice following exposure prenatally or via the mother's milk or following its s.c. injection to newborn mice (Rudali & Assa, 1978).
5. References

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HEXACHLOROPHENE


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METHOXYCHLOR

This substance was considered by a previous IARC Working Group, in October 1973 (IARC, 1974). Since that time new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.

A recent review on methoxychlor is available (Mercier, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Name: 1,1'- (2,2,2-Trichloroethylidene)bis (4-methoxybenzene)
Synonyms: 1,1-Bis(para-methoxyphenyl)-2,2, 2-trichloroethane; 2,2-bis(para-methoxyphenyl)-1,1,1-trichloroethane; 2,2-di-para-anisyl-1,1,1-trichloroethane; para,para'-dimethoxy diphenyltrichloroethane; dimethoxy-DDT; dimethoxy-DT; di(para-methoxyphenyl)trichloromethyl methane; DMDT; para,para'-DMDT; para, para'-methoxychlor; methoxy-DDT; 1,1,1-trichloro-2,2-bis(para-methoxyphenyl)ethane; 1,1,1-trichloro-2,2-di(4-methoxyphenyl)ethane
Trade names: Maralate; Marlrate; Metox

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{C}_{10}\text{H}_{15}\text{Cl}_{3}\text{O}_{2} & \quad \text{Mol. wt: 345.7}
\end{align*}
\]
1.3 Chemical and physical properties of the pure substance
From Spencer (1973), unless otherwise specified
(a) **Description:** Colourless crystals
(b) **Melting-point:** 89°C
(c) **Spectroscopy data:** λ max 275, 270, 238 and 230 nm (E l 1 = 183, 241, 458 and 575) in benzene; infra-red and nuclear magnetic resonance spectral data have also been tabulated (Grasselli & Ritchey, 1975).
(d) **Solubility:** Insoluble in water (0.1 mg/l at 25°C); moderately soluble in ethanol and petroleum oils; readily soluble in aromatic solvents
(e) **Stability:** Resistant to oxidation
(f) **Reactivity:** More stable than DDT to dehydrochlorination in alcoholic alkali; susceptible to catalytic dehydrochlorination by heavy metal catalysts

1.4 Technical products and impurities
Methoxychlor is available commercially in the US as a technical grade containing 88% of the pure chemical and 12% of isomers and other reaction products. 3,6,11,14-Tetramethoxydibenzo(g~p)chrysene is one of the impurities present in commercial samples (Grant *et al.*, 1976).

In the US, formulations of methoxychlor for various uses include wettable powders, emulsifiable concentrates, oil solutions, aerosols and dusts (Berg, 1978).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) **Production**
Methoxychlor was first synthesized in 1893, by the reaction of chloral hydrate with anisole in the presence of acetic acid and sulphuric acid (Prager *et al.*, 1918). It is produced commercially by the condensation of anisole with chloral in the presence of sulphuric acid (Windholz, 1976).
Commercial production of methoxychlor in the US was first reported in 1946 (US Tariff Commission, 1948). In 1975, 3 companies in the US produced a total of 2.5 million kg (US International Trade Commission, 1977a); 2 companies produced an undisclosed amount in 1976 (see pre-amble, p. 16) (US International Trade Commission, 1977b).

No data on its production in Europe or Japan were available.

(b) Use

The only known use for methoxychlor is as an insecticide. It is approved in the US for use on 78 agricultural crops (including several types of seed), with restrictions on the use of treated seeds. Methoxychlor is also approved for use as an insecticide on beef cattle, dairy cattle, goats, sheep and swine and for spray treatment of barns, grain bins, mushroom houses and other agricultural premises (US Environmental Protection Agency, 1972a).

In 1974, 1.5 million kg methoxychlor were used in the US, as follows: home and garden applications, 30%; livestock and poultry, 15%; alfalfa, 10%; soya beans, 10%; forests, 10%; ornamental shrubs, 10%; deciduous fruits and nuts, 5%; and vegetables, 5%.

Domestic use of methoxychlor as a substitute for DDT is increasing and is estimated to be 4.5 million kg a year in the US (Safe Drinking Water Committee, 1977).

Residue tolerances on raw agricultural commodities range from 0 in milk and 2 mg/kg on stored grains treated after harvest to 100 mg/kg on alfalfa (US Environmental Protection Agency, 1972b).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to methoxychlor not exceed an 8-hr time-weighted average of 15 mg/m$^3$ in the working atmosphere in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977).

In March 1965, the Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues established a temporary acceptable daily intake for man of 0-0.1 mg/kg bw (WHO, 1975); this was confirmed in 1977 (FAO/WHO, 1978).

No data on its use in Europe or Japan were available.
2.2 Occurrence

Methoxychlor is not known to occur as a natural product.

(a) Water and sediments

The half-life of methoxychlor in water is about 46 days. No residues of methoxychlor were detected in 500 samples of finished drinking-water from the Mississippi and Missouri Rivers or in 101 water samples from Hawaii. No methoxychlor was found during a survey of the drinking-water in New Orleans (Safe Drinking Water Committee, 1977).

Methoxychlor has been detected in: (1) several rivers, at levels of 2.9-89.1 µg/l; (2) one lake, at levels of up to 0.1 g/l (surface) and of 0.13-175 mg/l (sediment); (3) the effluent water from a biological sewage treatment plant, at levels of up to 106 µg/l (Eurocop-Cost, 1976); (4) 2 samples of ground-water (Shackelford & Keith, 1976); (5) the inlet waters of Lake Utah, in concentrations of 0-5.2 µg/l (Bradshaw et al., 1972); (6) rural drinking-water supplies, at levels of 0-312 ng/l (Sandhu et al., 1978); (7) municipal water in 5 locations (Luczak et al., 1972, 1973); and (8) shallow, underground waters in some rural regions (Uminska et al., 1973).

In studies of water and sediment pollution, methoxychlor has been detected in surface water and in drainage ditch and streambed sediments in a farming area, at levels of 0-43 µg/l (Burns et al., 1975); it has been found in tributary streams and in tributary and ravine sediments of Lake Michigan, at levels of 2.9-89.1 ng/l and 0.19-175 µg/l, respectively (Schacht, 1974).

(b) Soil

Of 1729 cropland soil samples tested in the US National Soils Monitoring Program, only one contained methoxychlor, at a level of 0.28 mg/kg (Wiersma et al., 1972). It was detected in the surface soils of 31 apple orchards, at levels in the range of 0-4 µg/kg (Frank et al., 1976).

(c) Food and drink

In a continuing programme involving the monitoring of pesticide residues in food, levels of methoxychlor in foods were measured during the period 1965-1974 and an average daily intake of methoxychlor was calculated. For the period 1965-1970, the average daily intake was 0.5 µg/day; this level dropped to 0.1134 µg/day in 1973 and rose to 0.7974 µg/day (US Food & Drug Administration, 1975, 1977).

Methoxychlor has also been detected in: (1) samples of liver pâté, at maximum concentrations of 0.27 mg/kg (De Battistis & Lucisano, 1973);
(2) fruit and vegetables (Polizu & Serban, 1973); (3) milk products, at maximum concentrations of 0.089 mg/l (Laskowski & Bierska, 1976); (4) meat and milk (Knoeppler, 1976); (5) cherries, at residue levels of more than 4 mg/kg (Haefner, 1976); and (6) lard, after storage for 17 months (Dzilinski & Raslawski, 1974).

Levels of pesticides (including methoxychlor) in specific crops in Finland have been tabulated by Siltanen & Rosenberg (1976).

(d) Animals

Methoxychlor has been detected in: (1) fat samples from raccoons, at levels of 0.16-36.82 mg/kg (Bigler et al., 1975; Nalley et al., 1975); (2) 61 frogs (Jaskoski & Kinders, 1974); (3) goldeye fish muscle tissue, at levels of < 0.01-1.5 mg/kg (Fredeen et al., 1975); (4) 2 lake fish, at levels of 56 and 62 µg/kg (Bradshaw et al., 1972); and (5) the edible portions of 5 species of lake fish, at levels of 0-0.1 mg/kg (wet-weight basis) (Schacht, 1974).

(e) Occupational exposure

Methoxychlor has been detected in the blood of agricultural workers (Kontek et al., 1976).

(f) Other

Methoxychlor has been detected in the following poultry feeds: soya bean meal (2-53 µg/kg); corn meal (91-151 µg/kg); alfalfa meal (7-1947 µg/kg); fish meal (15-232 µg/kg); and fats (91-151 µg/kg) (Waldron & Naber, 1974). Extensive tables have been published on the levels of pesticides, including methoxychlor, in over 9000 samples of animal feed (Maletto & Mussa, 1975).

Sixty days after spray application of 2.24 kg/ha methoxychlor, the residue level on pine branches was 4.63 mg/kg (Sundaram, 1977). Residues were also detected on four Dutch elm trees at levels of 50-955 mg/kg (Sundaram, 1976).

Methoxychlor has been detected in raw tobacco (Thurm, 1974) and in finished tobacco products (Thurm & Fensterer, 1972).

2.3 Analysis

Methods used for the analysis of methoxychlor in environmental samples are listed in Table 1.

Other methods for the separation of various pesticides include gel-permeation chromatography (Johnson et al., 1976); reverse-phase liquid chromatography, with a detection limit of 10 ng/sample (Seiber,
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Powders</td>
<td>Extract (carbon disulphide)</td>
<td>IR</td>
<td></td>
<td>US Environmental Protection Agency (1976)</td>
</tr>
<tr>
<td></td>
<td>Powders Extract (toluene), treat with sodium biphenyl</td>
<td>Titration (Vohlard)</td>
<td></td>
<td>Pease (1975)</td>
</tr>
<tr>
<td></td>
<td>Extract (toluene)</td>
<td>TLC (revelation: silver nitrate-ultra-violet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>Extract (benzene), TLC, elute from plate</td>
<td>Polarography</td>
<td></td>
<td>Maultz (1975)</td>
</tr>
<tr>
<td></td>
<td>Extract (hexane)</td>
<td>GC/ECD</td>
<td>1 µg/kg</td>
<td>Solomon &amp; Lockhart (1977)</td>
</tr>
<tr>
<td>Sediments</td>
<td>Extract (acetone), double CC</td>
<td>TLC (revelation: silver nitrate-ultra-violet)</td>
<td>25 µg/kg</td>
<td>Taylor et al. (1975)</td>
</tr>
<tr>
<td>Food &amp; drink</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit</td>
<td>Extract (benzene), evaporate, dissolve in petroleum ether, liquid/liquid partition, remove solvent, treat with potassium hydroxide, extract (petroleum ether), wash (ethanol), remove solvent, treat with sulphuric acid</td>
<td>Spectrophotometry (550 nm)</td>
<td></td>
<td>Horwitz (1965)</td>
</tr>
<tr>
<td>Fruit, vegetables, silage, dairy products</td>
<td>Extract (acetonitrile or aqueous acetonitrile), liquid/liquid partition, CC</td>
<td>GC/ECD, TLC &amp; PC 0.005 µg on (revelation: silver TLC plate nitrate-ultra-violet)</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
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<tr>
<td>Fish</td>
<td>Extract (hexane), defat by freezing, CC</td>
<td>GC/ECD</td>
<td>10 μg/kg</td>
<td>Solomon &amp; Lockhard (1977)</td>
</tr>
<tr>
<td>Raw sugar &amp; sugar products</td>
<td>Extract (petroleum ether-acetone), CC</td>
<td>GC/ECD</td>
<td>0.15 mg/kg</td>
<td>Kubacki &amp; Kasprzyczek (1972)</td>
</tr>
<tr>
<td>Margarine &amp; butter</td>
<td>Extract (petroleum ether), liquid/liquid partition, CC</td>
<td>GC/ECD</td>
<td></td>
<td>Kubacki et al. (1974)</td>
</tr>
<tr>
<td>Beer and hops</td>
<td>Beer: extract (petroleum ether-acetone); hops: extract (petroleum ether), CC of appropriate extract</td>
<td>GC/ECD</td>
<td>25.8 pg/sample</td>
<td>Lipowska et al. (1972)</td>
</tr>
<tr>
<td>Apples, potatoes and dry feed</td>
<td>Extract (naphtha ether), steam distill, CC</td>
<td>GC/ECD</td>
<td></td>
<td>Lewandowski et al. (1975)</td>
</tr>
<tr>
<td>Fruit</td>
<td>Extract (chloroform), remove solvent, redissolve (petroleum ether), liquid/liquid partition, CC</td>
<td>TLC (revelation: silver nitrate-ultra-violet)</td>
<td>0.4 mg/kg</td>
<td>Ciwerniewska (1973)</td>
</tr>
<tr>
<td>Animal fat</td>
<td>Homogenize (anhydrous sodium sulphate), extract (petroleum ether), CC</td>
<td>TLC (revelation: silver nitrate-ultra-violet)</td>
<td></td>
<td>Batista (1974)</td>
</tr>
</tbody>
</table>

Abbreviations: IR - infra-red spectrometry; GC/FID - gas chromatography/flame ionization detection; TLC - thin-layer chromatography; CC - column chromatography; ECD - electron capture detection; PC - paper chromatography
Gas chromatography has been used to determine methoxychlor in formulations (Sundaram, 1975) and in the tissues of chickens fed 7 chlorinated hydrocarbon insecticides at low levels (Onley et al., 1975).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 50 male and 50 female 5-7-week-old B6C3Fl hybrid mice were fed technical-grade methoxychlor (95% minimum purity) in the diet. Initially, high-dose animals received 2800 mg/kg diet for males and 1500 mg/kg diet for females, and low-dose animals received 1400 mg/kg diet for males and 750 mg/kg diet for females. After 1 week these doses were increased to 3500 mg/kg diet and 2000 mg/kg diet for high-dose groups and 1750 and 1000 mg/kg diet for low-dose groups; animals were maintained on these diets for 77 weeks, followed by 14-15 weeks on methoxychlor-free diets. The measured, time-weighted, average doses were 1746 (low dose) and 3491 (high dose) mg/kg diet for males and 997 (low dose) and 1994 (high dose) mg/kg diet for females. Groups of 20 male and 20 female mice served as matched controls and were maintained on methoxychlor-free diets for 92 weeks. Survival was reduced in male animals: 69% of the high-dose, 58% of the low-dose and 45% of control animals survived to 81 weeks. In females, survival to 92 weeks was 98% of high-dose, 90% of low-dose and 85% of control animals. In necropsied male mice, the numbers of tumour-bearing animals were 3/12 controls compared with 5/44 in the low-dose group and 9/47 in the high-dose group. In necropsied female mice, the respective numbers of tumour-bearing animals were 3/20 controls, 6/46 in the low-dose group and 3/50 in the high-dose group. Only 60-70% of the males and 28-32% of the females were examined histopathologically. Statistical analysis of the results revealed no obvious increase in the yield of benign and malignant neoplasms which could be ascribed to treatment with methoxychlor. There were no significant differences between test and control groups in the age at which tumours occurred (National Cancer Institute, 1978).

Rat: In a study by Nelson & Fitzhugh reported and reviewed by Lehman (1952, 1965) and by Deichmann et al. (1967), 6 groups of 24 Osborne-Mendel rats were fed diets containing 10-2000 mg/kg diet methoxychlor for 2 years, at which time 52% of the animals were still alive.
One rat fed 500 mg/kg diet and 5 rats fed 2000 mg/kg diet were found to have liver nodules, 4 of which were diagnosed as liver-cell adenomas. All but one liver-tumour-bearing animal survived for 2 years [The Working Group noted that the inaccessibility of the original data precluded any evaluation of this experiment].

Four groups of 25 male and 25 female rats (strain unspecified), about 4 weeks of age, were fed diets containing 0, 25, 200 or 1600 mg/kg diet methoxychlor for 2 years. No tumours were found in 13 controls which survived until the end of the experiment. One neurofibroma and 1 lung tumour were found in 13 survivors administered 25 mg/kg diet; 1 mammary tumour was found in 10 survivors administered 200 mg/kg diet; and 1 mammary tumour, 1 ovarian cystadenoma, 1 tumour of the abdominal wall, 1 adenocarcinoma of the pancreas and 1 epidermoid carcinoma were found in 16 survivors administered 1600 mg/kg diet (Hodge et al., 1952) [The increased number of tumours in animals fed 1600 mg/kg diet was considered by the authors to be coincidental; all of these tumours, with the exception of the adenocarcinoma of the pancreas, occur commonly in rats of that colony].

Two groups of 30 male and 30 female Osborne-Mendel rats were administered diets containing 0 or 80 mg/kg diet methoxychlor for 2 years. Malignant tumours were found in 5 treated females and in 9 control rats; benign tumours were present in 8 treated and in 6 control rats. The distribution of tumours by site and type was similar in the two groups (Radomski et al., 1965) [The Working Group noted the low dose used].

In a 27-month study, 30 male and 30 female Osborne-Mendel rats, about 4 weeks old, were administered 1000 mg/kg diet methoxychlor. At 18 months, 54/60 treated rats were still alive, compared with 48/60 controls. The incidence and distribution of benign and malignant tumours (mainly mammary and subcutaneous) were similar in treated (10 benign, 1 malignant) and control (14 benign, 1 malignant) groups (Deichmann et al., 1967).

Groups of 50 male and 50 female 5-7-week-old Osborne-Mendel rats were fed diets containing technical-grade methoxychlor of 95% minimum purity. High-dose animals received 720 mg/kg diet for 29 weeks in males and 1500 mg/kg diet for 55 weeks in females; the dose was increased to 1000 mg/kg diet for a further 29 weeks in males. For the remaining 16–17 weeks of treatment, males were fed 1000 mg/kg diet and females 1500 mg/kg diet for 4 weeks, followed by 1 week without treatment, and then the cycle was repeated. Low-dose animals received 360 mg/kg diet for 29 weeks and 500 mg/kg diet for 49 weeks for males and 750 mg/kg diet for 78 weeks for females. Low- and high-dose groups were maintained for a further 33–34 weeks on a methoxychlor-free diet. Time-weighted average doses were 448 and 750 mg/kg diet for males and females of the low-dose group and 845 and 1385 mg/kg diet for males and
females of the high-dose group. Groups of 20 animals of each sex were used as matched controls. At 100 weeks, 86% of high-dose males and 94% of high-dose females, 74% of low-dose males and 94% of low-dose females and 85% of male and 90% of female controls were still alive. Histopathology of all organ systems was performed on 82% or more of the animals entered into the study. The numbers of tumour-bearing animals (benign and malignant neoplasms) were, males: controls, 11/20; low dose, 23/44; high dose, 21/41; females: controls, 12/20; low dose, 30/47; high dose, 30/49. Haemangiosarcomas of the spleen in male rats were the only tumours that showed an increased incidence (1/20 controls, 6/44 in low dose, 2/42 in high dose). S.c. and abdominal haemangiosarcomas were observed in 3 low-dose males; although their incidence was not significantly increased, these tumours occur rarely in untreated Osborne-Mendel rats (National Cancer Institute, 1978).

(b) Skin application

Mouse: Two groups of 50 male and 50 female 2-4-month old C3H/Anf mice were painted weekly with either 0.1 or 10 mg/animal methoxychlor in 0.2 ml acetone (total dose, 0.1-10.4 mg/animal at the low level and 10-980 mg/animal at the high level). The mean survival time ranged from 342 days in females given the low dose to 450 days in the other groups. No skin tumours were observed (Hodge et al., 1966) [The Working Group noted the low dose used].

(c) Subcutaneous and/or intramuscular administration

Mouse: A group of 50 male and 50 female 2-4-month-old C3H/Anf mice were given single s.c. injections of 10 mg/animal methoxychlor in 0.02 ml trioctanoin. The mean survival times were 372 days in males and 419 days in females. No s.c. tumours were observed; histological observation was confined to 24 mice (Hodge et al., 1966) [The Working Group noted that a negative result obtained with a single s.c. injection is not an adequate basis for discounting carcinogenicity].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD$_{50}$ in rats is 5000-7000 mg/kg bw (Hodge et al., 1950), in mice, 2900 mg/kg bw and in monkeys, > 2500 mg/kg bw (Coulston & Serrone, 1969).

Dermal application of 2-3 ml of a 30% solution in dimethyl phthalate to rabbits on 5 days a week for 13 weeks produced paralysis of the forelimbs, some fatty degeneration of the liver and lesions of the central nervous system (Haag et al., 1950).
Dogs and pigs were fed 1000, 2000 or 4000 mg/kg diet methoxychlor for 2 years; and rats and monkeys were given 400, 1000 and 2500 mg/kg bw/day by gavage in 1% gum tragacanth for 3 and 6 months, respectively. In dogs, the 2 higher dose levels produced nervousness, apprehension, excess salivation, tremors and convulsions; in rats and monkeys, damage to the liver and small intestine was observed. Nephritis and mammary hyperplasia were observed in the pigs at autopsy (Stein, 1968).


Atrophy of the testes was observed in rats given 1% methoxychlor in their diet (Hodge et al., 1950). In rats given 100 or 200 mg/kg bw/day, arrested spermatogenesis was noticed after 70 consecutive days of treatment; and corpora lutea failed to develop in female rats treated with similar dosages for 14 days before and continuously after mating (Bal & Mungkornkarn, 1977).

Embryotoxicity and teratogenicity

It was reported in an abstract that methoxychlor did not affect the development of the chick embryo (Marlia, 1964). It was toxic to sea urchins and led to abnormal embryos (Bresch & Arendt, 1977).

Administration of 1000 mg/kg diet methoxychlor to pregnant rats caused early vaginal openings in their offspring; and both male and female offspring had reduced fertility when they attained maturity (Harris et al., 1974).

Oral administration of technical-grade and formulations of methoxychlor to pregnant rats reduced maternal body weight gain during gestation at all doses, ranging from 50-400 mg/kg bw. Both methoxychlor samples were foetotoxic at 200 and 400 mg/kg bw and produced a dose-related increase in the incidence of wavy ribs at 100, 200 and 400 mg/kg bw (Khera et al., 1978). No abortions were produced in pregnant cows given 10 mg/kg bw/day methoxychlor (Macklin & Ribelin, 1971).

Absorption, distribution, excretion and metabolism

In mice, 98% of labelled methoxychlor given orally was eliminated within 24 hrs. The main metabolic pathway was O-dealkylation to 2-(para-hydroxyphenyl)-2-(para-methoxyphenyl)-1,1,1-trichloroethane, 2,2-bis(para-hydroxyphenyl)-1,1,1-trichloroethane and its ethylene, and 4,4'-dihydroxybenzophenone which were excreted mainly as conjugates (Kapoor et al., 1970).
[\textsuperscript{14}C-l-phenyl]-Methoxychlor in oil emulsion given intravenously to rats at a dose of 1 mg in 0.5 ml emulsion was metabolized rapidly by the liver to unidentified hydrophilic products, which were excreted mainly in the faeces, by secretion from the liver into the bile, and to a lesser extent in the urine. Very little reabsorption occurred from the gastrointestinal tract (Weikel, 1957).

Weanling rats fed 500 mg/kg diet methoxychlor for 4-18 weeks stored 14-36 mg/kg in fat. Equilibrium was reached within 4 weeks, and methoxychlor disappeared from the fatty tissue within 2 weeks after end of exposure. Rats fed 100 mg/kg stored 1-7 mg/kg. No methoxychlor was stored in animals given 25 mg/kg diet, and no sex differences in storage were observed (Kunze et al., 1950).

Cluett et al. (1960) found residues in milk shortly after cows were sprayed with aqueous suspensions of methoxychlor. A maximum level of 0.1 mg/l was found 1 day after treatment, and detectable levels persisted for 1 week.

Mutagenicity and other related short-term tests

Technical-grade and purified methoxychlor were not mutagenic in plate tests with Salmonella typhimurium TA1535, TA1537, TA1538, TA98 and TA100, even with metabolic activation (Grant et al., 1976; Poole et al., 1977); however, 3,6,11,14-tetramethoxydibenzo(g,p)chrysene, one of the impurities present in commercial samples of methoxychlor, was mutagenic in strain TA98 in the presence of a liver microsomal activation system from phenobarbital-treated rats at concentrations of 100 and 200 µg/plate (Grant et al., 1976). Negative results were obtained with Escherichia coli WP2 and Saccharomyces cerevisiae D3 (Poole et al., 1977).

It was reported in an abstract that Phosan-plus (a mixture of methoxychlor and two organophosphates, dimethoate and malathion) did not induce reverse mutations in Schizosaccharomyces pombe (strain ade 7-C8) either in the presence or absence of a liver microsomal activation system (Degraeve et al., 1977).

Male mice that received a single i.p. injection of 30 µg/kg bw Phosan-plus showed no significant increase in chromosomal damage in their bone-marrow cells (polychromatic erythrocyte micronuclei, chromosome breakage) during the first 3 days after injection. In testis preparations from mice injected similarly, made at intervals ranging from 12 hrs to 44 days, a slight increase in chromosome breakage was detectable in spermatogonia after 24 and 48 hrs. However, there was no increase in sperm abnormalities 40 and 44 days after injection, and spermatocyte metaphases revealed no significant cytological damage. Dominant lethal tests were also negative (Degraeve et al., 1977).
METHOXYCHLOR

Injection of a 0.1% solution of methoxychlor did not induce sex-linked recessive lethals in male *Drosophila melanogaster* (Benes & Sram, 1969).

(b) **Humans**

The estimated fatal oral dose for humans is 450 g/subject (approximately 6 g/kg bw). An oral dose of 350 mg/subject/day (100 mg/kg diet) for 2 years produced no toxic symptoms, whereas 500 mg/kg diet (1750 mg/subject/day) produced unspecified tissue changes (American Conference of Governmental Industrial Hygienists, 1974).

3.3 **Case reports and epidemiological studies**

No data were available to the Working Group.

4. **Summary of Data Reported and Evaluation**

4.1 **Experimental data**

Methoxychlor was tested in one experiment in mice and in several experiments in rats by oral administration. The study in mice gave negative results. In at least four experiments in rats, dietary concentrations of 1000 mg/kg or more were used. A suggestion that it was hepatocarcinogenic, made in an earlier study that was inadequately reported, was not confirmed in three more recent experiments. Methoxychlor was inadequately tested in mice by repeated skin application and by subcutaneous injection of single doses.

Methoxychlor was not mutagenic in bacteria, yeast or *Drosophila melanogaster*. Cytogenic and dominant lethal tests in mice were also negative.

Methoxychlor is foetotoxic.

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1Subsequent to the meeting of the Working Group, the Secretariat became aware of a paper by Reuber (1979a), reporting the results of a study carried out in 1969 in which oral administration of methoxychlor induced testicular carcinomas in 27/51 male Balb/c mice, compared with 8/71 controls, but in none of the C3H mice tested. A further paper by Reuber (1979b) reported the results of a study carried out in 1951 in which oral administration of methoxychlor to Osborne-Mendel rats induced liver carcinomas.
4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and the widespread use of methoxychlor over the past several decades, together with the persistent nature of the compound, indicate that widespread human exposure occurs. This is confirmed by many reports of its occurrence in the general environment and by its presence in human blood.

4.3 Evaluation

The available data did not provide evidence that methoxychlor is carcinogenic in experimental animals.
5. References


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MIREX

This substance was considered by a previous IARC Working Group, in October 1973 (IARC, 1974). Since that time new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.

A review on mirex is available (French et al., 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: 1,1a,2,2,3,3a,4,5,5,5a,5b,6-Dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta(cd)pentalene

Synonyms: Dodecachlorooctahydro-1,3,4-methano-2H-cyclobuta(cd)pentalene; dodecachloropentacyclo(3.3.2.02,6.03,9.05,10) decane; ENT 25,719; hexachlorocyclopentadiene dimer; 1,2,3,4,5,5-hexachloro-1,3-cyclopentadiene dimer; perchlorodihomocubane; perchloropentacyclodecane; perchloropentacyclo(5.2.1.02,6.03,9.05,8)decane

Trade names: CG-1283; Dechlorane; Dechlorane 515; Dechlorane 4070; Dechlorane Plus; Dechlorane Plus 515; Ferriamicide; HRS 1276

1.2 Structural and molecular formulae and molecular weight

\[ \text{C}_{16}\text{Cl}_{12} \]

Mol. wt: 545.5
1.3 Chemical and physical properties of the pure substance

From Spencer (1973), unless otherwise specified

(a) **Description:** White crystals

(b) **Melting-point:** 485°C

(c) **Solubility:** Insoluble in water; soluble in dioxane (15.3%), xylene (14.3%), benzene (12.2%), carbon tetrachloride (7.2%) and methyl ethyl ketone (5.6%) (Windholz, 1976)

(d) **Volatility:** Vapour pressure is $3 \times 10^{-7}$ mm at 25°C (Hooker Chemical Corporation, 1968).

(e) **Stability:** Very stable at normal temperatures. Decomposes above 500°C to give hexachlorobenzene; hexachloropentadiene was found in small amounts in the thermal residue; the products identified from the vapour phase were carbon monoxide, carbon dioxide, hydrogen chloride, chlorine, carbon tetrachloride and phosgene (Holloman et al., 1975). Degrades in soil to give chlordecone (see monograph, p. 67) (Carlson et al., 1976). Its photodecomposition gives mainly photomirex (8-monohydromirex) (Hallett et al., 1978).

(f) **Reactivity:** Unaffected by sulphuric, nitric and hydrochloric acids

1.4 Technical products and impurities

A technical grade of mirex was formerly available in the US as a white crystalline solid in two average particle size ranges, 5-10 and 40-70 microns (Hooker Chemical Corporation, 1968). The term 'mirex' is also used in reference to a bait comprising corncob grits, soya bean oil and mirex (US Environmental Protection Agency, 1976a).

Insect bait formulations for aerial application, containing 0.3-0.5% mirex, and fire ant formulations containing 0.075-0.3% mirex have been used in the US (US Environmental Protection Agency, 1976a). Another formulation under consideration for limited interim use in the use is called 'Ferriamicide' and contains an amine and a metal salt, thus rendering the mirex unstable (Anon., 1977a).
Chlordecone has been found to be present in technical mirex at levels of up to 2.58 mg/kg and in mirex bait at levels of up to 0.25 mg/kg (US Environmental Protection Agency, 1976a).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Mirex was first synthesized in the mid-1940’s but was not offered for sale in commercial quantities in the US until 1958. It is made by the dimerization of hexachlorocyclopentadiene in the presence of aluminium chloride.

Only one company in the world is known to have manufactured technical-grade mirex, and that US company ceased production in 1967. Another company manufactured the insecticidal bait containing mirex, but discontinued this in 1975, when production of the bait was taken over by the state of Mississippi (Holden, 1976) until the supply of the chemical was exhausted. On the basis of reports of quantities used for fire ant control in the US (Anon., 1977b), it is estimated that at least 225 thousand kg of the chemical were produced in the US before production was stopped in 1967.

Mirex has been imported to the US from Brazil (Cookson, 1979).

(b) Use

The only known current use for mirex is as an insecticide, and by far the major application to date is believed to have been in the control of fire ants in the southern US, although it is reportedly also used against leaf cutters in South America, against harvester termites in South Africa, against Western harvester ants in the US, against the mealybug of pineapple in Hawaii, and has been investigated for use against yellow jacket wasps in the US (US Environmental Protection Agency, 1976a; Vaughn, 1971).

Under the name 'Dechlorane', mirex was marketed in the US in the period 1959-1972 as a stable, fire-retardant additive for use in thermoplastic, thermosetting and elastomeric resin systems. It was also reported to be useful in paper, paint, rubber, electrical, adhesive and textile applications (Hooker Chemical Corporation, 1968).

Mirex was introduced in the southern US in 1962 when the US Department of Agriculture initiated a 12-year programme to eradicate the fire ant. In the period 1962-1976, about 132 million acres (53.4 million hectares) in 10 states were treated with about 226 thousand kg
of mirex, initially at a rate of 4.2 g/ha, which was later reduced to 1.16 g/ha (Anon., 1977b). This programme was decelerated from 1971 when the US Environmental Protection Agency (EPA) issued a cancellation order for mirex. The order was appealed, and in 1972, following hearings, the EPA reinstated all mirex registrations and issued new guidelines calling for a modified spraying programme aimed at control, rather than eradication, of the ants. Hearings were reconvened in 1973, during which new evidence became available from the US National Cancer Institute (Holden, 1976). On 20 October 1976, a plan was announced by the EPA for phasing out the use of mirex for control of the fire ant in the southern US and suspension of the then pending hearings. The plan, developed by the state of Mississippi and the EPA, led to cessation of aerial application of the more concentrated forms of bait by the end of 1976 and of the dilute formulation by the end of 1977. Selective ground application of the dilute formulation was to be permitted through June 1978, at which time the use of the product was to be banned in the US, with the exception of continued use in Hawaii on pineapple until stocks on hand are exhausted (Holden, 1976; US Environmental Protection Agency, 1976a).

In December 1977, the state of Mississippi filed a request with the EPA for a specific exemption from the requirements of the law regulating the use of pesticides for a formulation of mirex called Ferriamicide, claiming the existence of emergency conditions. Approval was requested for aerial, ground and mound application of this formulation (Anon., 1977a). The requested exemption was granted in March 1978, but with the following limitations: application by ground equipment only; use to begin after 30 June 1978 and to end 1 July 1979; mound-to-mound application only on agricultural land and non-crop land other than parks and cemeteries; and not more than 5.3 thousand kg of mirex (2.7 million kg of bait) to be applied. Eight other states will be allowed to use Ferriamicide under the conditions granted to Mississippi (Anon., 1978a, b,c). The granting of this exemption by the EPA was challenged by the Environmental Defense Fund in a suit filed on 30 March 1978 (Anon., 1978d).

Tolerances for residues of mirex in food products in the US are as follows: 0.1 mg/kg in fat of meat from cattle, goats, hogs, horses, poultry and sheep, and in eggs and milk fat; and 0.01 mg/kg in or on all other raw agricultural commodities (US Environmental Protection Agency, 1976b).

No data on its use in Europe or Japan were available.

2.2 Occurrence

Mirex is not known to occur as a natural product. Its occurrence in the environment has been reviewed (Waters, 1976).
(a) Water

Mirex has been found in one sample of ground-water in the US (Shackelford & Keith, 1976). It has also been determined in rural drinking-water, at levels of 0-437 ng/l (Sandhu et al., 1978).

(b) Soil

Mirex has been detected in: (1) pineapple field soils, at levels of 10-18 µg/kg, 9 months after its application (Bevenue et al., 1975); (2) soil, at levels of 190-500 µg/kg, 12 years after application of 1 mg/kg; and (3) mud, at a level of 0.2 mg/kg, 5 years after the crash of an airplane carrying mirex bait; chlordecone was also found as a degradation product (Carlson et al., 1976).

(c) Food and drink

A survey of items in the human food chain showed that detectable residues of mirex were still present 1 year after a single aerial application of mirex bait, at levels of 1.7 g/acre (4.2 g/ha). The levels observed in various species were: (1) quail, 36 µg/kg; (2) bluegill fish, 18 µg/kg; (3) domestic chickens, 14 µg/kg; and (4) chicken eggs, 1 µg/kg. No mirex residues were detected in beef fat or milk after 1 year (Collins et al., 1974). Mirex has been detected at levels of 5-24 µg/kg in 9/77 composite samples of seafood, including oysters, crabs, shrimp, fish and fish products (Markin et al., 1974a).

Milk from cows grazed on pastures treated repeatedly with mirex contained residues of up to 0.3 µg/l (Hawthorne et al., 1974).

Residues of mirex were detected at levels of 0.01-1.71 mg/kg in soya bean, garden bean, sorghum and wheat seedlings when these were grown in prepared substrates containing 0.3-3.5 mg/kg mirex (de la Cruz & Rajanna, 1975).

(d) Animals

Mirex residues have been detected in pineapple-growing areas in: (1) birds, at levels of 0-10,400 µg/kg; (2) rodents, at levels of 5-9410 µg/kg; and (3) mongooses, at levels of 30-11,760 µg/kg (Bevenue et al., 1975).

Mirex residues have been detected in various wildlife samples including: (1) adipose tissue of deer, at levels of up to 0.3 mg/kg; (2) liver (up to 7.5 mg/kg) and fat (up to 104 mg/kg) from fish and birds; (3) brain tissue of birds, at levels of up to 1.8 mg/kg; (4) heart and muscle tissue of birds, at levels of up to 1.9 mg/kg; (5) insects, at levels of up to 1.2 mg/kg; and (6) earthworms, at levels of 0.03-0.076 mg/kg (Baetcke et al., 1972).
One year after a single aerial application of 0.6 g mirex/ha, residues were detected in 61 vertebrates, including: (1) mammals, at levels of 0.01-0.054 mg/kg; (2) birds, at levels of 0.012-3.6 mg/kg; (3) reptiles, at levels of 0-0.2 mg/kg; and (4) amphibians, at levels of 0.008-0.074 mg/kg (Collins et al., 1974). Seven months after a single aerial application of 0.85 g/acre (2.1 g/ha) mirex bait, residues were also detected in rodents (rats, mice, shrews) at levels of 0.01-1.9 mg/kg (Wolfe & Norment, 1973).

Mirex has been identified in seal fat (Ten Noever de Brauw et al., 1973); it has been detected in beef fat at levels of 0.001-0.125 mg/kg, with an average of 0.025 mg/kg (Ford et al., 1973).

As part of the US National Pesticides Monitoring Program, mirex was detected at levels of 0.01-1.66 mg/kg in starlings from 10/12 sites (Oberheu, 1972). Residues of mirex have been detected in the eggs of the following birds: (1) double-crested cormorants, at levels of 0.058-0.113 mg/kg (wet weight) (Zitko, 1976); (2) herring gulls, at levels of 0.028 mg/kg (wet weight) (Zitko, 1976); and (3) estuarine birds, at levels of 0-2.9 mg/kg (wet weight) (Ohlendorf et al., 1974).

Continuous exposure to low levels of mirex in feed (0.001-0.03 mg/kg) and in the soil of pens (0.03-0.25 mg/kg) resulted in residues at levels of 0.072-1.09 mg/kg in the abdominal fat of chicken within 8 weeks (Putnam et al., 1974). In a similar study, eggs of laying hens fed 0.01-1.06 mg/kg diet mirex showed residue levels of < 0.01-0.07 mg/kg within a week and levels of 0.01-2.03 mg/kg for the next 39 weeks. Residues in the tissues of hens fed 0.01 mg/kg and 1.06 mg/kg for 39 weeks were 0.01-0.3 mg/kg and 0.3-25 mg/kg, respectively (Woodham et al., 1975).

The milk of cattle fed 0.01 and 1 mg/kg diet mirex for 3 weeks showed residue levels of < 0.01-0.02 mg/l and 0.01-0.08 mg/l, respectively. Mirex was detected in the omental fat of these cows at levels of 0.06 and 1.87 mg/kg, respectively, and at levels of 0.08-2.52 mg/kg in the tissues of calves that received the milk (Bond et al., 1975).

Mirex residues have been detected in: (1) aquatic animals, at levels of 3-7 µg/kg (Bevenue et al., 1975); (2) crab and fish, at levels of < 0.01-0.12 mg/kg (Borthwick et al., 1974); (3) fish in streams, at levels of 0.01-1.02 mg/kg (Wolfe & Norment, 1973); (4) two lake fish, at levels of 0.02-0.05 mg/kg (Kaiser, 1974); (5) edible red crawfish, at levels of 0-0.07 mg/kg (Markin et al., 1972); (6) terrestrial and aquatic invertebrates 1 year after application of 2.5 kg/ha mirex bait, at levels of 0-0.092 mg/kg (Markin et al., 1974b); (7) fish and invertebrates, at levels of 0-1.02 mg/kg (Wolfe & Norment, 1973); and (8) catfish and aquatic organisms 16 months after application, at levels of 0.02-0.44 mg/kg (Collins et al., 1973).
Human exposure to mirex has been reviewed (US Environmental Protection Agency, 1976a).

Mirex has been detected in adipose tissue from 6 human subjects at levels of 0.16-5.94 mg/kg (Kutz et al., 1974). Average residues of mirex in the fat of residents of states where mirex is applied were 1.32 mg/kg fat (US Environmental Protection Agency, 1976a).

Traces of mirex have been detected in some human milk samples at 0.1-0.6 μg/kg (wet-weight basis) and 2.3-21.5 μg/kg (fat basis) (Mes et al., 1978).

2.3 Analysis

Methods used for the analysis of mirex in environmental samples are listed in Table 1.

Collaborative studies have been carried out to evaluate mirex in natural samples (Krause, 1973).

Other analytical methods to isolate and identify mirex include gel-permeation chromatography (Johnson et al., 1976) and gas chromatography/Coulson electrolytic conductivity detection (Su & Price, 1973). Mirex can be analysed among polychlorobiphenyls by gas chromatography/electron capture detection after photodegradation of the polychlorobiphenyls (Lewis et al., 1976).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 18 male and 18 female (C57BL/6xC3H/Anf)F1 mice and 18 male and 18 female (C57BL/6xAKR)F1 mice received mirex (98% pure) according to the following schedule: 10 mg/kg bw in 0.5% gelatin at 7 days of age by stomach tube and the same amount (not adjusted for

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1The Working Group was aware of a study in progress to assess the carcinogenicity in mice and rats administered mirex in the diet (IARC, 1978).
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Air</strong></td>
<td>Trap on polyurethane foam, extract (hexane-ether) in Soxhlet, wash</td>
<td>GC/ECD</td>
<td>0.1 ng/m³</td>
<td>Lewis et al. (1977)</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural potable</td>
<td>Extract (hexane), CC</td>
<td>GC/ECD</td>
<td>10 ng/l</td>
<td>Sandhu et al. (1978)</td>
</tr>
<tr>
<td><strong>Soil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soil, sediments</td>
<td>Extract (petroleum ether or acetone-petroleum ether) in Soxhlet, CC</td>
<td>GC/ECD</td>
<td>3-6 µg/kg</td>
<td>Bevenue et al. (1975)</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit and vegetables</td>
<td>Extract (acetonitrile or aqueous acetonitrile), liquid/liquid partition, CC</td>
<td>GC/ECD, TLC, PC</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Fatty products and fish</td>
<td>Mix with Florisil, extract (acetonitrile), liquid/liquid partition, CC</td>
<td>GC/ECD</td>
<td></td>
<td>Bong (1975, 1977)</td>
</tr>
<tr>
<td>Catfish</td>
<td>Grind with anhydrous sodium sulphate, extract (hexane), CC</td>
<td>GC/ECD</td>
<td>10 µg/kg</td>
<td>Collins et al. (1973)</td>
</tr>
<tr>
<td><strong>Biological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wildlife</td>
<td>Grind with anhydrous sodium sulphate, extract (hexane-isopropanol), wash (water), CC</td>
<td>GC/ECD</td>
<td>1 µg/kg</td>
<td>Collins et al. (1974)</td>
</tr>
<tr>
<td>Wildlife</td>
<td>Mix with Florisil, extract (5% water in acetonitrile), liquid/liquid partition, CC</td>
<td>GC/FID/ECD/CD, GC/MS</td>
<td></td>
<td>Hallett et al. (1976)</td>
</tr>
</tbody>
</table>

**Abbreviations:** GC/ECD - gas chromatography/electron capture detection; CC - column chromatography; TLC - thin-layer chromatography; PC - paper chromatography; FID - flame-ionization detection; CD - conductivity detection; MS - mass spectrometry
increasing body weight) daily up to 4 weeks of age; subsequently, the mice were fed 26 mg/kg diet mirex. The dose was the maximum tolerated dose for infant and young mice [but not necessarily that for adults]. The experiment was terminated at 70 weeks of age, when all animals had died. Tumour incidences were compared with those in 79-90 necropsied mice of each sex and strain, which had either been untreated or had received gelatine only. Hepatomas were found in 6/18 male and 8/16 female necropsied mice of the first strain (compared with 8/79 and 0/87 in the corresponding controls) and in 5/15 male and 10/16 female mice of the second strain (compared with 5/90 and 1/82 in the corresponding controls) [For each of the two sexes of the two strains, P < 0.05] (Innes et al., 1969; National Technical Information Service, 1968).

Rat: In a preliminary report of a study by the National Cancer Institute, groups of 26 CD rats of each sex, 6 weeks old, were fed 50 or 100 mg/kg diet mirex (99% pure) for 18 months, except during the first 10 weeks of treatment, when dietary concentrations were 40 and 80 mg/kg diet, respectively. The dietary concentration of 100 mg/kg had been identified from previous short-term experiments as the maximum tolerated dose. Twenty untreated rats of each sex were used as controls. All survivors were killed 24 months after treatment began; a dose-related effect on survival was noticed after the first year of treatment: at the end of the study 65% of the female and 55% of the male controls were still alive, but survival rates were poorer in the treated group. Liver changes were classified according to Squire & Levitt (1975). Neoplastic liver nodules up to 5 cm in diameter were observed in 2 males and 4 females given the lowest dose and in 7 males (P < 0.05) and 4 females given the highest dose. Of the 17 rats with neoplastic nodules, 1 male at the lowest dose and 4 males and 1 female at the highest dose also had well-differentiated liver-cell carcinomas. No metastases were observed (all lobes of the lung were examined routinely in histological sections). No neoplastic liver nodules were found among controls. Liver megalocytosis was observed in a total of 48 treated rats versus 0 in controls. Tumours of the breast and endocrine system were distributed uniformly among control and treated animals. Eight other tumours were found in treated animals: 1 lipoma and 1 squamous-cell carcinoma of the ear-duct in males given the lowest dose; 2 fibromas, 1 fibrosarcoma and 1 squamous-cell carcinoma of the ear-duct in males given the highest dose; 2 fibrosarcomas in females given the highest dose. No such tumours were observed in controls (Ulland et al., 1977).

(b) Subcutaneous and/or intramuscular administration

Mouse: Groups of 18 male and 18 female (C57BL/6xC3H/Anf)F1 mice and 18 male and 18 female (C57BL/6xA)F1 mice were given single s.c. injections of 1000 mg/kg bw mirex (98% pure) in 0.5% gelatin on the 28th day of life and were observed until they were about 78 weeks of age, at which time 16, 17, 17 and 15 mice were still alive. A group of negative controls comprised untreated animals and animals treated with gelatine, corn oil or dimethylsulphoxide. Proportions
of necropsied mice that developed reticulum-cell sarcomas were 6/18, 0/17, 1/17 and 3/18 in the four groups, respectively; 2/16 gelatin-treated control males and 8/141 negative control males of the first strain developed these tumours \( P > 0.05 \) and \( P < 0.01 \), respectively. The corresponding proportions of mice with hepatomas were 2/18, 0/17, 4/17 and 1/18; 1/18 gelatin-treated control males and 1/161 negative control males of the second strain developed such tumours \( P > 0.05 \) and \( P < 0.01 \), respectively. The total incidences in the two strains (males plus females) of reticulum-cell sarcomas was significantly greater than that in controls (6/35 versus 9/295, and 4/35 versus 5/318) (National Technical Information Service, 1968) [The Working Group noted that the statistical significance of the results disappears when only matched controls are considered].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD50 of mirex in corn oil in male rats is 740 mg/kg bw and in females, 600 mg/kg bw (Gaines, 1969). Acute hepatotoxic effects in rats after oral administration of mirex included hepatocyte enlargement, glycogen depletion, focal surface necrosis and periportal liposis (Kendall, 1974). Oral administration of 1 and 10 mg/kg bw to rats for 14 days enlarged the liver and led to fatty infiltration in the centrilobular region (Villeneuve et al., 1977).

I.p. injections of mirex increased liver mixed-function oxidase activity in mice, rats and monkeys (Baker et al., 1972; Byard et al., 1975; Davison et al., 1976; Fulfs et al., 1977). In rats, it increased microsomal protein and cytochrome P450 but did not affect hydroxylation of aniline or demethylation of aminopyrine (Davison et al., 1976).

When chickens were fed 5-160 mg/kg diet mirex for 12 and 16 weeks, and Japanese quail 5-80 mg/kg diet for 12 weeks, no effect was seen on the concentration of protein or cytochrome P450 in hepatic microsomes, nor on aniline hydroxylase or aminopyrine-\( N \)-demethylase levels. However, structural changes were apparent in the livers of chickens fed mirex at 10 mg/kg diet and above, including regions of necrosis, non-specific cellular aberrations and alterations of sinusoids and bile canaliculi (Davison et al., 1976).
Embryotoxicity and teratogenicity

Reduced litter size was noted in 2 strains of mice fed a dietary concentration of 5 mg/kg diet mirex before and after mating (Ware & Good, 1967). Progeny from female rats fed a diet containing 25 mg/kg diet mirex before and after mating had a reduced survival rate and a high incidence of cataracts, while progeny from females maintained on a level of 5 mg/kg diet appeared to be normal (Gaines & Kimbrough, 1970).

Rats were given daily oral doses of 1.5, 3, 6 and 12.5 mg/kg bw mirex on days 6-15 of gestation; the highest dose caused maternal toxicity, pregnancy failure, decreased foetal survival, reduced foetal weight and an increased incidence of visceral anomalies. Maternal toxicity and an increased incidence of foetal visceral anomalies were also observed with 6 mg/kg bw. Lower doses produced minimal or no adverse effects (Khera et al., 1976).

No perceptible reproductive effects were observed in bobwhite quail fed 40 mg/kg diet mirex or in mallard ducks fed 1 or 10 mg/kg diet (Heath & Spann, 1973).

Absorption, distribution, excretion and metabolism

In rats, more than 50% of an oral dose of 6 mg/kg bw $^{14}$C-mirex was excreted unchanged in the faeces within 48 hrs; thereafter, excretion dropped rapidly. Less than 1% unchanged mirex was found in the urine after 7 days, and tissues contained about 34%. No metabolites were found (Mehendale et al., 1972).

Rats given single oral doses of 0.2 mg/kg bw $^{14}$C-mirex excreted 15% in the faeces within 2 days and 3% over the subsequent 5 days; only traces were found in the urine. About 1 µg/g was found in adipose tissue throughout the 28 days of the experiment. Other tissue concentrations were lower and declined within the first 7 days after dosing (Gibson et al., 1972).

In a reproduction study in rats, mirex crossed the placental barrier and was also secreted in their milk (Gaines & Kimbrough, 1970).

$^{14}$C-Mirex administered at concentrations of 30 mg/kg diet was stored unchanged in the fat of quail and rats at levels up to 5500 mg/kg and was not appreciably metabolized or excreted, even when mirex was removed from the diet (Ivie et al., 1974). Similar observations were made in Macaca mulatta monkeys; a minor metabolite, accounting for less than 3% of the faecal radioactivity, was identified as a 9- or 10-monohydro derivative. The highest concentration of $^{14}$C was found in fat, followed by adrenal gland, peripheral nerve, thyroid gland and skin (Stein & Pittman, 1977; Wiener et al., 1976).
Mutagenicity and other related short-term tests

Male Wistar rats that received daily doses of 1.5, 3 and 6 mg/kg bw mirex by stomach tube for 10 consecutive days were mated sequentially with untreated females (1 male x 2 females) every 5 days over a period of 70 days (a total of 14 mating periods). The pregnant females were dissected 13-15 days after separation from the males to assess the incidence of dominant lethality. In none of the mating periods was there any significant difference (relative to controls) in the proportion of fertile matings, embryos/pregnancy or decidualomas/pregnancy, except for a decrease in the incidence of pregnancies in the group receiving 6 mg/kg bw in the first trial (Khera et al., 1976).

(b) Humans

Levels of mirex in human tissues are discussed in section 2.2 (e).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Mirex has been tested in one experiment in two strains of mice and in one experiment in rats by oral administration. It has also been tested in two strains of mice by subcutaneous injection of single doses. In the studies using oral administration, it produced benign and malignant liver tumours in mice and rats of both sexes. An excess of liver tumours was also found in males of one of the two strains of mice following a single subcutaneous injection; this experiment also suggested that it produced reticulum-cell sarcomas in males of both strains.

Mirex is foetotoxic and produces teratogenic effects. It was negative in a dominant lethal assay in mice.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and the widespread use of mirex since the late 1950s, together with the persistent nature of the compound, indicate that widespread human exposure has occurred. This is confirmed by many reports of its occurrence in the general environment and by its presence in human fat.
4.3 Evaluation

There is sufficient evidence that mirex is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard mirex as if it presented a carcinogenic risk to humans.
5. References


Anon. (1977b) Mississippi set to sell mirex insecticide bait for spray application. Chemical Marketing Reporter, 7 March, p. 4


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PENTACHLOROPHENOL

A review on pentachlorophenol is available (Mercier, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 87-86-5
Chem. Abstr. Name: Pentachlorophenol

Synonyms: Chlorophen; PCP; penchlorol; penta; pentachloro-
fenol; pentachlorofenol; pentachlorophenate; pentachlorphenol;
2,3,4,5,6-pentachlorophenol; pentanol

Trade names: Chem-Tol; Cryptogil 01; Dowcide 7; Dowicide 7;
Dowicide G; Durotox; EP 30; Fungifen; Grundier Arbezol;
Lauxtol; Lauxtol A; Liroprem; Pentacon; Penta-Kil; Pentasol;
Penwar; Peratox; Permacide; Permagard; Permasan; Permatox;
Permite; Santobrite; Santophen; Santophen 20; Sinituho; Term-
i-Trol; Thompson's Wood Fix; Weedone

1.2 Structural and molecular formulae and molecular weight

\[
\text{C}_6\text{HCl}_{15}\text{O} \quad \text{Mol. wt: 266.3}
\]

1.3 Chemical and physical properties of the pure substance

From Grasselli & Ritchey (1975), unless otherwise specified

(a) Description: White crystals

(b) Boiling-point: 309-310°C (decomposition) at 754 mm
(c) Melting-point: 174°C

(d) Spectroscopy data: $\lambda_{\text{max}}$ 280 nm ($E_1^1 = 34$), 273 nm ($E_1^1 = 39$), 224 nm ($E_1^1 = 309$) in methanol; infra-red and ultra-violet spectra have been tabulated (Core et al., 1971).

(e) Solubility: Slightly soluble in water (8 mg/100 ml) and cold petroleum ether; soluble in benzene, ethanol, diethyl ether (Windholz, 1976), and paraffinic petroleum oils (Mercier, 1977).

(f) Stability: Stable; prolonged heating above 200°C produces traces of octachlorodibenzo-para-dioxin (Langer et al., 1973).

(g) Reactivity: Forms salts with alkaline metals (Windholz, 1976); sodium pentachlorophenate is converted exothermically to octachlorodibenzo-para-dioxin at 360°C (Langer et al., 1973); heating of the sodium salt to 280°C produced 0.9 mg/kg octa- and 0.3 mg/kg hepta-chlorodibenzo-para-dioxins, together with 0.02-0.03 mg/kg hexa-, penta- and tetra-chlorodibenzo-para-dioxins (Rappe et al., 1978).

1.4 Technical products and impurities

Pentachlorophenol is available commercially in the US in prill, flake or block form (von Rumker et al., 1975). The typical composition of commercial pentachlorophenol is as follows: pentachlorophenol, 88.4%; tetrachlorophenol, 4.4%; trichlorophenol, < 0.1%; and higher chlorinated phenoxyphenols, 6.2%. The non-phenolic components fall into two chemical classes: polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. Commercial pentachlorophenol typically contains the following chlorinated dioxins: 2,3,7,8-tetrachlorodibenzo-para-dioxin, < 0.05 mg/kg; hexachlorodibenzo-para-dioxin, 4 mg/kg; heptachlorodibenzo-para-dioxin, 125 mg/kg; and octachlorodibenzo-para-dioxin, 2500 mg/kg. The typical dibenzofuran content of commercial pentachlorophenol is as follows: hexachlorodibenzo-furan, 30 mg/kg; heptachlorodibenzo-furan, 80 mg/kg; and octachlorodibenzo-furan, 80 mg/kg (Schwetz et al., 1974). Hexachlorobenzene is also found, at levels of 400 mg/kg, in commercial pentachlorophenol (Schwetz et al., 1978). One producer offers a commercial product in which the dioxin content is minimized; this product has the following composition: pentachlorophenol, 88%; 2,3,4,6-tetrachlorophenol, 12%; octachlorodibenzo-para-dioxin, 30 mg/kg max; and hexachlorodibenzo-para-dioxins, 1 mg/kg max (von Rumker et al., 1975).
PENTACHLOROPHENOL

In Japan, the technical-grade chemical contained a minimum of 95% pentachlorophenol.

Pentachlorophenol is available as its sodium salt as a 5% emulsifiable concentrate or as 3-40% solutions in oil or grease, and in formulations with other chlorophenols, methylene bisthiocyanate and copper naphthenate (von Rumker et al., 1975; US Environmental Protection Agency, 1975).

2. Production, Use, Occurrence and Analysis

A review is available (Gebefügi & Parlar, 1978).

2.1 Production and use

(a) Production

Pentachlorophenol was first prepared by Merz & Weith in 1872, by chlorination of a mixture of phenol and antimony trichloride at elevated temperatures (Prager et al., 1923). The process for commercial production of pentachlorophenol is similar, involving the chlorination of phenol at progressively higher temperatures, using anhydrous aluminium chloride (von Rumker et al., 1975) or ferric chloride as a catalyst in the final stages of chlorination. One commercial process is reported to involve a mixture of phenol and ortho-, 2,6-di- and 2,4,6-trichlorophenols as starting material. Pentachlorophenol has also been manufactured by the hydrolysis of hexachlorobenzene (Doedens, 1964).

In Japan, pentachlorophenol has been produced by chlorination of 2,4-dichlorophenol, derived from 1,2,4-trichlorobenzene.

Although use of pentachlorophenol as a wood preservative started in the late 1930's (Doedens, 1964), commercial production in the US was first reported only in 1950, by 2 companies (US Tariff Commission, 1951). US production of pentachlorophenol in the decade 1967-1976 was in the range of 20-23 million kg, with production in 1976 at the lower extreme of that range, at just under 20 million kg (US International Trade Commission, 1977). US imports of pentachlorophenol were last reported in 1974 when 56 thousand kg were imported through the principal customs districts (US International Trade Commission, 1976).

No data on its production in Europe were available.

In Japan, pentachlorophenol was first produced commercially in 1960. Production reached a level of 14.5 million kg in 1966 and decreased to 3.3 million kg in 1971, when production was discontinued.
(b) Use

The use pattern for the 23.4 million kg pentachlorophenol used in the US in 1974 was as follows: wood preservation, 84%; synthesis of sodium pentachlorophenate, 12%; and miscellaneous uses, 4%.

Pentachlorophenol is used to protect wood (primarily construction lumber, but also poles and posts) from attack by fungal rots and decay and to prevent stain. It may be used in combination with other chlorophenols, 2,4-dinitrophenol, sodium fluoride, dichromate salts, sodium arsenate or arsenious oxide (US Environmental Protection Agency, 1973).

It is also used as a herbicide and defoliant. About 700 thousand kg are used in the US in home and garden applications (von Rumker et al., 1975), primarily for preservation of various wooden articles and structures.

Sodium pentachlorophenate, produced from pentachlorophenol, is used as a wood preservative, as a fungicide in water-based latex paints, as a herbicide and as a slimicide.

The fungicidal and herbicidal uses of pentachlorophenol, including those cited above, are regulated by the US Environmental Protection Agency. It is registered in the US as a preharvest desiccant on alfalfa, clovers, lespedeza and vetch, but only when these crops are grown for the production of seed. Treated areas may not be grazed, and the treated forage or threshings may not be fed to livestock (US Environmental Protection Agency, 1970).

Other registered fungicidal uses of pentachlorophenol include treatment of beans to prevent seedling disease and a variety of miscellaneous agricultural uses involving preservation of wood, leather, burlap, twine and rope from attack by various fungi. Registered homeowner uses include maintenance of boats, trailers, station wagons, siding, fences, outdoor furniture and similar articles. There are a large number of registered industrial uses, such as in construction of boats and buildings, mould control in petroleum drilling and production, and treatment of cable coverings, canvas belting, nets, construction lumber and poles. Other industrial uses include incorporation in paints, pulp stock, in pulp and paper, cooling tower water, hardboard and particle board (US Environmental Protection Agency, 1975).

In France, pentachlorophenol is used as a fungicide, bactericide, algicide and anti-termite. In Japan, essentially all of the pentachlorophenol produced was used as a herbicide, with minor use as a fungicide.

Pentachlorophenol is being reviewed by the US Environmental Protection Agency for possible issuance of a notice of a rebuttable presumption
against renewal of registration (RPAR) (See General Remarks on Substances Considered, p. 31) on the basis of reproductive effects in experimental animals (Anon., 1978).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to pentachlorophenol not exceed an 8-hr time-weighted average of 0.5 mg/m³ in the working atmosphere in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977). The corresponding standard in the Federal Republic of Germany, the German Democratic Republic and Sweden is also 0.5 mg/m³; and the acceptable ceiling concentration of pentachlorophenol in the USSR is 0.1 mg/m³ (Winell, 1975).

2.2 Occurrence

It has been suggested, but not proven, that pentachlorophenol is a natural product, possibly a product of fungus metabolism (Arsenault, 1976). The occurrence of pentachlorophenol in the environment has been reviewed (Arsenault, 1976; Howard & Durkin, 1973).

(a) Air

Pentachlorophenol has been detected in the atmosphere of two towns, at levels of 0.25-0.93 and 5.7-7.8 ng/m³ air (Cautreels et al., 1977).

(b) Water

Pentachlorophenol has been detected in: (1) river water and effluent water from a chlorinated biological sewage treatment plant (Eurocop-Cost, 1976); (2) the effluent waters from various manufacturing and processing plants (Shackelford & Keith, 1976); and (3) well-water (Nomura, 1974).

It has also been detected in: (1) the sewage influent and effluent water of 3 cities, at levels of 1-5 μg/l; (2) a river, at levels of 0.1-0.7 μg/l (Buhler et al., 1973); (3) rain-, snow- and lake-water, at levels of 2-284, 14 and 10 ng/l, respectively (Bevenue et al., 1972); and (4) creek-water containing industrial discharges, at levels of 0.1-10 mg/l (Fountaine et al., 1976).

(c) Soil

After treatment of greenhouse soil with pentachlorophenol at levels of 15 and 45 kg/ha, residues in the soil were 20.4 and 69.1 mg/kg, respectively. Lettuce grown on this soil contained residues of 0.73 and 1.56 mg/kg, respectively. In a second experiment, the greenhouse soil was treated with 15 and 30 kg pentachlorophenol/ha, and residues
of 0.46 and 0.87 mg/kg, respectively, were detected in the lettuce (Casanova & Dubroca, 1973).

(d) Food

In a continuing programme involving the monitoring of pesticide residues in food, levels of pentachlorophenol in foods were measured for the period 1965-1970, and an average daily intake of pentachlorophenol was calculated. For the period 1965-1970, the average daily intake was 1.67 µg/day; this level dropped to 0.725 µg/day in 1973 and rose to 0.76 µg/day in 1974 (US Food & Drug Administration, 1975, 1977).

(e) Animals

Pentachlorophenol has been detected in: (1) fish, white shark liver, bird eggs and fish food, at levels of < 0.5-4, 10.8, 0.36-0.51 and 2.23 µg/kg (wet weight), respectively (Zitko et al., 1974); (2) birds, snails, frogs and fish, at levels of 0.04-0.49, 36.8, 8.1 and 0.37-59.4 mg/kg (mean wet weight), respectively (Vermeer et al., 1974); (3) fish extracts (Tokunaga, 1971); and (4) fish, at levels of 0.35-26 mg/kg (Renberg, 1974).

In the state of Michigan, herds of dairy cattle were contaminated with pentachlorophenol used to treat the wood of barns where they were housed and from feed bins treated with pentachlorophenol; the contaminating pentachlorophenol was said to contain 1-1000 mg/kg dioxin. Pentachlorophenol levels in 18 cows ranged from 58-1136 µg/kg (Anon., 1977a). Pentachlorophenol has been found in the blood of 8 such herds (Anon., 1977b). One sample of milk was found to contain 0.09 mg/kg (Anon., 1977c).

(f) Humans

Pentachlorophenol has been detected in human blood plasma at levels of 15.69-15.86 µg/l in haemodialysed patients and of 15.0 µg/l in the persons used as controls (Pearson et al., 1976). It has also been detected in the urine, seminal fluid (20-70 µg/kg) and fingernails of non-occupationally exposed individuals (Dougherty & Piotrowska, 1976a).

Pentachlorophenol was found in 85% of 416-418 samples of urine collected from the general population during the Health and Nutritional Examination Survey. The maximum level was 193 µg/l, and the mean level 6.3 µg/l (Kutz et al., 1978).

(g) Occupational exposure

The 1974 National Occupational Hazard Survey indicated that the workers primarily exposed to pentachlorophenol are those in the gas and
electric service industries; the potential exposure of hospital workers was also noted (National Institute for Occupational Safety & Health, 1977).

Air and urine samples taken at 25 factories using pentachlorophenol as a wood preservative showed that the average worker's exposure to pentachlorophenol in air was 0.013 mg/m³, with a maximum range of 0.004-1.000 mg/m³, and the level in urine ranged from 0.12-9.68 mg/l (Arsenault, 1976).

When worker exposure to pentachlorophenol at a wood-treatment plant was measured over a 5-month period, serum and urine levels of pentachlorophenol were 348.4-3963 μg/l and 41.3-760 μg/l, respectively. Pentachlorophenol residues in the workplace air were in the range of 5.1-15275.1 ng/m³ (Wyllie et al., 1975). It has also been detected in the workplace air of a sodium pentachlorophenate production plant (Melnikova et al., 1975).

(h) Other

Pentachlorophenol has been detected in 9/65 commercial samples of paints used on children's toys, at levels of 100-2700 mg/kg (van Langeveld, 1975); and in wood-shaving litter from chicken houses, at levels of 0.6-83 mg/kg (fresh) and 0-4.1 mg/kg (after 8 weeks) (Parr et al., 1974).

2.3 Analysis

Methods used for the analysis of pentachlorophenol in environmental samples are listed in Table 1 (Howard & Durkin, 1973).

Other proposed methods include high-pressure liquid chromatography (Ayres & Gopalan, 1976; US Environmental Protection Agency, 1976) and thin-layer chromatography (Dietz et al., 1976). Background levels of trace impurities in analytical reagents can introduce error in gas chromatography/electron capture determinations of 1.0 ng/kg to 1.0 μg/kg levels (Bevenue & Ogata, 1971).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 18 male and 18 female (C57BL/6xC3H/Anf)F1 mice and 18 male and 18 female (C57BL/6xAKR)F1 mice received pentachlorophenol
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td>Ignite with lime, neutralize</td>
<td>Volhard titration</td>
<td></td>
<td>Adams et al. (1974)</td>
</tr>
<tr>
<td>Air</td>
<td>Trap in potassium hydroxide, extract (hexane), methylate, CC</td>
<td>GC/ECD</td>
<td>20 µg/kg</td>
<td>Hoben et al. (1976a)</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural and waste</td>
<td>Extract (benzene), re-extract (potassium carbonate), acetylate, extract (hexane)</td>
<td>GC/ECD</td>
<td>10 ng/l</td>
<td>Chau &amp; Coburn (1974)</td>
</tr>
<tr>
<td>Domestic waste</td>
<td>Acidify, extract (dichloromethane), liquid/liquid partition, methylate</td>
<td>GC/FID</td>
<td>0.2 µg/l</td>
<td>Garrison et al. (1976)</td>
</tr>
<tr>
<td>Natural</td>
<td>Adsort on ion exchanger, remove water, extract (benzene), methylate</td>
<td>GC/ECD</td>
<td>1 ng/l</td>
<td>Renberg (1974)</td>
</tr>
<tr>
<td>River and waste</td>
<td>Make alkaline, wash (chloroform), UV, IR acidify, extract (chloroform), re-extract (sodium hydroxide) acidify</td>
<td></td>
<td></td>
<td>Fountaine et al. (1976)</td>
</tr>
<tr>
<td>Soil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sediment and sewage</td>
<td>Centrifuge, extract solid (acetone), liquid/liquid partition, transfer into trimethyl pentane, treat to remove sulphur, isolate in trimethyl pentane, methylate or acetylate</td>
<td>GC/ECD</td>
<td>1-10 µg/kg</td>
<td>Jensen et al. (1977)</td>
</tr>
<tr>
<td>Soil</td>
<td>Centrifuge slurry with alkali, adsorb on ion exchanger, extract (benzene), methylate</td>
<td>GC/ECD</td>
<td>0.1-1 µg/kg</td>
<td>Renberg (1974)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
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<tr>
<td>Food and drink</td>
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</tr>
<tr>
<td>Milk</td>
<td>Extract (benzene), re-extract from benzene (potassium carbonate solution), form pentachlorophenol acetate, extract (hexane)</td>
<td>GC/ECD</td>
<td>5 μg/kg</td>
<td>Erney (1978)</td>
</tr>
<tr>
<td>Beef fat and milk chocolate</td>
<td>Macerate, extract (hot caustic soda), cool, extract (hexane-2-propanol), reduce bulk, CC</td>
<td>MS (negative chemical ionization)</td>
<td>5 μg/kg</td>
<td>Dougherty &amp; Piotrowska (1976a,b)</td>
</tr>
<tr>
<td>Biological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue</td>
<td>Digest (potassium hydroxide), acidify, steam distill, extract distillate (toluene), ethylate</td>
<td>GC/ECD</td>
<td>1 μg/kg for fat, 0.1 μg/kg for muscle</td>
<td>Gee et al. (1974)</td>
</tr>
<tr>
<td>Tissue</td>
<td>Acidify, extract (hexane) in mixer, centrifuge, methylate, CC</td>
<td>GC/ECD</td>
<td>20 μg/kg</td>
<td>Hobern et al. (1976a)</td>
</tr>
<tr>
<td>Tissue</td>
<td>Homogenize with hexane-acetone, liquid/liquid partition, absorb on ion exchanger, extract (benzene), methylate</td>
<td>GC/ECD</td>
<td>0.1 μg/kg</td>
<td>Renberg (1974)</td>
</tr>
<tr>
<td>Human adipose tissue</td>
<td>Extract (hexane) in mixer, make alkaline, re-extract (hexane), acidify residue, extract (ether), ethylate, methylate</td>
<td>GC/ECD</td>
<td>5 μg/kg</td>
<td>Shafik (1973)</td>
</tr>
<tr>
<td>Plasma</td>
<td>Acidify, extract (benzene), centrifuge, ethylate, CC</td>
<td>GC/ECD</td>
<td>20 μg/l</td>
<td>Hobern et al. (1976a)</td>
</tr>
<tr>
<td>Blood and urine</td>
<td>Acidify, extract (benzene), centrifuge, methylate</td>
<td>GC/ECD</td>
<td>10 μg/l</td>
<td>Rivers (1972)</td>
</tr>
<tr>
<td>Rat urine</td>
<td>Acidify, reflux, make alkaline, extract (ether), ethylate, transfer to hexane, CC</td>
<td>GC/ECD</td>
<td>10 μg/l</td>
<td>Shafik et al. (1973)</td>
</tr>
<tr>
<td>Human urine</td>
<td>Make alkaline, extract (hexane), make acid, extract (hexane), methylate</td>
<td>GC/ECD</td>
<td>2.2 μg/l</td>
<td>US Food &amp; Drug Administration (1970)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
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<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
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<tr>
<td>Biological</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Human urine</td>
<td>Hydrolise (acid), extract (hexane-2-propanol), concentrate to 100 µl</td>
<td>MS (negative chemical ionization)</td>
<td>4-40 ng/l</td>
<td>Dougherty &amp; Piotrowska (1976a)</td>
</tr>
<tr>
<td>Urine</td>
<td>Acidify, extract (hexane), centrifuge, ethylate, GC</td>
<td>GC/ECD</td>
<td>20 µg/l</td>
<td>Hobern et al. (1976a)</td>
</tr>
<tr>
<td>Seminal fluid</td>
<td>Hydrolise (acid), extract (hexane-ether), concentrate to 100 µl</td>
<td>MS (negative chemical ionization)</td>
<td>1-10 µg/l</td>
<td>Dougherty &amp; Piotrowska (1976a)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood</td>
<td>Ignite with lime, neutralize</td>
<td>Volhard titration</td>
<td></td>
<td>Adams et al. (1974)</td>
</tr>
<tr>
<td>Wood</td>
<td>Extract (chloroform)</td>
<td>TLC (revelation: silver nitrate)</td>
<td>60 ng (on unwashed plates)</td>
<td>Henshaw et al. (1975)</td>
</tr>
<tr>
<td>Wood shavings</td>
<td>Digest (potassium hydroxide), acidify, steam distill, extract (toluene), ethylate</td>
<td>GC/ECD</td>
<td>10 µg/kg</td>
<td>Gee et al. (1974)</td>
</tr>
</tbody>
</table>

Abbreviations: CC - column chromatography; GC/ECD - gas chromatography/electron capture detection; MS - mass spectrometry; FID - flame-ionization detection; UV - ultra-violet spectrometry; IR - infra-red spectrometry
as the commercial product Dowcide-7 (impurities unspecified) according to the following schedule: 46.4 mg/kg bw in 0.5% gelatin at 7 days of age by stomach tube and the same amount (not adjusted for increasing body weight) daily up to 4 weeks of age; subsequently, the mice were fed 130 mg/kg diet until they reached 78 weeks of age, at which time 16, 18, 17 and 16 mice were still alive in the four groups, respectively. The dose was the maximum tolerated dose for infant and young mice [but not necessarily that for adults]. Tumours developed in 3/18, 4/18, 3/17 and 2/18 male and female necropsied mice; these incidences were not significantly greater than in 79-90 necropsied mice of each sex and strain, which had either been untreated or had received gelatin only (Innes et al., 1969; National Technical Information Service, 1968).

Rat: Six groups of 27 male and 27 female weanling Sprague-Dawley ( Spartan substrain) rats were given laboratory chow diet containing pentachlorophenol (sample XD-9108.002: pentachlorophenol, 90.4%; tetrachlorophenol, 10.4%; trichlorophenol, < 0.1%; hepta- and octachlorodibenzo-para-dioxins, about 21 mg/kg; hexa- and heptachlorodibenzofurans, about 5.2 mg/kg; and hexachlorobenzene, 400 mg/kg) to provide dose levels of 0, 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day. The pentachlorophenol was dissolved in anisole, and the concentrations were adjusted on a monthly basis to maintain the designated dose levels on a mg/kg bw/day according to the food consumption and body weight of the rats. Groups of 27 male and 27 female control rats received laboratory chow containing anisole only. Female rats were maintained on test diets for 24 months, but the male rats were taken off the test diets after 22 months because of high mortality among both control and experimental animals. The mean body weight of male rats was not significantly altered by ingestion of diets containing pentachlorophenol; among the female rats, the mean body weight of those receiving the highest dose level was significantly less than that of the control group; in the other groups body weight was comparable with that of the control groups. The total and individual tumour incidences by sites, the times of appearance of tumours and the average numbers of tumours per animal (predominantly benign neoplasms) were not significantly different from those observed in control rats. The numbers of rats with tumours/those examined were, in males: 11/27 (controls), 13/26 (1 mg/kg), 13/27 (3 mg/kg), 12/27 (10 mg/kg), 11/27 (30 mg/kg); in females: 27/27 (controls), 26/27 (1 mg/kg), 25/27 (at all other doses) (Schwetz et al., 1978).

(b) Subcutaneous and/or intramuscular administration

Mouse: Groups of 18 male and 18 female (C57BL/6xC3H/Anf)F1 mice and 18 male and 18 female (C57BL/6xAKR)F1 mice were given single s.c. injections of 46.4 mg/kg bw commercial pentachlorophenol (Dowcide-7; impurities unspecified) in corn oil at 28 days of age and were observed up to 78 weeks of age, at which time 14, 18, 18 and 16 mice in the four
groups, respectively, were still alive. Negative control groups consisted of animals that were either untreated or received gelatin, corn oil or dimethylsulphoxide and comprised 141 males and 154 females of the first strain and 161 males and 157 females of the second strain. The incidence of hepatomas (4/17) in males of the first strain was significantly increased \( P < 0.05 \) over that in controls (9/141) (National Technical Information Service, 1968).

3.2 Other relevant biological data

Commercially produced pentachlorophenol contains significant amounts of chlorinated dibenzo-\( \text{para} \)-dioxins and polychlorinated dibenzo-furans (see section 1.4). These contaminants may not be important in relation to the acute toxicity of pentachlorophenol but may be associated with those toxic or other biological effects that are seen after long-term exposure (Baader & Bauer, 1951; Goldstein et al., 1977).

(a) Experimental systems

Toxic effects

The oral LD\(_{50}\) in rats is 146-174 mg/kg bw, that by skin application 320-330 mg/kg bw (Gaines, 1969), and that by inhalation of aerosol 11.7 mg/kg bw (Hoben et al., 1976b).

The acutely toxic state is characterized by accelerated respiration, elevated body temperature, tachycardia, progressive neuromuscular weakness and death due to cardiac failure. Rigor mortis is instantaneous (Deichmann et al., 1942).

A commercial sample of pentachlorophenol produced positive responses in the chick oedema test and in the rabbit ear acnegenic test. Rats fed doses of 3, 10 and 30 mg/kg bw/day for 90 days showed haemolytic changes, increased liver and kidney weights and hepatic alterations (Johnson et al., 1973).

With a pentachlorophenol formulation that had 'markedly reduced levels of impurities', mild toxicity was observed in rats that received 30 mg/kg bw for 2 years. 'No effect' levels were reported to be 3 mg/kg bw/day for females and 10 mg/kg bw/day for males (Schwetz et al., 1978).

In an 8-month feeding study with female rats, analytical grade pentachlorophenol was compared with a technical grade. The latter produced hepatic porphyria and increased aryl hydrocarbon hydroxylase activity and glucuronyl transferase activity when given at 100 mg/kg
diet. Pure pentachlorophenol had no significant effect on aryl hydro-
carbon hydroxylase activity, but it increased glucuronyl transferase
when given at 500 mg/kg diet (Goldstein et al., 1977). The authors
attributed these effects to the chlorinated dibenzo-\textit{para}-dioxins present
in the commercial product.

Weinbach (1954) demonstrated that pentachlorophenol uncouples
oxidative phosphorylation in mitochondria. It also disturbs electron
transport from flavins to cytochromes in microsomes, suggesting micro-
somal detoxification malfunction (Arrhenius et al., 1977a,b).

**Embryotoxicity and teratogenicity**

Purified and commercial grades of pentachlorophenol were given
orally to rats at doses ranging from 5-50 mg/kg bw/day at various inter-
vals during days 6-15 of pregnancy. Signs of embryotoxicity and
foetotoxicity, such as resorptions, subcutaneous oedema, dilated ureters
and anomalies of the skull, ribs, vertebrae and sternebrae, were observed
at an incidence which increased with dose. Early organogenesis was the
most sensitive period. The no-effect dose level of the commercial
grade was 5 mg/kg bw/day; purified pentachlorophenol given at the same
dose level caused a statistically significant increase in the incidence
of delayed ossification of the skull bones but had no other effect on
embryonal or foetal development (Schwetz et al., 1974). Ingestion of
3 mg/kg bw/day of a commercially available purified grade of pentachloro-
phenol had no effect on reproduction, neonatal growth, survival or deve-
lopment (Schwetz et al., 1978).

A dose of 60 mg/kg bw pentachlorophenol (purity > 99\%) was given to
Charles River CD rats as a single oral dose at various times during days
8-13 of gestation. The incidence of resorptions was not significantly
greater than that in controls. Although malformations were observed,
the number was minimal, and the authors suggested that the effect could
have been due to toxic effects of the compound on the mothers (Larsen
et al., 1975).

In Syrian golden hamsters, foetal deaths and resorptions were
reported in 3/6 test groups after oral administration of doses varying
from 1.25-20.0 mg/kg bw/day pentachlorophenol from days 5-10 of gesta-
tion (Hinkle, 1973).

**Absorption, distribution, excretion and metabolism**

In mice, pentachlorophenol is excreted primarily in the urine, and
the rest in the faeces (Jakobsen & Yllner, 1971). Urinary excretion
in mice and rats is principally as free pentachlorophenol or tetrachloro-
hydroquinone, although glucuronide conjugates of both pentachlorophenol
and tetrachlorohydroquinone have been identified in rats (Ahlborg et al.,
1974, 1978). The metabolite tetrachlorohydroquinone was not found in
the urine of \textit{Macaca mulatta} monkeys (Braun & Sauerhoff, 1976).
In rats, dechlorination of pentachlorophenol is mediated by microsomal enzymes that can be induced by phenobarbital (Ahlborg et al., 1978) or by tetrachlorodibenzo-para-dioxin (Ahlborg & Thunberg, 1978).

Enterohepatic circulation of pentachlorophenol occurs in monkeys and mice (Braun & Sauerhoff, 1976; Jakobsen & Yllner, 1971). In rats, it is found mainly in plasma protein; liver and kidney have the highest tissue concentrations (Braun et al., 1977). The plasma half-lives of a 10 mg/kg bw dose were about 15 hrs in rats and 78 hrs in Macaca mulatta monkeys. There is no pharmacokinetic evidence that pentachlorophenol per se would have cumulative toxic effects (Braun & Sauerhoff, 1976; Braun et al., 1977).

**Mutagenicity and other related short-term tests**

In feeding experiments with Drosophila melanogaster, 7 mM pentachlorophenol failed to induce sex-linked recessive lethals in meiotic and postmeiotic stages of male germ cells (Vogel & Chandler, 1974).

In lateral roots of Vicia faba seedlings treated with 43.5-174 mg/l pentachlorophenol, there was an increase in the frequency of abnormal cell divisions (e.g., stickiness and lagging of chromosomes and chromosome fragmentation); these abnormalities were more frequent during metaphase than in later stages and, in general, increased with increasing concentration (Amer & Ali, 1969).

(b) Humans

Toxic effects and fatalities due to occupational and accidental exposures to pentachlorophenol have been reviewed by Mercier (1977). Nine sawmill workers died after exposure to impregnated wood (Menon, 1958); 2 deaths were reported among 20 infants intoxicated in a hospital in which there was misuse of a laundry product containing 22.9% sodium pentachlorophenol, 4% 3,4,4-trichlorocarbanilide and sodium salts of other chlorophenols and inert materials (Mercier, 1977; Robson et al., 1969).

One case of fatal aplastic anaemia was associated with exposure to pentachlorophenol and tetrachlorophenol (Roberts, 1963).

Extended periods of exposure to pentachlorophenol have resulted in persistent chloracne and disorders of the nervous system and liver (Baader & Bauer, 1951; Vinogradova et al., 1973).

Average serum and urine levels of pentachlorophenol were about 30% and 50% higher in 6 exposed workers than in 4 control workers (Wyllie et al., 1975). The urine of workers exposed to pentachlorophenol contained unchanged compound and tetrachlorohydroquinone (Ahlborg et al., 1974). For the occurrence of pentachlorophenol in serum and urine, see section 2.2 (e).
In lymphocyte cultures of 6 workers exposed to pentachlorophenol at a factory, the incidence of chromosome aberrations (breaks and gaps) was not significantly different from that in 4 'control' workers (Wyllie et al., 1975).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Pentachlorophenol was tested in one experiment in two strains of mice and in one experiment in rats by oral administration at dose levels sufficiently high to cause mild toxicity: no carcinogenic effect was seen in either species. Pentachlorophenol was also tested in one experiment in mice of two strains by subcutaneous injection of single doses; it produced hepatomas in males of one strain.

Pentachlorophenol did not induce sex-linked recessive lethals in Drosophila melanogaster.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production of pentachlorophenol and its use for wood preservation and, to a lesser extent, in homes and gardens, together with the persistent nature of the compound, indicate that widespread human exposure occurs. This is confirmed by many reports of its occurrence in the general environment and its presence in body fluids, both in the general population and in exposed workers. Several episodes of occupational intoxication have been reported.

4.3 Evaluation

The available data do not permit an evaluation of the carcinogenicity of pentachlorophenol to be made.
5. References


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PENTACHLOROPHENOL


1. **Chemical and Physical Data**

1.1 **Synonyms and trade names**


Chem. Abstr. Name: Toxaphene

Synonyms: Camphechlor; camphochlor; chlorinated camphene; chlorocamphene; kamfochlor; octachlorocamphene; polychlorocamphene; polychlorocamphene; toxafeen; toxaphen

Trade names: Agricide Maggot Killer; Alltex; Alltox; Camphofene Huileux; Chem-Phene; Clor Chem T-590; Compound 3956; Crestoxo; Cristoxo-90; ENT 9,735; Estonox; Fasco-Terpene; Geniphene; Gy-Phene; Hercules 3956; Hercules Toxaphene; M 5055; Melipax; Motox; Penphene; Phenacide; Phenatox; Strobane-T; Synthetic 3956; Toxadust; Toxakil; Toxon 63; Toxyphen; Vertac 90%

1.2 **Structural and molecular formulae and molecular weight**

![Structural formula](attachment:image.png)

Empirical formula: C\textsubscript{10}H\textsubscript{10}Cl\textsubscript{8}  
Mol. wt: 414 (average)

1.3 **Chemical and physical properties of the substance**

From Hawley (1977), unless otherwise specified

(a) **Description:** Amber, waxy solid
(b) **Melting range:** 65-90°C

(c) **Solubility:** Soluble in common organic solvents; practically insoluble in water (Windholz, 1976)

(d) **Stability:** Dehydrochlorinates in the presence of alkali, prolonged exposure to sunlight and at temperatures of about 155°C (Windholz, 1976)

(e) **Reactivity:** Noncorrosive in absence of moisture (Spencer, 1973)

1.4 Technical products and impurities

The exact composition of toxaphene is unknown. Technical toxaphene consists predominantly of polychlorinated camphenes with 4-12 chlorine atoms per molecule, and contains 67-69% chlorine (Parlar et al., 1977). In one study, toxaphene was found to contain at least 177 components (Holmsted et al., 1974).

Toxaphene is available in the US in the following formulations: a wettable powder (40% active), emulsifiable concentrates of various strengths, dusts (10% and 20%), granules (10% and 20%), baits (1% in bran), an oil solution (90%), an emulsion containing 2 parts toxaphene and 1 part DDT, and a dust containing 14% toxaphene and 7% DDT.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

It is believed that toxaphene was first introduced in 1948. It was prepared by chlorination of camphene in 1953 (Buntin, 1953). Toxaphene is currently produced commercially in the US by chlorination of camphene until a chlorine content of 67-69% is obtained (Spencer, 1973).

Commercial production of toxaphene in the US was first reported in 1947 (US Tariff Commission, 1948). In 1976, 3 US companies produced a total of 19 million kg (US International Trade Commission, 1977), which represented a decline of 29% from the 1975 production level of 27 million kg (US International Trade Commission, 1976). No data were available on US imports and exports.

Toxaphene is not known to be produced commercially in western Europe or Japan; all toxaphene used in western Europe is imported from the US.
(b) Use

Toxaphene is used as an insecticide for the control of grasshoppers, army-worms, cutworms and all major cotton pests. It is also recommended for the control of livestock pests such as flies, lice, ticks, scab mites and mange (Berg, 1978). An estimated 20 million kg toxaphene were used in the US in 1974, as follows: cotton, 85%; livestock and poultry, 7%; other field crops, 5%; soya beans, 3%; and sorghum, less than 1%.

No data on its use in Europe were available; it is not known to have been used in Japan.

Tolerances for residues of toxaphene in or on raw agricultural commodities in the US have been established at 0.1-7 mg/kg for a variety of about 50 fruit, vegetable and meat products (US Environmental Protection Agency, 1976a). The ambient water criterion for toxaphene in US navigable waters is 5 ng/l (US Environmental Protection Agency, 1977a).

A notice of rebuttable presumption against registration and continued registration (RPAR) (see General Remarks on Substances Considered, p. 31) of pesticide products containing toxaphene was issued by the US Environmental Protection Agency on 25 May, 1977 on the basis of possible mutagenic, endocrine, enzymatic and reproductive effects and population reductions in avian species (US Environmental Protection Agency, 1977b). The future insecticidal use of toxaphene will depend largely on the outcome of this action.

The US Occupational Safety and Health Administration's health standards for air contaminants require that an employee's exposure to toxaphene not exceed an 8-hr time-weighted average of 0.5 mg/m³ in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977).

2.2 Occurrence

Toxaphene is not known to occur as a natural product. Reviews on its occurrence and environmental fate have been published (Sheets et al., 1972; US Environmental Protection Agency, 1976b).

(a) Air

Atmospheric levels of toxaphene measured during 1973-1974 ranged from < 0.02-3.3 ng/m³ at a tower on the south shore of Bermuda to < 0.04-1.6 ng/m³ from the bow of a ship in the western North Atlantic; 1.7-5.2 ng/m³ were found in the spring of 1975 at Sapelo Island, Georgia (Bidleman & Olney, 1975).

Weekly air samples were taken in a primary cotton-growing area during 1972-1974. Average monthly atmospheric levels of toxaphene were
found to range from 0-1540 ng/m$^3$, with maximum levels occurring during the late summer months and minimum levels in winter (Arthur et al., 1976).

(b) Water

Toxaphene has been found in 2 US rivers (Shackelford & Keith, 1976), in land run-off water from crop spraying, and in river-water, lakes, aquatic plants, fish and sediments (Eurocop-Cost, 1976). It was detected in 5/8 samples of rainwater, at levels ranging from 44-280 ng/l (Munson, 1976).

(c) Soil and sediments

Toxaphene levels in soil samples from 3 locations in 8 cities during the summer and autumn of 1969 were 0.11, 12 and 15-53 mg/kg (Wiersma et al., 1972); those in 14 US cities during the summer and autumn of 1970 were 7.7-33.4 mg/kg in 3/28 samples from one location and 16.1 mg/kg in 1/27 samples from another (Carey et al., 1976).

Sediment samples, collected at varying depths by 10 cm increments up to 80 cm, were taken 0.2, 0.8 and 1.4 miles from the outfall of a toxaphene plant. Toxaphene levels ranged from 5.27 mg/kg (in a 70-80 cm sediment sample from the site farthest from the plant) to 1,858 mg/kg (in a surface-10 cm sample from the site closest to the toxaphene plant) (Durant & Reimold, 1972).

Forty-five percent of toxaphene applied to sandy loam soil in 1951 remained 20 years later (Nash et al., 1973).

(d) Animals

Toxaphene was found in 96% of samples of 50 catfish taken from commercial ponds in spring 1970, at an average concentration of 1.98 mg/kg (Hawthorne et al., 1974).

Samples of meat were collected from bobwhite quail, rabbits and white-tailed deer found in or near toxaphene-treated soya bean fields during the summer and autumn of 1960 and 1969. Toxaphene was found in 5/20 quail, in amounts ranging from 10.3-88.9 mg/kg; in 2/31 rabbits, at levels of 1.2 and 12.35 mg/kg; and in 3/22 deer, at levels of 1.7-8.7 mg/kg (Causey et al., 1972).

Toxaphene was detected in all 21 brown pelican eggs collected during 1973 in a small breeding colony, at levels ranging from 0.12-0.58 mg/kg (Blus et al., 1975). It was also detected in 3/50 bats (Reidinger, 1976).
(e) Occupational exposure

Toxaphene levels in the air of manufacturing plants in the USSR were found to exceed by 5-6 times the permissible level of 0.2 mg/m³. By the end of the work shift, concentrations on uncovered parts of the skin of employees were 30-1000 mg/m²; covered skin areas had toxaphene concentrations of up to 40 mg/m² (Ashirova, 1971).

(f) Other

Toxaphene levels in samples of cigarettes, cigars, smoking tobacco, chewing tobacco and snuff purchased at a retail market over the period 1971-1973 were found to decrease: in cigarettes, the average concentration decreased from 3.3 to 1.4 mg/kg (Domanski et al., 1974).

Residues of toxaphene in 6 brands of cigars purchased in 5 cities ranged from < 0.5-3.42 mg/kg (Domanski & Guthrie, 1974).

Toxaphene levels in auction-market flue-cured, Burley and fire- and air-cured tobacco were sampled in 1970 and 1972. In 1972, 90% of the flue-cured samples contained toxaphene, at mean concentrations of 0.51-1.93 mg/kg; whereas in 1970 less than 30% contained toxaphene. In 1972, 50% of the Burley tobacco samples had toxaphene concentrations greater than 0.5 mg/kg, whereas in 1970, only 18% of the samples were found to contain toxaphene. Fire- and air-cured tobaccos contained mean levels of 0.19-1.20 mg/kg toxaphene in 1972 (Domanski et al., 1975). Toxaphene residues in individual samples of flue-cured tobacco ranged from < 0.3-7.7 mg/kg (Domanski & Sheets, 1976).

Toxaphene residue levels in sugarbeet pulp samples collected from 57 processing plants in 16 states in the autumn of 1970 ranged from 0-0.34 mg/kg (Yang et al., 1976).

2.3 Analysis

After fractionation using silica-gel column chromatography, combined gas chromatography/chemical ionization/mass spectrometry was used to establish that commercial toxaphene is a complex mixture of at least 177 polychlorinated 10-carbon derivatives (Holmsted et al., 1974). Infra-red and mass spectrometry and hydrogen and carbon-13 nuclear magnetic resonance spectral analysis have been used to characterize its composition (Parlar et al., 1977).

The Association of Official Analytical Chemists' method to determine the contamination of other pesticide formulations by chlorinated pesticides (Horwitz, 1975) has been studied collaboratively, and a discussion of the method and the problems encountered has been published (Bontoyan & Jung, 1972). The recovery procedures of this method have also been discussed in detail in the Pesticide Analytical Manual,
published by the US Food and Drug Administration. More than 80% of toxaphene was found to be recovered by this procedure (US Food & Drug Administration, 1975).

Pesticide residues, including toxaphene, have been recovered quantitatively from flour, fruit, vegetables and tobacco by steam distillation followed by continuous extraction of the distillate with toluene (Stijve & Cardinale, 1973).

Methods used for the analysis of toxaphene in environmental samples are listed in Table 1.

Reverse-phase partition thin-layer chromatography has also been used to separate toxaphene from other chlorinated hydrocarbons, with detection of levels of 2.5 µg/sample (Ismail & Bonner, 1974). Thin-layer chromatography has been used to determine toxaphene in soil, beetroots and potatoes (Kosmatyi & Gritsaenko, 1970) and in prepared samples (Geike, 1971; Thielemann, 1973).

The Pesticide Analytical Manual cites two colorimetric methods to determine toxaphene: (1) in all types of environmental samples, by fusion with diphenylamine in the presence of zinc chloride, with a limit of detection of 2 mg/kg in fats and 0.1 mg/kg in crops; and (2) by extraction in ethanol, boiling with dilute nitric acid, treatment with sodium hydroxide and pyridine, and measurement at 410 and 440 nm (US Food & Drug Administration, 1975).

Toxaphene has been determined colorimetrically in water by treatment with pyridine, alkali and ethyl cyanoacetate and measurement of the resulting complex at 550 nm, with a limit of detection of 15 µg/l (Hempel et al., 1971).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female 5-week-old B6C3F1 mice were fed technical-grade toxaphene in the diet. Initially, high-dose animals received 320 mg/kg diet for 19 weeks followed by 160 mg/kg diet for a further 61 weeks; low-dose animals received 160 mg/kg diet for 19 weeks and 80 mg/kg diet for a further 61 weeks. A toxaphene-free diet was then fed for 10-11 weeks. A group of 10 male and 10 female mice served as matched controls and received untreated diet for 90-91 weeks. The time-weighted average doses were 99 mg/kg diet (low dose) and 198 mg/kg
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
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<tr>
<td><strong>Formulations</strong></td>
<td>Formulations contaminated with 0.05-0.1% toxaphene</td>
<td>Extract (acetone), centrifuge</td>
<td>TLC (revelation: silver nitrate-ultra-violet)</td>
<td>Horwitz (1975)</td>
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<tr>
<td><strong>Air</strong></td>
<td>Workplace</td>
<td>Trap on cellulose membrane, extract (petroleum ether)</td>
<td>GC/ECD</td>
<td>0.225-1.155 mg/m³</td>
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<td><strong>Water</strong></td>
<td>Fish-tank</td>
<td>Extract (acetone-petroleum ether) in a special syphon system, wash resulting water-acetone layer (petroleum ether), bulk petroleum ether fractions, GC</td>
<td>GC/ECD, GC/MS</td>
<td>10 µg/l</td>
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<td><strong>Soil</strong></td>
<td>Extract (hexane-acetone-methanol): in Soxhlet or on a column, or extract by shaking (hexane-acetone-ammonium chloride solution)</td>
<td>GC/ECD</td>
<td>GC/ECD</td>
<td>0.05-0.1 mg/kg</td>
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<td>Moisten (water), extract (hexane-isopropanol), wash (water)</td>
<td>GC/ECD</td>
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<td>Extract (hexane-isopropanol), filter, wash (water)</td>
<td>GC/flame photometric detection</td>
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<td>Molasses</td>
<td>Dilute (water), extract (hexane-isopropanol)</td>
<td>GC/ECD</td>
<td>0.03 mg/kg</td>
<td>Yang et al. (1976)</td>
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<td>Fitch</td>
<td>Extract (hexane-isopropanol) in blender, filter, wash (water), liquid/liquid partition, CC</td>
<td>GC/ECD</td>
<td>0.01 mg/kg</td>
<td>Hawthorne et al. (1974)</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td>Extract (acetone) in blender, filter, extract (petroleum ether-dichloromethane), wash aqueous phase (dichloromethane), bulk solvent extracts, evaporate to small bulk, add acetone, reduce volume and repeat, CC</td>
<td>GC/ECD</td>
<td></td>
<td>Luke et al. (1975)</td>
</tr>
<tr>
<td><strong>Fish</strong></td>
<td>Freeze, grind in blender with dry ice, place in freezer overnight to allow dry ice to sublime, mix with anhydrous sodium sulphate, extract (ether-petroleum ether) in a column, add cyclohexane, reduce volume, multiple CC (an additional wash with sodium hydroxide may be required)</td>
<td>GC/ECD</td>
<td>30 µg/kg</td>
<td>Stalling &amp; Huckins (1976)</td>
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<td><strong>Biological</strong></td>
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<tr>
<td>Tissues</td>
<td>Macerate, add anhydrous sodium sulphate, extract (acetone), add water, extract (chloroform), wash (potassium hydroxide-water)</td>
<td>TLC (revelation: 14 reagents compared)</td>
<td>1 µg (on the plate)</td>
<td>Tewari &amp; Sharma (1977)</td>
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<tr>
<td>Stomach washings and urine</td>
<td>Extract (hexane)</td>
<td>TLC (revelation: 14 reagents compared)</td>
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<td>Tewari &amp; Sharma (1977)</td>
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<tr>
<td>Blood</td>
<td>Add dilute sulphuric acid and sodium tungstate solution, filter extract (hexane)</td>
<td>TLC (revelation: 14 reagents compared)</td>
<td></td>
<td>Tewari &amp; Sharma (1977)</td>
</tr>
</tbody>
</table>

Abbreviations: TLC - thin-layer chromatography; GC/ECD - gas chromatography/electron capture detection; CC - column chromatography; MS - mass spectrometry
diet (high dose). Further control data were obtained from 50 male and 50 female pooled controls from other experiments. There was a dose-related decrease in survival of male mice and a decrease in the survival of high-dose females: in male mice, 46/50 (92%) of the high-dose group, 49/50 (98%) of the low-dose group and all 10 animals of the matched control group lived beyond week 52 of the study; in females, 46/50 (92%) of the high-dose group, 46/50 (92%) of the low-dose group and 9/10 (90%) of the matched control group lived beyond week 52 of the study; at 90 weeks, 21/50 (42%) high-dose males and 37/50 (74%) high-dose females were still alive. An increased incidence of hepatocellular carcinomas was found in treated mice: in males: matched controls, 0/10; pooled controls, 4/48 (8%); low dose, 34/49 (69%); high dose, 45/46 (98%); in females: matched controls, 0/9; pooled controls, 0/48; low dose, 5/49 (10%); high dose, 34/49 (69%). In addition, neoplastic nodules of the liver occurred in 2/10 matched control males, 6/49 low-dose males, 0/9 matched control females, 13/49 low-dose females and 6/49 high-dose females (National Cancer Institute, 1979).

Rat: Groups of 50 male and 50 female 5-week-old Osborne-Mendel rats were fed diets containing technical-grade toxaphene. High-dose male rats received 2560 mg/kg diet for 2 weeks, 1280 mg/kg diet for 53 weeks, 640 mg/kg diet for a further 25 weeks, followed by a toxaphene-free diet for 28 weeks. High-dose females received 1280 mg/kg diet for 55 weeks, 640 mg/kg diet for 25 weeks, followed by a toxaphene-free diet for 30 weeks. Low-dose males received 1280 mg/kg diet for 2 weeks, 640 mg/kg diet for 53 weeks, 320 mg/kg diet for 25 weeks, followed by a toxaphene-free diet for 28 weeks. Low-dose females received 640 mg/kg diet for 55 weeks, 320 mg/kg diet for 25 weeks, followed by a toxaphene-free diet for 30 weeks. Time-weighted average doses were 556 and 540 mg/kg diet for low-dose males and females, and 1112 and 1080 mg/kg diet for high-dose males and females, respectively. Groups of 10 male and 10 female rats that served as matched controls were given a toxaphene-free diet for 108-109 weeks; 55 untreated male and 55 untreated female rats from other experiments served as pooled controls. In male rats, 45/50 (90%) of the high-dose group, 47/50 (94%) of the low-dose group and all 10 rats of the matched control group were still alive at week 52 of the study; in females, 48/50 (96%) of the high-dose group, 46/50 (92%) of the low-dose group and all 10 rats of the matched control group were still alive at week 52. In male rats, the combined incidence of follicular-cell carcinomas and adenomas of the thyroid was increased to a statistically significant extent in the high-dose group, compared with pooled controls (P = 0.008) (1/7 in matched controls, 2/44 in pooled controls, 7/41 in low-dose and 9/35 in high-dose animals). In females, the incidences of follicular-cell adenomas of the thyroid were 0/6 in matched controls, 1/46 in pooled controls, 1/43 in low-dose animals and 7/42 in high-dose animals (P = 0.021 compared with pooled controls). The incidence of adenomas, chromophobe adenomas or carcinomas of the pituitary in high-dose females was 23/39, compared with
3.2 Other relevant biological data

A review on toxaphene is available (Pollock & Kilgore, 1978).

(a) Experimental systems

Toxic effects

In Sherman rats, the oral LD₅₀ of technical-grade toxaphene is 90 mg/kg bw in males and 80 mg/kg bw in females (Gaines, 1960). In male Wistar rats fed a 3.5% casein diet, the oral LD₅₀ of technical-grade toxaphene is 80 mg/kg bw; in those fed a 26% casein diet, 293 mg/kg bw; and in those fed standard laboratory chow, 220 mg/kg bw (Boyd & Taylor, 1971). In fasted dogs, the oral LD₅₀ of toxaphene is 25 mg/kg bw (Lackey, 1949). In male mice, the i.p. LD₅₀ of technical-grade toxaphene is 42 mg/kg bw. Two toxic fractions gave i.p. LD₅₀ values of 3.1 and 6.6 mg/kg bw (Khalifa et al., 1974); the first was identified as a mixture of 2,2,5-endo,6-exo,8,8,9,10-octachlorobornane and 2,2,5-endo,6-exo,8,9,9,10-octachlorobornane (Turner et al., 1975) and the second as 2,2,5-endo-6-exo,8,9,10-heptachlorobornane (Casida et al., 1974).

In Sherman rats, the dermal LD₅₀ of technical-grade toxaphene is 1075 mg/kg bw in males and 780 mg/kg bw in females (Gaines, 1960).

The LC₅₀ in mice for inhalation of an oil-based mist of toxaphene was 20 mg/m³ air over a 2-hr exposure (Conley, 1952).

Signs of acute toxaphene poisoning are clonic-tonic convulsions, salivation, vomiting and hyperreflexia; death has been attributed to respiratory failure (Boyd & Taylor, 1971; Conley, 1952; Lackey, 1949). In rats, renal tubular damage and fatty degeneration of the liver with necrosis are observed (Boyd & Taylor, 1971).

Feeding of 5, 50 and 100 mg/kg diet toxaphene to chickens for 31 weeks produced sternal deformation, resembling osteomalacia, and nephrosis of the kidney. Occasional keel deformation, involving the cartilaginous tissue as well as an apparent increase in the growth of cartilage, was found in birds fed 0.5 mg/kg diet toxaphene (Bush et al., 1977).

In some Sherman rats fed 50 and 200 mg/kg diet toxaphene for 2-9 months, centrilobular hypertrophy of liver cells was observed (Ortega et al., 1957); however, no effects on liver-cell histology were observed by Clapp et al. (1971) in rats fed up to 189 mg/kg diet toxaphene for 12 weeks.
Alterations to serum alkaline phosphatase activity, indicating liver damage, have been observed in rats fed toxaphene (Gertig & Nowaczyk, 1975; Crebenyuk, 1970); it induces various hepatic microsomal enzymes, such as O- and N-demethylases (Kinoshita et al., 1966) and androgen hydroxylase (Peakall, 1976); it also stimulates oestrone metabolism in rats (Welch et al., 1971). Phenobarbital sleeping times were reduced in rats given toxaphene orally by gavage (Schwabe & Wendling, 1967).

Administration of 5, 50 or 500 mg/kg diet toxaphene to quail for up to 4 months produced hypertrophy of the thyroid, with increased uptake of $^{131}$I and adrenal hypertrophy (Hurst et al., 1974).

Embryotoxicity and teratogenicity

Administration of 25 mg/kg diet toxaphene to mice through 5 generations produced no embryotoxicity or teratogenicity (Keplinger et al., 1968). In a 3-generation reproduction study, Sprague-Dawley rats received either 25 or 100 mg/kg diet toxaphene; no effects on litter size, pup survival, weanling body weights or reproductive capacity were observed (Kennedy et al., 1973).

Toxaphene was administered by oral intubation to CD-1 mice and CD rats during the period of embryonic organogenesis (days 7-16 of gestation) at dose levels of 0, 15, 25 and 35 mg/kg bw/day. The highest dose produced marked maternal mortality in rats and mice and an increase in the incidence of encephaloceles among offspring of mice. Foetal mortality was slightly increased in mice at all three dose levels. Small decreases in foetal body weight and in the number of sternal and caudal ossification centres were seen in rats, mostly in those receiving the 25 mg/kg bw dose (Chernoff & Carver, 1976).

Injection of 1.5 mg/egg toxaphene had no effect on hatchability rates of the eggs of chickens (Smith et al., 1970). In a similar study, no embryotoxicity was observed in chicken embryos hatched from eggs previously injected with 400 or 500 mg/kg toxaphene in acetone; although when it was dissolved in corn oil embryotoxicity was seen with 300-400 mg/kg (Dunachie & Fletcher, 1969).

Absorption, excretion, distribution and metabolism

In mice and rats, toxaphene is absorbed through the skin and gastrointestinal tract, at a rate depending upon the vehicle used for its administration. Of a single oral dose of 20 mg/kg bw technical-grade $^{36}$Cl-toxaphene administered in 0.5 ml peanut oil/acacia gum to rats, about 52% was excreted within 9 days: 15% in the urine, mainly as $^{36}$Cl-ion, and 37% in the faeces (Crowder & Dindal, 1974).

Three percent of an oral dose of $^{14}$C-toxaphene was excreted unchanged in the faeces of rats. More than 5% of the administered dose was excreted
in the urine and faeces as completely dechlorinated metabolites and 27% as partially dechlorinated metabolites; 2% of the activity was found in expired air, probably as $^{14}$CO$_2$. Less than 1 $\mu$g toxaphene or metabolites was found in each of fat, liver, kidney, blood, bone, brain, heart, lung, muscle, spleen and testis 14 days after a 19 mg/kg bw dose of $^{14}$C-toxaphene. Following administration of $^{36}$Cl-toxaphene, 50% of the activity was excreted as $^{36}$Cl- ion in the urine (Ohsawa et al., 1975).

Administration of 2.5-20 mg/kg diet toxaphene to cows resulted in a dose-related increase in the excretion of toxaphene in the milk (0.043-0.179 mg/l) (Zweig et al., 1963).

**Mutagenicity and other related short-term tests**

Toxaphene is mutagenic in the Salmonella typhimurium test without requiring liver homogenate for activity (Hooper et al., 1979).

Toxaphene did not induce dominant lethal mutations in ICR/Ha Swiss mice. When males were injected intraperitoneally with 36 and 180 mg/kg bw and bred with untreated females during 8 weeks, the frequency of early foetal deaths and preimplantation losses was within control limits. Negative results were also obtained in animals treated orally for 5 successive days with 40 or 80 mg/kg bw (Epstein et al., 1972).

(b) **Humans**

The acute lethal dose for humans has been estimated to be between 2-7 g/person (Conley, 1952).

A 9-month-old child poisoned with a 2:1 mixture of toxaphene:DDT died after convulsions and respiratory arrest. The ratio of toxaphene: DDT in the brain and liver was 10:1 and in the kidneys 3:1 (Haun & Cueto, 1967). Four other cases of acute poisoning in children, 3 of which were fatal, have been reported (McGee et al., 1952).

Allergic bronchopneumonia was observed in two workers using toxaphene sprays (Warraki, 1963).

Eight women working in an area which had been sprayed with 2 kg/ha toxaphene by aircraft had a higher incidence of chromosome aberrations (acentric fragments and chromatid exchanges), as observed in lymphocyte cultures, compared with an unspecified number of control individuals: 13.1% versus 1.6% (Samosh, 1974).

No significant levels of toxaphene were found in skin fat and attached subcutaneous tissue taken from 68 newborns in 13 cities in the US (Zavon et al., 1969).
3.3 Case reports and epidemiological studies

Two cases of acute aplastic anaemia associated with dermal exposure to toxaphene: lindane mixtures have been reported. One of these cases terminated in death due to acute myelomonocytic leukaemia (US Environmental Protection Agency, 1978).

An increased incidence of lung cancer (10 observed versus 0.54 expected) was reported among 285 workers who applied various pesticides in agricultural settings. Some of these workers were exposed to toxaphene (Barthel, 1976) [The Working Group noted that since they may have been exposed to compounds other than toxaphene or in addition to toxaphene, no evaluation specific for toxaphene could be made on the basis of this study; see also monograph on hexachlorocyclohexane (technical HCH and lindane), p. 195].

In a survey of 199 employees who worked or had worked with toxaphene between 1949 and 1977, with exposures ranging from 6 months to 26 years (mean, 5.23 years), 20 employees died, 1 with cancer of the colon; none of these deaths appeared to be related to exposure to toxaphene (Anon., 1977; Ottoboni, 1977; US Environmental Protection Agency, 1977c).

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Toxaphene (polychlorinated camphenes) was tested in one experiment in mice and in one in rats by oral administration: a dose-related increase in the incidence of hepatocellular carcinomas was observed in male and female mice, and an increased incidence of thyroid tumours was observed in male and female rats.

Toxaphene is mutagenic in Salmonella typhimurium; it did not induce dominant lethals in mice.

4.2 Human data

No epidemiological studies relating specifically to the carcinogenicity of toxaphene were available to the Working Group.

Two cases of acute aplastic anaemia associated with dermal exposure to toxaphene: lindane mixtures have been reported, one terminating in death due to acute myelomonocytic leukaemia. The only epidemiological study that related to possible carcinogenic effects of toxaphene in humans has weaknesses which prevented the Working Group from drawing any conclusion specific to toxaphene.
An increased frequency of chromosomal aberrations has been observed in the lymphocytes of workers exposed to toxaphene.

The extensive production and the widespread use of toxaphene, together with the persistent nature of the compound, indicate that human exposure occurs. This is confirmed by many reports of its occurrence in the general environment.

4.3 Evaluation

There is sufficient evidence that toxaphene is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard toxaphene as if it presented a carcinogenic risk to humans.
TOXAPHENE

5. References


TOXAPHENE

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2,4,5- AND 2,4,6-TRICHLOROPHENOLS

1. Chemical and Physical Data

1.1 Synonyms and trade names

2,4,5-Trichlorophenol
Chem. Abstr. Services Reg. No.: 95-95-4
Chem. Abstr. Name: 2,4,5-Trichlorophenol
Trade names: Collunosol; Dowicide 2; Dowicide B; Nurelle; Preventol I

2,4,6-Trichlorophenol
Chem. Abstr. Name: 2,4,6-Trichlorophenol
Synonym: Trichlorfenol
Trade names: Dowicide 2S; Omal; Phenachlor

1.2 Structural and molecular formulae and molecular weights

2,4,5-Trichlorophenol

\[
\text{C}_6\text{H}_3\text{Cl}_3\text{O} \quad \text{Mol. wt: 197.5}
\]

2,4,6-Trichlorophenol

\[
\text{C}_6\text{H}_3\text{Cl}_3\text{O} \quad \text{Mol. wt: 197.5}
\]
1.3 Chemical and physical properties of the pure substances

2,4,5-Trichlorophenol

From Windholz (1976), unless otherwise specified

(a) Description: Grey flakes (Hawley, 1977)

(b) Boiling-point: 248°C (746 mm); 253°C (760 mm)

(c) Melting-point: 67°C

(d) Spectroscopy data: \( \lambda_{\text{max}} \) 299 nm \( (E_1^1 = 140) \); 292 nm \( (E_1^1 = 145) \) in methanol; infra-red, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(e) Solubility: g/100 g solvent at 25°C: acetone, 615; benzene, 163; carbon tetrachloride, 51; diethyl ether, 525; denatured ethanol, 525; methanol, 615; liquid petrolatum (at 50°C), 56; soya bean oil, 79; toluene, 122; water, < 0.2

(f) Volatility: Vapour pressure is 1 mm at 72°C (Perry & Chilton, 1973).

(g) Stability: Stable up to its melting-point

(h) Reactivity: Can be converted to sodium salt by reaction with sodium carbonate; the hydroxyl group forms ethers, esters and salts with metals and amines; aromatic portion undergoes substitution reactions such as nitration, alkylation, acetylation and halogenation; chlorine atoms can be hydrolysed to produce polyhydroxyl benzenes, by reaction with bases at elevated temperatures and pressures; oxidative decomposition occurs with strong oxidizing agents (Howard & Durkin, 1973).

2,3,7,8-Tetrachlorodibenzo-\( \text{para} \)-dioxin may be formed as a by-product during the synthesis of 2,4,5-trichlorophenol by the hydrolysis of 1,2,4,5-tetrachlorobenzene using methanol and sodium hydroxide at elevated pressure or ethylene glycol and sodium hydroxide at atmospheric pressure. In the latter case,
if the reaction temperature exceeds the normal 180°C process temperature, 2,3,7,8-tetrachlorodibenzo-\textit{para}-dioxin is formed by the condensation of two molecules of sodium 2,4,5-trichlorophenate under the influence of the exothermic decomposition of sodium-2-hydroxyethanol (Milnes, 1971). For additional information see IARC monograph on chlorinated dibenzo-\textit{para}-dioxins (IARC, 1977a).

\textbf{2,4,6-Trichlorophenol}

From Windholz (1976), unless otherwise specified

(a) \textbf{Description}: Yellow flakes (Hawley, 1977)

(b) \textbf{Boiling-point}: 246°C

(c) \textbf{Melting-point}: 69°C

(d) \textbf{Spectroscopy data}: \mbox{$\lambda_{\text{max}}$} 296 nm ($E_{1}^{1} = 129$); 289 nm ($E_{1}^{1} = 125$) in methanol; infra-red, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(e) \textbf{Solubility}: g/100 g solvent at 25°C: acetone, 525; benzene, 113; carbon tetrachloride, 37; diaceton alcohol, 335; diethyl ether, 354; denatured ethanol, 400; methanol, 525; pine oil, 163; Stoddard solvent, 16; toluene, 100; turpentine, 37; water, < 0.1

(f) \textbf{Volatility}: Vapour pressure is 1 mm at 76.5°C (Perry & Chilton, 1973).

(g) \textbf{Stability}: Stable up to its melting-point. Heating of the phenate to 280°C produced < 0.1 mg/kg octa- and heptachlorinated dibenzo-\textit{para}-dioxins and < 0.02-0.03 mg/kg hexa-, penta- and tetrachlorinated dibenzo-\textit{para}-dioxins (Rappe \textit{et al}., 1978).

(h) \textbf{Reactivity}: Can be converted to sodium salt by reaction with sodium carbonate; the hydroxyl group forms ethers, esters and salts with metals and amines; the aromatic portion undergoes
substitution reactions such as nitration, alkylation, acetylation and halogenation; chlorine atoms can be hydrolysed to produce polyhydroxy benzenes, by reaction with bases at elevated temperatures and pressures; oxidative decomposition occurs with strong oxidizing agents (Howard & Durkin, 1973).

1.4 Technical products and impurities

2,4,5-Trichlorophenol is available in the US as a 95% technical grade product. Formulations available in the US are concentrated aqueous and non-aqueous solutions, concentrated solids and emulsifiable concentrates. A liquid formulation contains 45.9% 2,4,5-trichlorophenol as the sodium salt.

2,4,6-Trichlorophenol available in Japan has a purity of 97%. It is available in the US in aqueous formulations.

2,3,7,8-Tetrachlorodibenzo-\textit{para}-dioxin was found in 3/6 samples of 2,4,5-trichlorophenol (or its sodium salt) in the range of 0.07–6.2 mg/kg. 2,7-Dichloro-, 1,3,6,8-tetrachloro- and pentachlorodibenzo-\textit{para}-dioxins were found in concentrations of 0.72, 0.30 and 1.5 mg/kg, respectively (Firestone \textit{et al.}, 1972).

1,3,6,8-Tetrachlorodibenzo-\textit{para}-dioxin and 2,3,7-trichlorodibenzo-\textit{para}-dioxin were found in a sample of 2,4,6-trichlorophenol at levels of 49 and 93 mg/kg, respectively. In the same study, tri-, tetra- and pentachlorodimethoxy-dibenzofurans were present in 3/6 samples of 2,4,5-trichlorophenol or its sodium salt; and tetra-, penta- and hexachlorodibenzo-furans were found in one sample of 2,4,6-trichlorophenol (Firestone \textit{et al.}, 1972).

In a Swedish sample of 2,4,6-trichlorophenol, 1.5 mg/kg 2,3,7,8-tetrachlorodibenzo-furan was found, as well as 17.5, 36 and 4.8 mg/kg penta-, hexa- and heptachlorodibenzo-furans; less than 3 mg/kg poly-chlorinated dibenzo-\textit{para}-dioxins were found (Rappe \textit{et al.}, 1979).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

2,4,5-Trichlorophenol

2,4,5-Trichlorophenol was first prepared in 1920 by heating 1,2,4,5-tetrachlorobenzene with sodium methoxide (Richter, 1944). It was
manufactured in the US by the hydrolysis of 1,2,4,5-tetrachlorobenzene with methanolic sodium hydroxide at 160°C (Doedens, 1964).

Commercial production of 2,4,5-trichlorophenol in the US was first reported in 1950 (US Tariff Commission, 1951). In 1976, one US company reported production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977a); 87.2 thousand kg were imported through the principal US customs districts in that year (US International Trade Commission, 1977b).

An annual production of 2,4,5-trichlorophenol in Austria is estimated to be 1-10 million kg. It was previously produced in Italy (see IARC, 1977a).

Japanese production of 2,4,5-trichlorophenol was stopped in 1971. Imports since that year have amounted to approximately 10-15 thousand kg annually.

2,4,6-Trichlorophenol

2,4,6-Trichlorophenol was prepared by Laurent in 1836 by chlorination of phenol (Prager et al., 1923), and this method is currently used in the US (Doedens, 1964). In Japan, it is produced as a co-product of ortho- or para-chlorophenol manufacture by the chlorination of phenol.

Commercial production of 2,4,6-trichlorophenol in the US was first reported in 1950 (US Tariff Commission, 1951). In 1974, the last year in which production was reported, one company reported production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1975). In 1976, 1000 kg were imported through the principal US customs districts (US International Trade Commission, 1977b).

No data on its production in Europe were available.

2,4,6-Trichlorophenol has been produced commercially in Japan since 1965. In 1977, one company produced an estimated 120 thousand kg. None was imported or exported.

(b) Use

2,4,5-Trichlorophenol

The major use for 2,4,5-trichlorophenol is as an intermediate in the manufacture of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (see IARC, 1977b) and its esters (Doedens, 1964). It is also used in the manufacture of 3 other chemicals used as pesticides: Silvex [2-(2,4,5-trichlorophenoxy)propionic acid], Ronnel (O,O-dimethyl-O-2,4,5-
trichlorophenyl phosphorothioate) and sodium 2,4,5-trichlorophenate (Sittig, 1977). Minor uses of 2,4,5-trichlorophenol itself are as a fungicide and in the manufacture of hexachlorophene (see monograph, p. 241).

The systemic herbicide 2,4,5-T is used to control woody and herbaceous weeds by air or ground spray applications (Hilton et al., 1974). In 1975, an estimated 2 million kg were used for commercial and industrial (non-crop) weed control, and 1 million kg were used on pasture and rangeland. For additional information on 2,4,5-T, see IARC (1977b).

The herbicide Silvex is used to control woody plants, particularly oak and maple; it is also used for weed control in water and turf (Spencer, 1973). In 1975, an estimated 454 thousand kg were used for industrial and commercial weed control, 227 thousand kg for aquatic weed control and 227 thousand kg on pasture and rangeland.

The systemic insecticide Ronnel is used primarily on livestock (Spencer, 1973). In 1974, an estimated 318 thousand kg were used on livestock and poultry and 182 thousand kg for commercial, household and industrial establishment uses.

Sodium 2,4,5-trichlorophenate is registered for use as a fungicide by the US Environmental Protection Agency for pulp and paper mill wet-end systems (US Environmental Protection Agency, 1973) and is approved by the US Food and Drug Administration for use as a preservative in defoaming agents and as a slimicide in the manufacture of paper and paperboard intended for contact with food (US Food & Drug Administration, 1977).

2,4,5-Trichlorophenol is registered for use in the US as a fungicide in polyvinyl acetate emulsions used in adhesives (see IARC, 1979) and as a rubber additive (US Environmental Protection Agency, 1973).

A notice of rebuttable presumption against renewal of registration (RPAR) (see General Remarks on Substances Considered, p. 31) has been issued for 2,4,5-trichlorophenol and its salts, because of carcino- genetic and foetotoxic effects and possible effects of chlorinated dibenzo-para-dioxins (US Environmental Protection Agency, 1978).

No data on its use in Europe were available.

2,4,5-Trichlorophenol is used in Japan primarily for antiseptic applications in industrial use.

2,4,6-Trichlorophenol has been used as a wood preservative, glue preservative, insecticide ingredient, bactericide and an antimildew
treatment for textiles (Doedens, 1964). It can also be used to prepare the following fungicides (although they are not believed to be produced commercially from 2,4,6-trichlorophenol): chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone), pentachlorophenol and 2,3,4,6-tetrachlorophenol (Doedens, 1964; Sittig, 1977).

No data on its use in Europe were available.

In Japan, 2,4,6-trichlorophenol is used primarily as a wood preservative.

2.2 Occurrence

2,4,5- and 2,4,6-Trichlorophenol are not known to occur as natural products. 2,4,5-Trichlorophenol is a major contaminant of 2,4,5-T, Silvex and Ronnel (IARC, 1977b; Sittig, 1977).

(a) Water

Trichlorophenol (unspecified isomers) has been found in 1 river-water sample, 4 finished drinking-water samples, 4 chemical plant effluent water samples and 2 sewage treatment plant effluent samples in the US (Shackelford & Keith, 1976).

Trichlorophenol (unspecified isomers) has been detected in river-water, landfill leachate (at a level of 40 μg/l), tap-water (at levels of 2 and 4 ng/l), and in chlorinated, biologically-treated effluent from a sewage plant (Eurocop-Cost, 1976).

2,4,5-Trichlorophenol was detected at unspecified concentrations in drinking-water in 1975 (Deinzer et al., 1975).

(b) Animals

2,4,6-Trichlorophenol was found at levels of 16-45 mg/kg in body fat of rainbow trout after experimental exposure to sulphate pulp bleaching effluents diluted 40 times with brackish water (Landner et al., 1977).

(c) Food

Following treatment of corn and pea seedlings with γ-pentachlorocyclohex-1-ene, a metabolic product of lindane in plants, the plant roots were homogenized and extracted with hexane. The extract of corn seedlings were found to contain 2,4,5-trichlorophenol and the pea seedling extract both 2,4,5- and 2,4,6-trichlorophenol (Mostafa & Maza, 1973).
(d) Occupational exposure

A 1974 National Occupational Hazard Survey estimated that workers primarily exposed to 2,4,5-trichlorophenol were those in the crude petroleum and natural gas and telephone and telegraph industries. Worker exposure to 2,4,6-trichlorophenol was primarily in hospitals, where it is used as a bactericide, and in the leather tanning and finishing industry (National Institute for Occupational Safety & Health, 1977).

2.3 Analysis

Analytical techniques used to determine chlorophenols, including 2,4,5- and 2,4,6-trichlorophenols, in trace amounts in environmental samples have been reviewed (Howard & Durkin, 1973).

Methods used for the analysis of 2,4,5- and 2,4,6-trichlorophenols in environmental samples are listed in Table 1.

A method employing reverse osmosis to concentrate 2,4,6-trichlorophenol and other organic contaminants from a 1600-litre sample of tap-water has been described (Deinzer et al., 1975). Ultra-violet spectrometry at 312 nm has been evaluated as a method for the determination of 2,4,6-trichlorophenol in water samples in the range of 0-20 mg/l (Shibata et al., 1976).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 18 male and 18 female (C57BL/6xC3H/Anf)F1 mice and 18 male and 18 female (C57BL/6xAKR)F1 mice received commercial 2,4,6-trichlorophenol (Omal; Dowicide 2S; impurities unspecified) according to the following schedule: 100 mg/kg bw in 0.5% gelatin at 7 days of age by stomach tube and the same amount (not adjusted for increasing body weight) daily up to 4 weeks of age; subsequently, the mice were fed 260 mg/kg diet until they reached 78 weeks of age, at which time 10, 16, 16 and 17 mice were still alive in the 4 groups, respectively. The dose was the maximum tolerated dose for infant
# Table 1. Methods for the Analysis of 2,4,5- and 2,4,6-Trichlorophenols

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Extraction/Clean-Up</th>
<th>Detection</th>
<th>Limit of Detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Adsorb on ion exchanger, remove water, extract (benzene), methylate</td>
<td>GC/ECD</td>
<td>1 ng/l</td>
<td>Renberg (1974)</td>
</tr>
<tr>
<td>Soil</td>
<td>Centrifuge, extract solid (acetone), liquid/liquid partition, transfer into trimethyl pentane, treat to remove sulphur, isolate in trimethylpentane, methylate or acetyl-ate</td>
<td>GC/ECD</td>
<td>1-10 µg/kg</td>
<td>Jensen et al. (1977)</td>
</tr>
<tr>
<td>Sediment and sewage sludge</td>
<td>Centrifuge slurry with alkali, adsorb on ion exchanger, extract (benzene), methylate</td>
<td>GC/ECD</td>
<td>0.1 µg/kg</td>
<td>Renberg (1974)</td>
</tr>
<tr>
<td>Food</td>
<td>Hydrolyse (acid), extract (ether), CC</td>
<td>GC/ECD or micro-coulometry</td>
<td>50 µg/l</td>
<td>Bjerke et al. (1972)</td>
</tr>
<tr>
<td>Biological</td>
<td>Distill from acid into alkali, acidify distillate, extract (dichloromethane), remove solvent, dissolve (hexane), silylate</td>
<td>GC/ECD</td>
<td>50 µg/kg</td>
<td>Clark et al. (1975)</td>
</tr>
<tr>
<td>Muscle, fat, liver and kidney</td>
<td>Digest (caustic potash), then proceed as above</td>
<td>GC/ECD</td>
<td>50 µg/kg</td>
<td>Clark et al. (1975)</td>
</tr>
<tr>
<td>Rat urine</td>
<td>Hydrolyse (acid), extract (ether), ethylate, CC</td>
<td>GC/ECD</td>
<td>10 µg/l</td>
<td>Shafik et al. (1973)</td>
</tr>
<tr>
<td>Tissue</td>
<td>Homogenize (hexane-acetone), liquid/liquid partition, adsorb on ion exchanger, extract (benzene), methylate</td>
<td>GC/ECD</td>
<td>0.1 µg/kg</td>
<td>Renberg (1974)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
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<tr>
<td>---------------------</td>
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<td>-----------</td>
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<td>---------------------------</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broiler house litter</td>
<td>Extract (pentane), re-extract (sodium hydroxide), acidify, extract (pentane), methylate</td>
<td>GC/ECD</td>
<td></td>
<td>Land et al. (1975)</td>
</tr>
<tr>
<td>Bleach liquors</td>
<td>Extract (ether), wash extract (sodium hydrogen carbonate), re-extract (sodium hydroxide), acidify, extract (ether), transfer to isooctane-ethanol, purify by HPLC, ethylate</td>
<td>GC/FID</td>
<td>pg range</td>
<td>Lindström &amp; Nordin (1976)</td>
</tr>
</tbody>
</table>

Abbreviations: GC - column chromatography; GC/ECD - gas chromatography/electron capture detection; FID - flame-ionization detection; MS - mass spectrometry; HPLC - high-pressure liquid chromatography
and young mice [but not necessarily that for adults]. The total numbers of tumour-bearing animals were 9/18, 7/18, 3/17 and 2/17 in treated males and females of the 2 strains, compared with 22/79, 8/87, 16/90 and 7/82 in pooled controls. Statistically significant increases \[P < 0.05\] in the incidences of hepatomas (5/36) and reticulum-cell sarcomas (6/36) were observed in mice of the first strain when the numbers of tumours in males and females were combined (Innes et al., 1969; National Technical Information Service, 1968) [The Working Group noted, however, that the statistical significance of the results disappears when the incidences in males and females are considered separately, or when matched controls are considered].

(b) Subcutaneous and/or intramuscular administration

**Mouse:** Groups of 18 male and 18 female (C57BL/6xC3H/Anf)F1 mice and 18 male and 18 female (C57BL/6xAKR)F1 mice were given single s.c. injections of 464 mg/kg bw commercial 2,4,6-trichlorophenol (Omal; Dowicide 2S; impurities unspecified) in corn oil at 28 days of age. Similar groups received 1000 mg/kg bw commercial 2,4,5-trichlorophenol (Collunol; Dowicide 2; impurities unspecified) in corn oil. Animals were observed until about 78 weeks of age, when all mice treated with 2,4,6-trichlorophenol and 16, 11, 18 and 18 mice treated with 2,4,5-trichlorophenol were still alive in the 8 groups, respectively. A negative control group comprised of animals that were either untreated or received gelatin, corn oil or dimethylsulphoxide and comprised 141 males and 154 females of the first strain and 161 males and 157 females of the second strain. Tumour incidences were not increased in the treated mice \[P > 0.05\] (National Technical Information Service, 1968) [The Working Group noted that a negative result obtained with a single s.c. injection is not an adequate basis for discounting carcinogenicity].

(c) Other experimental systems

**Promotion:** A single application of 75 \(\mu\)g dimethylbenz[\(\alpha\)]anthracene (DMBA) (25 \(\mu\)l of a 0.3% solution in acetone) was painted on the dorsal skin of 20 female Sutter mice, 2-3 months old, followed by application of one drop (approximately 25 \(\mu\)l) of commercial 2,4,5-trichlorophenol (producer and impurities unspecified) dissolved in reagent-grade acetone (21% solution), twice a week for 16 weeks, at which time the experiment was terminated. No mice were treated with 2,4,5-trichlorophenol alone. At termination of the experiment, skin papillomas were observed in 8/19 surviving mice. No skin tumours were found in 18 surviving controls of the same strain and sex treated with acetone alone; 1/21 surviving male mice (strain unspecified) treated with 75 \(\mu\)g DMBA alone developed a papilloma (Boutwell & Bosch, 1959) [The Working Group noted the inadequacy of the experimental design].
3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

Trichlorophenols may contain 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD), which is formed during its synthesis (IARC, 1977a).

The acute i.p. LD₅₀s in rats for the 2,4,5- and 2,4,6-trichlorophenols are 355 and 276 mg/kg bw, respectively (Farquharson et al., 1958). The acute oral LD₅₀ in rats of 2,4,5-trichlorophenol administered by gavage is about 3 g/kg bw (McCollister et al., 1961).

In a 98-day feeding study in rats, 0.3 g and 1 g/kg bw/day doses of 2,4,5-trichlorophenol retarded weight gain and caused diuresis, mild centrilobular changes in the liver, moderate degenerative changes in the convoluted tubules of the kidneys and early proliferative changes in kidney interstitial tissue. Slight proliferation of bile ducts and early portal cirrhosis were also observed. The severity of effects was dose-related. No significant effects were observed with doses of 100 mg/kg bw/day (0.1% in diet) or less (McCollister et al., 1961).

2,4,6-Trichlorophenol produces symptoms of central nervous depression. The toxicity of 2,4,5-trichlorophenol was characterized by an ascending hypotonia leading to prostration, flaccid paralysis, dyspnoea and death. Rapid development of rigor mortis, sometimes evident before death, is a characteristic finding, analogous to that seen with pentachlorophenol (Farquharson et al., 1958). It has been suggested that the mechanism of action of 2,4,6-trichlorophenol is interference with mitochondrial oxidative phosphorylation and inhibition of cytochrome P450-dependent mixed-function oxidases (Arrhenius et al., 1977).

No data on the embryotoxicity or teratogenicity of trichlorophenols were available to the Working Group.

Absorption, distribution, excretion and metabolism

The 2,4,5-trichlorophenol-derived herbicides, 2,4,5-T and Silvex, were fed at dose levels of 0, 300, 1000 and 2000 mg/kg diet to adult cattle and sheep for 28 days; tissues were sampled 1 day and 1 week after the last dose was given. No residues of 2,4,5-trichlorophenol were found in the fat of sheep receiving 2000 mg/kg diet 2,4,5-T (0.05 mg/kg detection limit); average residue levels in liver were over 6 times the average in kidney: 6.1 versus 0.90 and 4.4 versus 0.81 mg/kg in tissues taken 1 day and 7 days after treatment, respectively. Muscle and fat of sheep and cattle fed Silvex contained no detectable levels of 2,4,5-trichlorophenol residues; levels were slightly higher in liver than in
kidney: 0.06-0.63 mg/kg in liver and < 0.05-0.17 mg/kg in kidney (Clark et al., 1975).

Cows were fed rations containing 2,4,5-T and Silvex at 6 levels (10-1000 mg/kg diet) for 2 or 3 weeks; milk and cream samples were collected at various intervals during the feeding of the chemicals and during the 7 days following withdrawal of the highest level. No residue of 2,4,5-trichlorophenol greater than 0.05 mg/kg was found in milk or cream from those fed the 10-30 mg/kg diet levels; with 1000 mg/kg diet, average residues were 0.23 mg/kg 2,4,5-trichlorophenol in milk and 0.19 mg/kg in cream. No residues of 2,4,5-trichlorophenol were found in any of the samples of milk or cream from cows fed Silvex (Bjerke et al., 1972).

**Mutagenicity and other related short-term tests**

Repeated spraying of flower buds of *Vicia faba* with an aqueous solution of 2,4,5-trichlorophenol increased the frequency of abnormalities in pollen mother cells, including stickiness and lagging of chromosomes during cell division and chromosome fragments (Amer & Ali, 1974).

(b) **Humans**

Adverse health effects have been seen in workers exposed to chlorophenols contaminated with TCDD or to products synthesized from trichlorophenol (IARC, 1977c; Jirasek et al., 1974; Schulz, 1957). These effects, probably due to TCDD, include persistent chloracne, liver dysfunction, neuromuscular weakness, porphyria and psychological changes.

The general population was exposed to 2,4,5-trichlorophenol and its contaminants (in particular, TCDD) in Seveso, Italy, due to an accident in a 2,4,5-trichlorophenol plant (see IARC, 1977c).

3.3 **Case reports and epidemiological studies**

No data were available to the Working Group.
4. Summary of Data Reported and Evaluation

4.1 Experimental data

2,4,6-Trichlorophenol was tested in one experiment in two strains of mice by oral administration, and 2,4,5- and 2,4,6-trichlorophenols were tested in one experiment by subcutaneous injection in two strains of mice. 2,4,5-Trichlorophenol was also tested in one experiment for its promoting activity in female mice. All three experiments were considered to be inadequate.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and the widespread use of trichlorophenols over the past several decades in agriculture indicate that exposure of workers and of the general population occurs.

4.3 Evaluation

The available data do not permit an evaluation of the carcinogenicity of 2,4,5- and 2,4,6-trichlorophenols to be made.

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1 Subsequent to the meeting of the Working Group, the Secretariat became aware of carcinogenicity studies in B6C3Fl mice and Fischer rats given 2,4,6-trichlorophenol (96-97% pure) orally. Groups of 50 male mice were administered 5000 and 10,000 mg/kg diet 2,4,6-trichlorophenol for 105 weeks; and groups of 50 female mice were given 10,000 and 20,000 mg/kg diet for 38 weeks, then 2500 and 5000 mg/kg diet for 67 weeks. Survival was 80% or more in all groups. Hepatocellular carcinomas or adenomas occurred in both male and female mice; their incidence was statistically higher in low-dose males (32/49) and high-dose males (39/47) (controls, 4/20) and in high-dose females (24/48) (low-dose, 12/50; controls, 1/20). Groups of 50 rats of each sex were given 5000 or 10,000 mg/kg diet 2,4,6-trichlorophenol for 106-107 weeks. Survival to the end of the experiment was 68% or more in all groups. In male rats, the increased incidences of lymphomas and leukaemias were statistically significant in low-dose (25/50) and high-dose (29/50) groups (controls, 4/20). The incidence of leukaemia in female rats was not significantly greater than in controls (National Cancer Institute, 1979).


IARC (1977a) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, 15, Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals, Lyon, pp. 41-102

IARC (1977b) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, 15, Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins, and Miscellaneous Industrial Chemicals, Lyon, pp. 273-299

IARC (1977c) Long Term Hazards of Polychlorinated Dibenzodioxins and Polychlorinated Dibenzofurans, Internal Technical Report 78/001, Lyon


Rappe, C., Marklund, S., Buser, H.R. & Bosshardt, H.-P. (1978) Formation of polychlorinated dibenzo-para-dioxins (PCDDs) and dibenzofurans (PCDFs) by burning or heating chlorophenates. Chemosphere, 7, 269-281


SOLVENTS
CARBON TETRACHLORIDE

This substance was considered by a previous IARC Working Group, in December 1971 (IARC, 1972). Since that time new data have become available, and these have been incorporated into the monograph and taken into account in the present evaluation.

A review on carbon tetrachloride is available (Mercier, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Name: Tetrachloromethane
Synonyms: Carbona; carbon chloride; carbon tet; methane tetrachloride; perchloromethane; tetrachlorocarbon
Trade names: Benzinoform; Fasciolin; Flukoids; Freon 10; Halon 104; Necatorina; Necatarine; Tetrafionol; Tetraform; Tetrasol; Univerm; Vermeestricid

1.2 Structural and molecular formulae and molecular weight

\[
\text{CCl}_4
\]

Mol. wt: 153.8

1.3 Chemical and physical properties of the pure substance

From Hawley (1977), unless otherwise specified

(a) Description: Colourless liquid
(b) Boiling-point: 76.7°C
(c) Freezing-point: -23°C
1.4 Technical products and impurities

Carbon tetrachloride is available in the US in technical and chemically pure grades. Typical specifications for the technical grade are as follows: specific gravity (25/25°C), 1.588-1.590; acidity (as hydrogen chloride), 5 mg/kg max; residue, 5 mg/kg max; cloud-point, -10°C max; chlorides, none; free halogen, none; residual odour, none; and distillation range, 1°C including 76.7°C.

In Japan, technical-grade carbon tetrachloride has a purity of 99.9%; it may contain other chlorinated hydrocarbon impurities.
2. Production, Use, Occurrence and Analysis

2.1 Production and use

A review article on carbon tetrachloride has been published (Hardie, 1964).

(a) Production

Carbon tetrachloride was prepared in 1839 by Regnault, by chlorinating chloroform. Dumas prepared it shortly thereafter by chlorinating methane. In 1843, Kolbe produced carbon tetrachloride by reacting carbon disulphide with chlorine (Hardie, 1964).

Carbon tetrachloride is produced commercially in the US by 6 companies using the following processes: (1) as coproduct with tetrachloroethylene, by the chlorination of short-chain hydrocarbons or their partially chlorinated derivatives; (2) by the chlorination of methane; and (3) by the chlorination of carbon disulphide. Six plants use the first method, two plants use the second method, and one plant uses the third method. As much as 50% of US capacity is based on co-production with tetrachloroethylene, which involves the use primarily of propane and propylene as raw materials.

In western Europe, carbon tetrachloride is produced primarily by the chlorination of propylene.

In Japan, 62% of carbon tetrachloride is produced by the chlorination of methane, and 32% is obtained as a coproduct of tetrachloroethylene production.

Production of carbon tetrachloride on a large scale in the US began in about 1907. By 1914, production was about 4.5 million kg annually (Hardie, 1964); and in 1976, US production reached 390 million kg (US International Trade Commission, 1977). In 1976, US imports of carbon tetrachloride amounted to 3.2 million kg, with 66.1% from the Federal Republic of Germany, 33.5% from Canada and 0.4% from at least one other country (US Department of Commerce, 1977a). The US exported a total of 7 million kg carbon tetrachloride in 1976, to the following countries (percent of total exports): Japan (48), The Netherlands (29), Mexico (17), and at least two other countries (6) (US Department of Commerce, 1977b).

Production of carbon tetrachloride in western Europe is more than 320 million kg annually. France and the Federal Republic of Germany are the major producing countries (more than 100 million kg per year); Benelux, Italy, Spain and the UK are intermediate producers (10-100 million kg per year); and Austria, Scandinavia and Switzerland are
minor producing countries (less than 100 thousand kg per year). Annual production of carbon tetrachloride in eastern Europe is 5-100 million kg.

Carbon tetrachloride has been produced commercially in Japan since 1946. In 1977, 7 companies produced an estimated 51.5 million kg; imports amounted to 2.5 million kg and exports were 200 thousand kg.

(b) Use

In 1975, carbon tetrachloride was used in the US as follows: for synthesis of dichlorofluoromethane (Fluorocarbon 12), 57%; for synthesis of trichlorofluoromethane (Fluorocarbon 11), 34%; and miscellaneous uses, 9%, including its use as a fumigant. Fluorocarbons 11 and 12 are produced by the liquid-phase reaction of carbon tetrachloride with anhydrous hydrogen fluoride in the presence of an antimony halide catalyst. The degree of fluorination can be varied by changing conditions of temperature, pressure and fluoride concentration.

Miscellaneous applications for carbon tetrachloride include use in solvents, grain fumigants, pesticides (used in a mixture with carbon disulphide and as a raw material in the manufacture of other agricultural chemicals) and in the formulation of petrol additives.

Carbon tetrachloride was formerly used as a solvent (spot remover) domestically, but its use in this way in the US was banned by the US Food and Drug Administration as of 11 November, 1970 (US Environmental Protection Agency, 1970). It has also been used as a vermidical agent in human medicine (Von Oettingen, 1964).

In 1975, an estimated 9.1 million kg carbon tetrachloride were used in the US as a fumigant for commodities and buildings. In 1977, a total of 3.1 thousand kg carbon tetrachloride were used as a pesticide in California on a variety of grain crops, and in structures (California Department of Food & Agriculture, 1978).

In Europe, carbon tetrachloride is used primarily in the production of fluorocarbons (90%) and as a solvent (10%). In Japan in 1977, 87% was used for the synthesis of fluorocarbons and 13% for solvent and miscellaneous uses.

Carbon tetrachloride was evaluated by the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. The following residue levels were recommended for use as guidelines: in raw cereals, at point of entry into a country or when supplied for milling, provided that the commodity is freely exposed to air for a period of at least 24 hrs after fumigation and before sampling, 50 mg/kg (ppm); in milled cereal products that are to be subjected to baking or cooking, 10 mg/kg (ppm);
in bread and other cooked cereal products, 0.05 mg/kg (i.e., at or about the limit of determination) (WHO, 1972).

Carbon tetrachloride is exempted from the requirement of a tolerance for residues when used as a fumigant for barley, corn, oats, popcorn, rice, rye, sorghum and wheat (US Environmental Protection Agency, 1976). An exemption from a tolerance is granted when it appears that the total quantity of the pesticide chemical in or on all raw agricultural commodities for which it is of current or prevailing use will involve no hazard to public health.

Carbon tetrachloride is presently registered for use as an insecticide in the US for fumigation of barley, corn, oats, rice, rye, sorghum and wheat, and for agricultural premises, including grain bins and granaries (US Environmental Protection Agency, 1971). However, it was scheduled to have a rebuttable presumption against registration (RPAR) (see General Remarks on Substances Considered, p. 31) issued in 1977 on the basis of carcinogenicity (Anon., 1976); this has not yet been issued.

Permissible levels of carbon tetrachloride in the working environment have been established in various countries. The US Occupational Safety and Health Administration's health standards require that an employee's exposure to carbon tetrachloride at no time exceed a time-weighted average of 65 mg/m³ (10 ppm) in any 8-hr shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977). The corresponding standard in the Federal Republic of Germany and Sweden is also 65 mg/m³, and in the German Democratic Republic and Czechoslovakia, 50 mg/m³; the ceiling concentration in the USSR is 20 mg/m³ (Winell, 1975).

In February 1976, the US National Institute for Occupational Safety and Health recommended that occupational exposure to carbon tetrachloride not exceed 12.6 mg/m³ (2 ppm), determined as a time-weighted average exposure for up to a 10-hr work day in a 40-hr work week (National Institute for Occupational Safety & Health, 1976).

2.2 Occurrence

Carbon tetrachloride is formed in the troposphere by solar-induced photochemical reactions of chlorinated alkenes (Singh et al., 1975). Its occurrence in the US environment has been reviewed (Johns, 1976).

(a) Air

Air samples taken at 42 locations in the US contained an average concentration of 1.4 µg/m³ (0.22 ppb) carbon tetrachloride. Of 4 halo-carbons measured, carbon tetrachloride showed the least variation in concentration, with more than 86% of all measurements falling within the
Maximum levels of carbon tetrachloride found in the atmosphere ranged from 0.9-113 μg/m³ (0.14-18 ppb); minimum levels, 0.3-1.3 μg/m³ (0.05-0.20 ppb); and mean levels, 0.6-10.3 μg/m³ (0.09-1.63 ppb) (Lillian et al., 1975). In 3 locations, atmospheric concentrations of carbon tetrachloride ranged from 0.4-0.7 μg/m³ (0.07-0.11 ppb), 0.56-0.63 μg/m³ (0.09-0.10 ppb) and 0.4-0.5 μg/m³ (0.07-0.08 ppb) (Hanst et al., 1975).

Carbon tetrachloride was detected in a rural atmosphere at a level of 756 ng/m³ (120 ppt) (Grimsrud & Rasmussen, 1975). Levels of carbon tetrachloride determined in other rural air samples ranged from 500-700 ng/m³ (80-100 ppt) (Russell & Shadoff, 1977).

The ambient air in a Japanese town was sampled at 26 sites on 3 or 4 days of every month from May 1974 to April 1975: the annual average concentration of carbon tetrachloride was 8.8 μg/m³ (1.4 ppb). The distribution of carbon tetrachloride in the atmosphere was found to correlate with the location of chemical factories (Ohta et al., 1976).

Atmospheric concentrations of carbon tetrachloride at ground level measured at sites in the northern and southern hemispheres were 700 ng/m³ (111 ppt) and 434 ng/m³ (68.9 ppt), respectively (Cox et al., 1976).

Formation of carbon tetrachloride in the troposphere by solar-induced photochemical reactions of chlorinated alkenes was studied experimentally by simulated tropospheric irradiations of synthetic mixtures of tetrachloroethylene in air. It was found that tetrachloroethylene photodecomposition leads to an average formation of about 8% by weight carbon tetrachloride. The relatively uniform global concentrations, significant atmospheric loading and almost exclusive use of carbon tetrachloride for fluorocarbon synthesis had led to earlier speculation that there was a natural source of carbon tetrachloride. This study shows, however, that tetrachloroethylene (found at several locations in relatively large concentrations) could account for a significant percentage of atmospheric carbon tetrachloride (Singh et al., 1975).

(b) Water

In a summary of the frequency of reports of the occurrence of organic compounds in water, it was indicated that carbon tetrachloride has been found in rivers, lakes, raw-water, finished drinking-water, effluent water from commercial manufacturing sources and sewage treatment plant effluent water taken from 43 sites in the US and Europe (Shackelford & Keith, 1976).

Carbon tetrachloride has been detected in a lake, and in subterranean (0.5-6 ng/l) and tap (5 ng/l) water (Eurocop-Cost, 1976).
A National Organics Reconnaissance Survey performed by the US Environmental Protection Agency in 1975 reported levels of carbon tetrachloride in 80 water supplies distributed over various regions of the US, representing a wide variety of raw-water sources and treatment techniques. Carbon tetrachloride was detected in 12.5% of finished waters, up to a level of 4 μg/l (Symons et al., 1975).

Carbon tetrachloride was found in 8/10 water supply utilities (Safe Drinking Water Committee, 1977) and in the drinking-water of 2 cities (Saunders et al., 1975).

Carbon tetrachloride, benzene and dichloroethane were detected together in river water at the entrance to a water treatment facility, at the clarifier effluent stage of the water-treatment process, and in finished water, at total relative concentrations of 12.27:3.26:36.61 (Dowty et al., 1975a,b).

Periods of high agricultural runoff have been associated with peak concentrations of halomethanes, including carbon tetrachloride, due to increased turbidity of the raw water (Morris & Johnson, 1976).

In a survey sampling 172 stations of bay-water, the maximum concentration of carbon tetrachloride was 2.4 μg/l and the average concentration of combined 1,1,1-trichloroethane and carbon tetrachloride was 0.25 μg/l (Pearson & McConnell, 1975).

Carbon tetrachloride was identified as a major constituent of organic compounds found in a river (Zuercher & Giger, 1976).

(c) Food and drink

Carbon tetrachloride, in combination with ethylene dibromide and ethylene dichloride, has been applied to wheat stored in paper laminate bins; concentrations of carbon tetrachloride gas were greatest at the bottoms of the bins. Carbon tetrachloride residues in the wheat varied, depending on bin location and contact time, from 3.2-72.6 mg/kg. Residues on bran and middlings derived from the treated wheat ranged from 0.2-2.23 mg/kg; in bread made from the wheat, residues ranged from 0-0.04 mg/kg (Berck, 1974).

The following concentrations of carbon tetrachloride were found in foodstuffs in the UK in 1973: dairy produce, 0.2-14 μg/kg; meat, 7-9 μg/kg; oils and fats, 0.7-18 μg/kg; beverages, 0.2-6 μg/kg; and fruits and vegetables, 3-8 μg/kg (McConnell et al., 1975).

(d) Animals

Five species of fish and 3 species of molluscs were collected from relatively clean sea-water. Concentrations in the various organs ranged from 2-114 μg/kg (dry-weight basis) in molluscs and from 3-209 μg/kg
(dry-weight basis) in fish. The relative concentrations in organs of the fish were: brain > gill > liver > muscle (Dickson & Riley, 1976).

(e) Occupational exposure

A 1974 National Occupational Hazard Survey estimated that workers exposed to carbon tetrachloride are primarily those at blast furnaces and steel mills, in the air transportation industry, and in motor vehicle and telephone and telegraph equipment manufacturing (National Institute for Occupational Safety & Health, 1977a).

2.3 Analysis

Gas chromatographic methods to collect and determine halocarbons, including carbon tetrachloride, in the ambient air (Appleby, 1976) and sampling and analytical methods for trace determination of carbon tetrachloride in water (Bertsch et al., 1975) have been reviewed. Table 1 lists methods used for the analysis of carbon tetrachloride in environmental samples.

The efficiency of charcoal for trapping carbon tetrachloride from air has been studied collaboratively (Reckner & Sachdev, 1975).

Other analytical methods to isolate and identify carbon tetrachloride include use of gas-phase coulometry (Lillian & Singh, 1974; Seto et al., 1977) and ultra-violet spectrometry (Ellison & Wallbank, 1974).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Strain A mice of both sexes, 2½-3 months of age at the beginning of treatment, were given oral doses of 0.1, 0.2, 0.4, 0.8 and 1.6 ml/kg bw (0.16, 0.32, 0.64, 1.28 and 2.5 g/kg bw) carbon tetrachloride in olive oil; the interval between consecutive doses was 1-5 days; each animal received 30 doses. The experiment was terminated at 150 days. No hepatomas were seen in the group given 30 doses of 1.6 ml/kg bw over a period of 30 days, whereas a significant number of hepatomas was observed in all groups that received 30 doses of 0.1 ml/kg bw or more over a period of 90 days or more (Eschenbrenner & Miller, 1944).

Groups of 50 male and 50 female B6C3F1 hybrid mice, 5 weeks of age, received carbon tetrachloride as a 2-5% solution in corn oil by oral
<table>
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<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
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<tr>
<td>Formulations</td>
<td></td>
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<td></td>
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<tr>
<td>Encapsulated liquids and</td>
<td>Transfer to ethanol, dilute as appropriate, transfer to</td>
<td>IR</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>cough syrups</td>
<td>separator containing 10% sucrose solution and carbon</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>disulphide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsules and drugs</td>
<td>Heat under pressure with alcoholic potassium hydroxide to</td>
<td>Titration</td>
<td></td>
<td>Horwitz (1970)</td>
</tr>
<tr>
<td></td>
<td>dechlorinate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap in pyridine, add aqueous solution of sodium</td>
<td>Colorimetry</td>
<td>157 mg/m³</td>
<td>Gage et al. (1962)</td>
</tr>
<tr>
<td></td>
<td>hydroxide, allow colour to develop</td>
<td>at 525 nm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap in Drechsel flask fitted with rubber septum, sample</td>
<td>GC/ECD</td>
<td>0.2 μg/m³</td>
<td>Bureau International Technique des</td>
</tr>
<tr>
<td></td>
<td>with gas syringe</td>
<td></td>
<td></td>
<td>Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap in glass container, inject on GC column</td>
<td>GC/ECD</td>
<td></td>
<td>Ohta et al. (1976)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap by cryogenic method, vaporize into second trap,</td>
<td>IR</td>
<td></td>
<td>Hanst et al. (1975)</td>
</tr>
<tr>
<td></td>
<td>analyse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>Trap on porous polymer, desorb by heating, retrap in</td>
<td>GC/ECD</td>
<td>190-800 ng/m³</td>
<td>Russell &amp; Shadoff (1977)</td>
</tr>
<tr>
<td></td>
<td>line on GC column</td>
<td>GC/MS confirmation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td>Trap on charcoal, desorb (carbon disulphide), extract</td>
<td>GC/FID</td>
<td>Range of application: 65-299 mg/m³</td>
<td>National Institute for Occupational</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Safety &amp; Health (1977b)</td>
</tr>
<tr>
<td>Atmosphere</td>
<td>Trap on polymer, desorb by heating, retrap in line on</td>
<td>GC/MS</td>
<td>30 ng/m³</td>
<td>Dowty et al. (1975a,b)</td>
</tr>
<tr>
<td></td>
<td>GC column</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atmosphere</td>
<td>Inject directly</td>
<td>GC/MS</td>
<td>30 ng/m³</td>
<td>Grimsrud &amp; Rasmussen (1975)</td>
</tr>
</tbody>
</table>
### TABLE 1. METHODS FOR THE ANALYSIS OF CARBON TETRACHLORIDE (continued)

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea and fresh water</td>
<td>Extract (pentane), dry</td>
<td>GC/ECD</td>
<td>25 ng/kg</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>River</td>
<td>Cool to 4°C, extract (pentane)</td>
<td>GC/FID</td>
<td>10 µg/l</td>
<td>Dietz &amp; Traud (1973)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Inject directly</td>
<td>GC/ECD</td>
<td>0.1 µg/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td><strong>Sediments</strong></td>
<td>Wash (water), cool to 4°C, extract (pentane)</td>
<td>GC/FID</td>
<td>10 µg/l</td>
<td>Dietz &amp; Traud (1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC/ECD</td>
<td>10 ng/l</td>
<td></td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cereals and other</td>
<td>Extract (acetone-water, acetonitrile-water), dry</td>
<td>GC/ECD, FID</td>
<td>0.1 mg/kg</td>
<td>Heuser &amp; Scudamore (1969)</td>
</tr>
<tr>
<td>foodstuffs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cereals</td>
<td>Extract (acetone-water)</td>
<td>GC/FID, ECD</td>
<td>0.1 mg/kg</td>
<td>Heuser &amp; Scudamore (1968)</td>
</tr>
<tr>
<td>Grains</td>
<td>3 possible extraction methods: sweep co-distillation,</td>
<td>GC/ECD</td>
<td>0.1 mg/kg</td>
<td>Malone (1969)</td>
</tr>
<tr>
<td></td>
<td>steam distillation, acid reflux</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grains</td>
<td>Grind in dry ice, boil in acid, trap volatile fumigant in</td>
<td>GC/ECD</td>
<td>40 µg/kg</td>
<td>Malone (1970)</td>
</tr>
<tr>
<td></td>
<td>cold solvent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Put in sealed tube, equilibrate in water bath (27°C) for</td>
<td>GC/FID</td>
<td></td>
<td>Premel-Cabic et al. (1974)</td>
</tr>
<tr>
<td></td>
<td>30 min, head-space analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>Adsorb on polymer, desorb by heating, GC/MS retap in</td>
<td></td>
<td></td>
<td>Dowty et al. (1975a)</td>
</tr>
<tr>
<td></td>
<td>line on GC column</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** IR - infra-red spectroscopy; GC/FID - gas chromatography/flame-ionization detection; ECD - electron capture detection; MS - mass spectrometry
gavage 5 times weekly at dose levels of 1250 and 2500 mg/kg bw for 78 weeks. Pooled control (77 males and 80 females) and matched controls, (18 males and 18 females) were treated with corn oil only. The experiment was terminated 90-92 weeks from the start. Hepatocellular carcinomas developed in nearly all treated mice: 49/49 and 47/48 male, 40/40 and 43/45 female mice given low and high dose levels, respectively, compared with 5/77 male and 1/80 female pooled controls and 3/18 and 1/18 matched controls. In this experiment, carbon tetrachloride was used as a positive control (National Cancer Institute, 1976; Weisburger, 1977).

Groups of male C3H mice, 2 months old, received doses of 0.2, 0.4 and 1.6 g/kg bw carbon tetrachloride in corn oil intragastrically 3 times weekly for 10 weeks. The experiment was terminated 150 days after the first treatment, at which time 8/30, 18/60 and 6/30 treated animals and 18/30 vehicle controls were still alive. Hepatomas developed in 5, 4 and 1 mice; the number of hepatomas per animal varied from 1-6. No hepatomas were seen in 28 untreated controls or in 18 vehicle controls (Kiplinger & Kensler, 1963).

Rat: In an experiment in which carbon tetrachloride was used as a positive control, groups of 50 male and 50 female 45-day-old Osborne-Mendel rats were treated 5 times weekly by gavage with carbon tetrachloride in corn oil for 78 weeks. Males received 47 and 94 mg/kg bw, and females 80 and 160 mg/kg bw. Surviving animals were then fed a control diet and killed at 110 weeks. Hepatocellular carcinomas occurred in 2/49 and 2/50 males, compared with 0/20 matched controls [P > 0.05]; neoplastic nodules of the liver occurred in 9 and 3 males treated with the low and high doses. In females, hepatocellular carcinomas occurred in 4/50 and 2/49 rats, compared with 1/20 in matched controls [P > 0.05]; neoplastic nodules of the liver were found in 11 and 9 treated females, and in 1 female control. Among pooled controls, 1/99 males and 0/98 females had hepatocellular carcinomas and 0/99 males and 2/98 females had neoplastic nodules of the liver (National Cancer Institute, 1976; Weisburger, 1977).

Hamster: Ten 12 week-old Syrian golden hamsters of each sex received 30 weekly doses of 6.25-12.5 ml (10-20 mg) carbon tetrachloride in 5% corn oil solution. All 5 animals of each sex that survived 10 or more weeks after the end of treatment had liver-cell carcinomas (Della Porta et al., 1961) [The Working Group noted that no data on controls were reported].

Trout: Rainbow trout were given diets containing 3200 and 12,800 mg/kg diet carbon tetrachloride. Four out of 44 animals given the lower dose level and 3/34 given the higher dose level developed hepatomas after 20 months, whereas no tumours were found in the controls (Halver, 1967).
(b) Inhalation and/or intratracheal administration

Rat: A group of albino rats (sex unspecified) that had inhaled carbon tetrachloride (dose and schedule unspecified) daily for 7 months were killed 2-10 months after the end of treatment. Among 30 survivors, 12 had 'adenocirrhosis' and 10 had liver nodules measuring up to 1 cm, diagnosed histologically as early or established liver carcinomas (Costa et al., 1963) [The Working Group noted that no controls were used in this study].

(c) Subcutaneous and/or intramuscular administration

Rat: A group of 49 male Wistar rats weighing about 120 g received 2-3 ml/kg bw (3.2-4.8 g/kg bw) carbon tetrachloride in olive oil twice weekly for 25-35 weeks and were killed 4-78 weeks after the end of treatment; hepatomas (malignant, according to the author, but degree of malignancy not specified) were found in 2 animals (Kawasaki, 1965) [The Working Group noted that no controls were used in this study].

In a study in which 12-week-old male rats were given s.c. injections of 1.3 ml/kg bw (2 g/kg bw) of a 50% solution of carbon tetrachloride in corn oil twice weekly, 4/12 Wistar rats, 8/13 Osborne-Mendel rats and 12/15 Japanese rats that survived 68 or more weeks had hepatocellular carcinomas. No liver tumours were found in 12 control rats of each strain (Reuber & Glover, 1970). In an earlier experiment on groups of 10-14 Buffalo male and female rats, 4, 12, 24 and 52 weeks old, in which the same schedule of treatment was used, a low yield of hepatomas was observed (Reuber & Glover, 1967).

Thirty white female rats, 5-6 months old at the start of the experiment, received twice weekly s.c. injections of 1 ml/kg bw (1.6 g/kg bw) carbon tetrachloride for 2 years. Eight rats developed mammary adenocarcinomas, the first of which appeared 13 months after the beginning of treatment; 3 of these rats also had fibroadenomas of the mammary glands; 1 rat developed only a mammary fibroadenoma. No mammary tumours were observed in an untreated control group of 15 rats (Alpert et al., 1972).

(d) Other experimental systems

Intrarectal administration: Twenty-five C3H male mice received biweekly intrarectal administrations of 0.1 ml of a 40% solution of carbon tetrachloride in olive oil for 20-26 weeks and were killed 1-37 weeks later. A total of 13 mice had liver tumours, described as nodular hyperplasia. No such tumours developed in 10 olive-oil-treated control mice (Confer & Stenger, 1965).
(e) Combined administration with other agents  [These studies were not carried out to test carbon tetrachloride for carcinogenic activity]

Administration of a single dose of N-nitrosobutylurea to mice treated 24 hrs earlier with a single dose of carbon tetrachloride resulted in an increased incidence of hepatomas and leukaemia, as compared with mice treated with N-nitrosobutylurea alone (Yokoro et al., 1973). An increased incidence of liver and kidney tumours was observed in mice treated with a single dose of N-nitrosodiethylamine 24 or 48 hrs after a single injection of carbon tetrachloride (Pound, 1978).

(C57L x A)F1 mice that had received a single whole-body exposure to fast neutrons (165-306 rad) received a single s.e. injection of carbon tetrachloride (0.15 ml of a 40% solution in sesame oil) 2-18 months later. The frequency of hepatomas was increased from 19-61%. No hepatomas appeared in controls given carbon tetrachloride only (Cole & Nowell, 1964). Similar findings were reported by Curtis & Tilley (1972).

Administration of a single dose of N-nitrosodimethylamine to rats treated 24 hrs earlier with a single dose of carbon tetrachloride resulted in an increased incidence of liver and kidney tumours, as compared with corresponding controls (Pound et al., 1973a). An increased incidence of hepatomas and a shortening of the latent period of tumour induction were observed in rats that received a single dose of aflatoxin followed by chronic administration of carbon tetrachloride (Lemmonier et al., 1974).

Carbon tetrachloride promoted the hepatocarcinogenesis induced by 3'-methyl-4-dimethylaminoazobenzene in female Donryu rats (Kanematsu, 1976).

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The single oral LD50 of carbon tetrachloride in rats is 2.92 g/kg bw (Klaassen & Plaa, 1969; Smyth et al., 1970); that in mice is 12.1-14.4 g/kg bw (Dybing & Dybing, 1946); and that in dogs 2.3 g/kg bw (Klaassen & Plaa, 1967). The i.p. LD50 in mice is 4.1 g/kg bw (Klaassen & Plaa, 1966); the s.c. LD50 in mice is 30.4 g/kg bw (Plaa et al., 1958). The s.c. LD33 in cats is 4.8 g/kg bw (Cantarow et al., 1938).

The minimal lethal i.v. dose of carbon tetrachloride in dogs was 125 mg/kg bw (Barsoum & Saad, 1934). Single exposures to 315 mg/m3 (50 ppm) carbon tetrachloride vapour for 7 hrs had no adverse effect
upon male rats (Adams et al., 1952); however, alterations in liver biochemistry can be produced by oral doses of carbon tetrachloride as small as 15.4 mg/kg bw (Rechnagel & Ghoshal, 1966).

Variations in data on acute toxicity may be due to different observation times (1-10 days). High doses kill animals by central nervous depression within hours; smaller and subnarcotic doses produce death by liver damage after several days.

After 40-150 exposures to carbon tetrachloride vapour for 7 hrs/day over about 200 days, toxic effects were seen with 315 mg/m³ (50 ppm) in rabbits and guinea-pigs and with 100 ppm in rats and monkeys. Adverse effects included increased liver weight, moderate fatty degeneration and cirrhosis; slight effects were seen with 25 ppm (Adams et al., 1952).

In rats, an i.g. dose of 3.8 g/kg bw carbon tetrachloride greatly reduced N-nitrosodimethylamine-demethylase activity in the liver for 42-72 hrs but did not alter the activity of this enzyme in the kidney (Pound et al., 1973b).

Changes have been observed in mammalian liver cells following administration of carbon tetrachloride: diene conjugation of the polyenoic fatty acids of the endoplasmic membrane, lipid peroxidation, scission of carbon chains, covalent binding of carbon tetrachloride metabolites to cellular constituents, triglyceride accumulation, membrane damage, leakage of enzymes, fatty degeneration and centrilobular necrosis (Recknagel, 1967; Recknagel & Glende, 1973; Smuckler, 1976; Uehleke et al., 1977).


Embryotoxicity and teratogenicity

Increased foetal mortality was observed in pregnant mice given single doses of 150 mg/animal carbon tetrachloride in a 40% oily solution during the last part of pregnancy. The adverse effect was more pronounced after i.p. than after s.c. administration. Cause of death was suggested to be failure of peripheral circulation, mainly due to foetal liver damage. Moreover, circulatory disturbances and necroses were found in the placentas, which probably also contributed to the death of the foetuses (Roschlau & Rodenkirchen, 1969).
The foetuses of rats exposed for 7 hrs/day on days 6-15 of gestation to concentrations of 1890 and 6300 mg/m³ (300 and 1000 ppm) carbon tetrachloride in air showed retarded development (Schwetz et al., 1974).

Absorption, distribution and excretion

Carbon tetrachloride is absorbed rapidly after ingestion, inhalation or application to injured skin (Von Oettingen, 1964).

After oral administration of carbon tetrachloride to rats, blood and liver concentrations increased during the following 90 min and then decreased continuously (Recknagel & Litteria, 1960). I.g. administration to rats of 4.4 mg/kg bw carbon tetrachloride produced peak liver concentrations after 4 hrs and highest blood levels after 2 hrs. The elimination rate was 7.6% per hr from liver and 2.5% per hr from blood (Nachtomi & Alumot, 1972).

After dogs were exposed by inhalation to 94.5 g/m³ (15,000 ppm) carbon tetrachloride in air, blood and liver concentrations were comparable (Von Oettingen, 1964). The highest concentrations of carbon tetrachloride in monkeys exposed to 315 mg/m³ (50 ppm) of ¹⁴C-carbon tetrachloride for 140-340 min were found in fat, liver, bone marrow, blood, brain and kidney. Approximately 50% of the retained amount was exhaled unchanged; some labelled material was exhaled after 20 days (McCollister et al., 1951).

Cutaneous absorption of 7.2 g/m³ (1150 ppm) ¹⁴C-labelled carbon tetrachloride vapours by a monkey produced blood levels of 0.3 mg/l after 270 min (McCollister et al., 1951).

Metabolism

The toxicity of carbon tetrachloride results from its biotransformation. In monkeys, 11% of a ¹⁴C-labelled dose of carbon tetrachloride was exhaled as ¹⁴CO₂ over 18 hrs (McCollister et al., 1951). In dogs, chloroform was identified among the expired compounds (Butler, 1961). Liver microsomes metabolize carbon tetrachloride to CO₂ (Rubinstein & Kanics, 1964); this reaction is increased both in vivo and with liver microsomes after pretreatment of the animals with phenobarbital or DDT (Garner & McLean, 1969; Seawright & McLean, 1967).

Lipid peroxidation, presumably initiated by a free-radical metabolite of carbon tetrachloride (Butler, 1961), seems to be the most important factor in carbon tetrachloride-induced liver toxicity (Glende et al., 1976; Ghoshal & Recknagel, 1965; Recknagel, 1967; Recknagel & Glende, 1973; Recknagel & Ghoshal, 1966; Slater, 1966). Similar events may be responsible for extrahepatic tissue damage (Von Oettingen, 1964) in lung (Chen et al., 1977), kidney (Von Oettingen, 1964), testes
Carbon tetrachloride binds to cytochrome P450 in hepatic microsomes. It may also destroy P450 by lipid peroxidation (Glende et al., 1976; Sasame et al., 1968; Smuckler et al., 1967).

**Binding to macromolecules**

The irreversible (covalent) binding of hepatic macromolecules with carbon and chlorine from carbon tetrachloride \((^{14}\text{C} \text{ or } ^{36}\text{Cl})\) suggests that its toxic action on the liver is mediated by a chemical attack of carbon tetrachloride cleavage products on lipids and proteins, preferentially of the endoplasmic reticulum (Cessi et al., 1966; Gordis, 1969; Rao & Recknagel, 1969; Reynolds, 1967).

Less than 0.2% radioactivity was found in ribosomal RNA or nuclear DNA from rats dosed with \(^{14}\text{C}\)-labelled carbon tetrachloride (Reynolds, 1967), or in ribosomal RNA from microsomes taken from phenobarbital-treated rats and rabbits and incubated with carbon tetrachloride (Uehleke & Werner, 1975); however, radioactivity was bound to soluble nucleotides (Harders et al., 1976). Diaz Gomez & Castro (1978) claim that radioactivity of \(^{14}\text{C}\)-tetrachloride binds to nuclear DNA in rats and mice.

**Mutagenicity and other related short-term tests**

In plate tests with *Salmonella typhimurium* TA100, TA1535 and TA1538, carbon tetrachloride was non-mutagenic both in the presence and absence of a microsomal activation system (McCann & Ames, 1976; McCann et al., 1975; Uehleke et al., 1977). It was also negative with *Escherichia coli* K12 (Uehleke et al., 1976). However, it has been claimed that it interacts with cellular macromolecules (including DNA) of mammalian cells both *in vivo* and *in vitro* if the animals (rats and mice) have been pretreated with 3-methylcholanthrene (Rocchi et al., 1973).

**Humans**

Numerous poisonings and fatalities have occurred due to accidental or suicidal ingestion of carbon tetrachloride or from its medical use; the majority of cases resulted from the inhalation of carbon tetrachloride vapours used as a solvent or dry-cleaning agent (Von Oettingen, 1964). The major pathological changes are seen in liver and kidney.

Death has been reported after ingestion of as little as 1.5 ml; some patients have been known to survive after swallowing more than 100 ml. When inhaled, it may cause central nervous system depression, pulmonary oedema, alveolitis and fatal cardiac arrhythmias (Bagnasco et al., 1978).
Renal failure due to carbon tetrachloride is increased by the consumption of alcohol (New et al., 1962).

After exposure of male volunteers to 315 mg/m$^3$ (49 ppm) carbon tetrachloride vapours in air during 70 min or to 63 mg/m$^3$ (10 ppm) for 180 min, concentrations in the expired air were 11 mg/m$^3$ (1.7 ppm) and 4.4 mg/m$^3$ (0.7 ppm) after 1 hr; these decreased exponentially (Stewart et al., 1961). Carbon tetrachloride could be detected 450 hrs after the accidental intake of a large quantity (Stewart et al., 1963).

After 30 min immersion of one thumb in carbon tetrachloride, volunteers exhaled concentrations of 3 mg/m$^3$ (0.64 ppm); expiration half-time was approximately 2 hrs (Stewart & Dodd, 1964).

3.3 Case reports and epidemiological studies

Cases of liver cancer have been reported in humans several years after carbon tetrachloride poisoning. Johnstone (1948) reported the case of a woman who developed nodular cirrhosis of the liver followed by cancer of the liver, and who died 3 years after first exposure. She had suffered from periodic jaundice for 5 years before exposure to carbon tetrachloride. Simler et al. (1964) reported that a firefighter who was acutely intoxicated by carbon tetrachloride developed cirrhosis and an 'epithelioma' of the liver 4 years after exposure.

Tracey & Sherlock (1968) reported a hepatocellular carcinoma with concomitant fibrosis in a 59-year-old man 7 years after acute poisoning with carbon tetrachloride during a short (a few days) exposure to the compound used for cleaning his rug.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Carbon tetrachloride was tested in several experiments in mice by oral and intrarectal administration and in rats by oral and subcutaneous administration and by inhalation exposure; it was also tested in one experiment in hamsters and one in trout by oral administration. In various strains of mice, it produced liver tumours, including hepatocellular carcinomas. In various strains of rats, it produced benign and malignant liver tumours; and in one experiment with subcutaneous injection, an increased incidence of mammary adenocarcinomas was observed. In hamsters and trout, increased incidences of liver tumours were observed; however, these studies were considered to be inadequate.

Carbon tetrachloride is foetotoxic. It was not mutagenic in bacteria.
4.2 Human data

No epidemiological studies were available to the Working Group. Three case reports were available describing the appearance of liver tumours associated with cirrhosis following exposure to carbon tetrachloride. In one of the cases, a single, high-level exposure was thought to have occurred; in another, exposure was limited to a period of a few days.

The extensive production and widespread use of carbon tetrachloride indicate that human exposure occurs. This is confirmed by many reports of its occurrence in the general environment and of numerous poisonings and fatalities due to this compound.

4.3 Evaluation

There is sufficient evidence that carbon tetrachloride is carcinogenic in experimental animals. There are suggestive case reports of liver cancer in humans. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard carbon tetrachloride as if it presented a carcinogenic risk to humans.

1Subsequent to the meeting of the Working Group, the Secretariat became aware of a study of 330 deceased laundry and dry-cleaning workers who had been exposed to carbon tetrachloride, trichloroethylene and tetrachloroethylene. An excess of lung, cervical and skin cancers and a slight excess of leukaemias and liver cancers were observed (Blair et al., 1979).
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CHLOROFORM

This substance was considered by a previous Working Group, in December 1971 (IARC, 1972). Since that time new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

Three reviews on chloroform, including a literature collection, are available (Berkowitz, 1978; Mercier, 1977; Winslow & Gerstner, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: Trichloromethane

Synonyms: Formyl trichloride; methane trichloride; methenyl chloride; methenyl trichloride; methyl trichloride; trichloroform

Trade names: Freon 20; R 20; R 20 [refrigerant]

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{CHCl}_3 & \quad \text{Mol. wt: 119.4}
\end{align*}
\]

1.3 Chemical and physical properties of the pure substance

From Hawley (1977), unless otherwise specified

(a) **Description**: Clear, colourless liquid

(b) **Boiling-point**: 61.2°C

(c) **Freezing-point**: -63.5°C

(d) **Density**: \( d_{20}^{20} = 1.485 \)
(e) **Spectroscopy data:** $\lambda_{\text{vap}} < 200 \text{ nm}$; infra-red, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(f) **Refractive index:** $n^D_{25} 1.4422$

(g) **Solubility:** Miscible with ethanol, diethyl ether, benzene, solvent naphtha and fixed and volatile oils; slightly soluble in water (0.822 g/100 g water at 20°C) (Hardie, 1964)

(h) **Volatility:** Vapour pressure is 200 mm at 25.9°C (Perry & Chilton, 1973).

(i) **Stability:** Decomposes slowly on prolonged exposure to sunlight in the presence or absence of air, and in the dark when air is present (Hardie, 1964).

(j) **Reactivity:** Oxidized by strong oxidizing agents such as chromic acid, with formation of phosgene and chlorine gas; reacts readily with halogens or halogenating agents, forming various products depending on the reactants and reaction conditions; reacts with primary amines to form isonitriles; reacts with phenols in alkaline solution, forming hydroxy-substituted aromatic aldehydes (Hardie, 1964)

(k) **Conversion factor:** 1 ppm in air is equivalent to approximately 4.9 mg/m$^3$.

1.4 **Technical products and impurities**

Typical specifications for National Formulary grade chloroform are as follows: boiling-range, 59.8-71.3°C (760 mm); acidity, as hydrogen chloride, 0.0002% max; specific gravity at 25/25°C, 1.474-1.478; residue on evaporation, 0.0013% max; and stabilizer, 0.5-1.0% ethanol by volume.

Technical-grade chloroform has the following specifications: boiling-range, 59.8-61.3°C (760 mm); acidity, as hydrogen chloride, 0.002% max; specific gravity at 25/25°C, 1.476-1.480; residue on evaporation, 0.0007% max; moisture, 0.0150% max; and stabilizer, 0.5-1.0% ethanol by volume.
The following impurities have been detected in chloroform: bromochloromethane, bromodichloromethane, bromodichloroethane, carbon tetrachloride (see monograph, p. 371), dibromodichloroethane, dibromodichloromethane, 1,1-dichloroethane, 1,2-dichloroethane (see monograph, p. 429), vinylidene chloride (see IARC, 1978a), cis-1,2-dichloroethene, trans-1,2-dichloroethylene, dichloromethane (see monograph, p. 449), diethyl carbonate, ethylbenzene, 2-methoxyethanol, nitromethane, pyridine, 1,1,2,2-tetrachloroethane (see monograph, p. 477), trichloroethylene (see monograph, p. 545), meta-xylene, ortho-xylene and para-xylene.

N-Nitrosomorpholine was found in 4/10 batches of analytical grade chloroform, at levels of 2-376 µg/l (Eisenbrand et al., 1978; IARC, 1978b).

In Japan, chloroform has a minimum purity of 99.95% and may contain water and chlorinated hydrocarbons as impurities.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Chloroform was prepared, almost simultaneously in 1831, by Liebig (by the action of alkali on chloral) and by Soubeirain (by treating bleaching powder with ethanol or acetone) (Hardie, 1964). It is currently manufactured in the US by hydrochlorination of methanol or by chlorination of methane. All chloroform production in Japan and western Europe is by chlorination of methane.

Although one US manufacturer began chloroform production in 1903, by reduction of carbon tetrachloride, commercial production was not reported until 1922 (US Tariff Commission, 1923). Immediately prior to World War II, total combined annual output of the US and the UK was 1-1.5 million kg (Hardie, 1964). In 1976, 5 US producers reported a total production of 133 million kg (US International Trade Commission, 1977). Preliminary data indicated that US production in 1977 was 137 million kg (US International Trade Commission, 1978). US imports in 1976 amounted to 503 thousand kg, 99% of which was from Spain (US Department of Commerce, 1977a); 8.8 million kg were exported to the following countries (percent of total exports): The Netherlands (37), Canada (23), Brazil (19), Mexico (12), Argentina (5) and at least one other country (4) (US Department of Commerce, 1977b).

Annual production of chloroform in eastern Europe is estimated to be 10-50 million kg, and that in western Europe 50-100 million kg.

Benelux, the Federal Republic of Germany, France and the UK are the major producing regions; and Austria, Italy, Scandinavia, Spain and Switzerland are minor producers.
Chloroform has been produced commercially in Japan since 1950. In 1976, 4 companies produced an estimated 20 million kg, and exports were negligible.

The estimated world production of chloroform in 1973 was 245 million kg (Pearson & McConnell, 1975).

(b) Use

Use of chloroform in the US in 1974 was as follows: synthesis of chlorodifluoromethane (Fluorocarbon 22) for use in refrigerants and propellants, 51.3%; synthesis of Fluorocarbon 22 for use in plastics, 24%; and miscellaneous uses, 24.7%.

In 1976, US production of Fluorocarbon 22 amounted to 77.1 million kg (US International Trade Commission, 1977). In 1973, 40.4 million kg Fluorocarbon 22 were used for air conditioning and refrigeration purposes. It is used in residential and commercial unit air conditioners, heat pumps, centrifugal chillers and motor vehicle air conditioners (US Department of Commerce, 1975). Fluorocarbon 22 is pyrolysed to produce polytetrafluoroethylene (see IARC, 1978c), the major volume fluoroplastic. Fluorocarbon 22 is also used to foam plastics, although Fluorocarbons 11 and 12 are most commonly used for this purpose (US Department of Commerce, 1975).

Miscellaneous uses of chloroform have been in drugs and cosmetics (including toothpastes), in the extraction and purification of penicillin and other antibiotics, in the solvent extraction of vitamins and flavours, in grain fumigants, as a general solvent (e.g., for adhesives, resins and pesticides) and as an intermediate in the preparation of dyes, drugs and pesticides.

Chloroform was first employed medically as an orally administered stimulant and as an inhalant for treatment of asthma; it was first used as an anaesthetic in obstetrics in 1847. Before World War II, chloroform was still being used primarily as an anaesthetic and in pharmaceutical preparations; but by 1964, only about 10% was so used (Hardie, 1964).

In western Europe, chloroform is used primarily in the synthesis of Fluorocarbon 22. In Japan, in 1976, 80% was used as a refrigerant and 20% for solvent uses.

In April 1976, the US Food and Drug Administration (FDA) listed approximately 1900 human drug products that contained chloroform. These included cough syrups, expectorants, antihistamines, liniments and decongestants (US Food & Drug Administration, 1976a). The FDA banned the use of chloroform as an ingredient (active or inactive) in human drug and cosmetic products as of 29 July, 1976. However, any drug product containing chloroform in residual amounts from its use as a processing
solvent in manufacture or as a by-product from the synthesis of an ingredient is not considered to contain chloroform as an ingredient (US Food & Drug Administration, 1976b).

Chloroform is registered for use in the US as an insecticidal fumigant on stored barley, corn, oats, popcorn, rice, rye, sorghum and wheat (US Environmental Protection Agency, 1971). In 1971, farmers used approximately 51 thousand kg chloroform for fumigant purposes. Chloroform is exempted from the requirement of a tolerance for residues on agricultural commodities when used as a solvent and when used as a fumigant after harvest for the following grains: barley, corn, oats, popcorn, rice, rye, sorghum and wheat (US Environmental Protection Agency, 1976a).

A notice of rebuttable presumption against registration and continued registration (RPAR) (see General Remarks on Substances Considered, p. 31) of pesticide products containing chloroform was issued by the US Environmental Protection Agency on 6 April, 1976 (US Environmental Protection Agency, 1976b). The future use of chloroform in agriculture in the US depends largely on the outcome of these actions.

The US Occupational Safety and Health Administration's health standards require that an employee's exposure to chloroform at no time exceed 240 mg/m$^3$ (50 ppm) (US Occupational Safety & Health Administration, 1978). On 9 June 1976, the US National Institute for Occupational Safety and Health recommended that occupational exposure to chloroform be controlled so that no employees be exposed to chloroform in excess of 9.78 mg/m$^3$ (2 ppm) in air as determined by a 1-hr air sample (National Institute for Occupational Safety & Health, 1976).

2.2 Occurrence

Chloroform may be formed in the troposphere by solar-induced photochemical reactions of trichloroethylene (Appleby et al., 1976).

(a) Air

Maximum levels of chloroform found in the atmosphere at any one location ranged from < 0.05-73.5 μg/m$^3$ (< 0.01-15 ppb); minimum levels were all less than 0.05 μg/m$^3$ (0.01 ppb); and mean levels, 0.045-5 μg/m$^3$ (0.009-1.03 ppb) (Lillian et al., 1975). Background concentrations of atmospheric chloroform, defined numerically as the average of the lower 50% of data points, were determined for two sites as 100 and 130 ng/m$^3$ (Singh et al., 1977).

Chloroform was detected in rural atmospheres at levels of 100 ng/m$^3$ (Grimsrud & Rasmussen, 1975) and 100-180 ng/m$^3$ (Russell & Shadoff, 1977).
Atmospheric concentrations of chloroform at ground level at sites in the northern and southern hemispheres were 130 ng/m³ and < 15 ng/m³, respectively (Cox et al., 1976).

Chloroform has been detected as a photochemical product in simulated ambient air containing trichloroethylene. It is suggested that a portion of the total atmospheric content of chloroform may result from tropospheric irradiation of trichloroethylene in air (Appleby et al., 1976).

(b) Water

The occurrence and formation of chloroform in drinking-water have been reviewed (Bellar et al., 1974; Morris & McKay, 1975).

Chloroform has been found in rivers, lakes, ground-water, commercial effluent water and sewage treatment plant effluent water at nearly 100 US and European locations (Shackelford & Keith, 1976). It has been detected in tap-water in the US and Czechoslovakia in concentrations ranging from 1.7-910 µg/l, and in waste-water discharges from the treatment of sewage and industrial wastes in concentrations ranging from 0.077-12.1 µg/l (Eurocop-Cost, 1976).

In 1975, a National Organics Reconnaissance Survey measured levels of chloroform in 80 US water supplies distributed over various regions of the US and representing a wide variety of raw-water sources and treatment techniques. Chloroform was present in raw water at 49 locations, in concentrations of < 1 µg/l, with the exception of one source that was receiving chlorinated raw water. All of the finished waters tested contained chloroform in concentrations ranging from < 0.1-311 µg/l (Symons et al., 1975).

Chloroform was found at concentrations of 47-92 µg/l in drinking-water at 4 locations (Kleopfer, 1976), at about 5 µg/l at another location (Saunders et al., 1975) and in 2 other locations (Bertsch et al., 1975).

It was detected in river water at the entrance to a water treatment facility, in the clarifier effluent stage of the water treatment process and in the finished water, at relative concentrations of 1.17:1.87:8.73 (Dowty et al., 1975).

Periods of high agricultural runoff have been found to be associated with peaks in chloroform concentrations, due to the increased turbidity of the raw water (Morris & Johnson, 1976).

Chloroform has been detected in drinking-water in Japan; the concentration at one site was 18-36 µg/l and was reportedly related to the chlorine dosing rate at the water purification plant and to the types of residual chlorine present (Kajino, 1977; Morita, 1976).
The maximum concentration of chloroform found in a survey sampling bay-water at 172 stations was 1 μg/l (Pearson & McConnell, 1975).

(c) Food

Residues of a fumigant mixture of carbon disulphide, carbon tetrachloride, chloroform and trichloroethylene were determined in cereals aired at 17°C and 30°C. Initial chloroform residues in barley aired at the two temperatures were 123 and 132 mg/kg. After 60 days, residues had disappeared from that aired at 17°C but were still present at 16 mg/kg in that aired at 30°C. Initial residues in corn were 189 and 224 mg/kg; after 60 days they had disappeared at 17°C but were still present at 16 mg/kg at 30°C. Initial residues in sorghum were 176 mg/kg at 17°C and 178 mg/kg at 30°C; after 25 days, residues had disappeared at 17°C, but they were still present at 22 mg/kg after 60 days at 30°C (Alumot & Bielorai, 1969).

The following concentrations of chloroform were found in foodstuffs in the UK in 1973: dairy produce, 1.4-33 mg/kg; meat, 1-4 mg/kg; oils and fats, 2-10 mg/kg; beverages, 0.4-18 mg/kg; and fruits and vegetables, 2-18 mg/kg (McConnell et al., 1975).

(d) Marine organisms

Concentrations of chloroform in 5 species of fish and 3 species of molluscs collected from relatively clean sea-water ranged from 56-1040 μg/kg (dry-weight basis) in the various organs of molluscs and from 7-851 μg/kg (dry-weight basis) in fish. Relative concentrations in the organs of fish were found to be: brain > gill > liver > muscle (Dickson & Riley, 1976).

(e) Humans

Chloroform has been detected in post-mortem human tissue samples, at levels of 1-68 μg/kg (wet tissue) (McConnell et al., 1975). In expired air, traces to 11 μg/hr/subject have been found (Conkle et al., 1975).

(f) Occupational exposure

A 1974 National Occupational Hazard Survey noted that workers primarily exposed to chloroform were those in hospitals, department stores and in the biological products, internal combustion engine and building paper and board industries (National Institute for Occupational Safety & Health, 1977a).

2.3 Analysis

Analytical methods to determine chloroform in environmental samples, mostly based on chromatographic techniques, have been reviewed (Fishbein, 1973; National Institute for Occupational Safety & Health, 1974).
Methods of analysis used for the analysis of chloroform in environmental samples are listed in Table 1.

A number of comparative studies on analytical techniques have been undertaken. An Official First Action method for determining volatile denaturants, including chloroform, in ethanol used in flavours (Horwitz, 1970, 1975) was studied collaboratively by 6 laboratories. Chloroform was determined by gas chromatography with flame ionization detection in alcoholic solution by 10 different collaborators (Martin & Figert, 1974). The initial results of a collaborative study by 15 US laboratories on chloroform in workplace air involved collection on activated charcoal at 4 levels, ranging from 12-485 mg/m³ (2.4-98.6 ppm), with analysis by gas chromatography (Reckner & Sachdev, 1975).

In one study, the efficiency of the removal of organic compounds, including chloroform, from aqueous solution by gas stripping, adsorption on polymeric adsorbant, thermal desorption and analysis by gas chromatography with flame ionization detection at the µg/l (ppb) level has been described (Kuo et al., 1977).

Sparging of drinking-water to strip organic pollutants was compared with extraction by carbon tetrachloride or nitrobenzene. No pollutants were found by solvent extraction, but the inert gas technique resulted in the identification of a number of organic compounds, including chloroform, at a concentration of 0.91 µg/l (ppb) (Novak et al., 1973).

Gas chromatography combined with infra-red and ultra-violet spectroscopy has been used to detect and identify immiscible solvents, including chloroform, in industrial waste waters, sewage and sludges (Ellison & Wallbank, 1974).

Ambient air sampling and analysis has been carried out by gas chromatography, with levels of detection of 0.3 µg/m³ (0.06 ppb) (Lillian et al., 1976). Chloroform has also been determined in ambient air using gas chromatography/mass spectrometry, with a limit of detection of 250 ng/m³ (5 ppt) (Grimsrud & Rasmussen, 1975).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 5 A mice of each sex, 3 months old at the beginning of the experiment, were given 30 oral doses of 0.1, 0.2, 0.4, 0.8 or 1.6 ml/kg bw (0.15-2.4 g/kg bw) chloroform in olive oil at 4-day intervals.
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td></td>
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<tr>
<td>Drugs</td>
<td>Heat under pressure with ethanolic potassium hydroxide to dechlorinate</td>
<td>Titration</td>
<td></td>
<td>Horwitz (1970, 1975)</td>
</tr>
<tr>
<td>Capsules &amp; cough syrups</td>
<td>Mix contents with ethanol, add 10% sucrose solution, extract (carbon disulphide)</td>
<td>IR</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trap on charcoal, extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Working range, 99.8-416 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977b)</td>
<td></td>
</tr>
<tr>
<td>Trap in pyridine, add sodium hydroxide solution, heat</td>
<td>Spectrophotometry (525 nm)</td>
<td>340 mg/m³ (75 ppm) (v/v 20°C/760 mm)</td>
<td>Gage et al. (1962)</td>
<td></td>
</tr>
<tr>
<td>Trap on charcoal or chromosorb 101, desorb by heating, retrap in line on GC column</td>
<td>GC/FID</td>
<td>Working range, 0.2-200 mg/m³ (40 ppb-40 ppm)</td>
<td>Parkes et al. (1976)</td>
<td></td>
</tr>
<tr>
<td>Environmental air &amp; stacks</td>
<td>Trap on porous polymer (Tenax), desorb by heating, retrap in line on GC column</td>
<td>GC/FID, ECD</td>
<td>1.5 µg/m³</td>
<td>Parsons &amp; Mitzner (1975)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap in Drexsel flask fitted with rubber septum, sample with gas syringe</td>
<td>GC/ECD</td>
<td>1.5 µg/m³</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Inject directly</td>
<td>GC/ECD</td>
<td>1 µg/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td></td>
<td>Sparge (carrier gas, helium), retrap on GC column</td>
<td>GC/Hall</td>
<td>0.1 µg/l</td>
<td></td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Extract (tetraclin)</td>
<td>GC/FID</td>
<td>0.04 µg/l</td>
<td>Keith et al. (1976)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Trap on adsorbent, desorb by heating, retrap in line on GC column</td>
<td>GC/MS</td>
<td>0.1 µg/l</td>
<td>Coleman et al. (1976)</td>
</tr>
</tbody>
</table>
### Table 1. Methods for the Analysis of Chloroform (continued)

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Extraction/Clean-Up</th>
<th>Detection</th>
<th>Limit of Detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinking-water</td>
<td>Inject directly</td>
<td>GC/ECD</td>
<td>&lt; 1 μg/l</td>
<td>Hammarstrand (1976)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Inject directly</td>
<td>GC/MS</td>
<td>0.1 μg/l</td>
<td>Fujii (1977)</td>
</tr>
<tr>
<td>Drinking, natural or effluent water</td>
<td>Cool to 4°C, extract (pentane)</td>
<td>GC/FID</td>
<td></td>
<td>Dietz &amp; Traud (1973)</td>
</tr>
<tr>
<td>Drinking, natural or effluent water</td>
<td>Add sodium chloride, extract (methylcyclohexane)</td>
<td>GC/ECD</td>
<td>&lt; 1 μg/l</td>
<td>Mieure (1977); Richard &amp; Junk (1977)</td>
</tr>
<tr>
<td>Surface and drinking-water</td>
<td>Headspace analysis</td>
<td>GC/ECD</td>
<td>0.1 μg/l</td>
<td>Kaiser &amp; Oliver (1976); Rook et al. (1975)</td>
</tr>
<tr>
<td>Municipal, artesian, deionized, charcoal-filtered water</td>
<td>Sparge (helium), trap on para-2,6-diphenylphenylene oxide, desorb by heating, retap in line on GC</td>
<td>GC/MS</td>
<td></td>
<td>Dowty et al. (1975)</td>
</tr>
<tr>
<td>Sea- and fresh-water</td>
<td>Extract (pentane), dry</td>
<td>GC/ECD</td>
<td>80 ng/l</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
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<td>Food</td>
<td>Extract (acetone-water or acetonitrile-water), decant, add sodium chloride</td>
<td>GC/ECD</td>
<td>0.1 mg/kg</td>
<td>Heuser &amp; Scudamore (1969); Thompson et al. (1974a)</td>
</tr>
<tr>
<td></td>
<td>Extract (acetone-water)</td>
<td>GC</td>
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<tr>
<td>Biological</td>
<td>Headspace analysis</td>
<td>GC/FID</td>
<td>1.5 mg/l</td>
<td>Premel-Cabic et al. (1974)</td>
</tr>
<tr>
<td>Blood</td>
<td>Shake, centrifuge</td>
<td>GC/FID</td>
<td>Working range, 10-500 mg/l</td>
<td>Poobalasingam (1976)</td>
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Abbreviations: IR - infra-red spectrometry; GC/FID - gas chromatography/flame-ionization detection; UV - ultra-violet spectrometry; ECD - electron capture detection; Hall - Hall conductivity detection; MS - mass spectrometry
Survivors were killed 1 month after the last treatment. All females at the 3 highest doses and all males at the 3 highest doses died early in the experiment. Nonmetastasizing hepatomas and cirrhosis were found in all surviving females given 0.8 or 0.4 ml/kg bw per dose. No hepatomas were observed in those at the two lowest dose levels or in the controls (Eschenbrenner & Miller, 1945).

A group of 24 XVII/G mice (sex unspecified), 3 months old at the start of treatment, were administered 0.1 ml of a 40% oily solution of chloroform by stomach tube twice weekly for 6 months. Of 5 animals that survived 297 days, 3 developed hepatomas (Rudali, 1967) [The Working Group noted that no data on controls were reported].

Groups of 50 male and 50 female B6C3F1 mice, 5 weeks of age, received a 2-5% solution of chloroform (USP grade) in corn oil by gavage 5 times weekly for 78 weeks. The initial dose levels for males were 100 and 200 mg/kg bw, and those for females 200 and 400 mg/kg bw. These doses were increased after 18 weeks to 150 and 300 mg/kg bw for males and 250 and 500 mg/kg bw for females, so that the average levels were 138 and 277 mg/kg bw for males and 238 and 477 mg/kg bw for females. Pooled control groups, consisting of 77 male and 80 female mice, and matched control groups, consisting of 20 males and 20 females, were treated with corn oil only. The experiment was terminated at 92-93 weeks. The incidence of hepatocellular carcinomas in all treated groups of mice was statistically significant (P < 0.001) when compared with that in controls (see Table 2) (National Cancer Institute, 1976).

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, 52 days old, received a 10% solution of chloroform (USP grade) in corn oil by gavage 5 times weekly. Males were given doses of 90 and 180 mg/kg bw for 78 weeks; female rats started on dose levels of 125 and 250 mg/kg bw, but these were lowered to 90 and 180 mg/kg bw after 22 weeks, giving an average level of 100 and 200 mg/kg bw for the study. Pooled control groups of 100 males and 100 females and matched control groups of 20 males and 20 females were treated with the vehicle only. The experiment was terminated at 111 weeks. The incidence of kidney epithelial tumours in male rats was statistically greater (P=0.0016) than that in controls (see Table 2) (National Cancer Institute, 1976).

(b) Subcutaneous and/or intramuscular administration

Newborn mouse: An unspecified number of (C57 x DBA2 F1) mice received subcutaneously either a single dose of 200 μg chloroform in 0.02 ml arachis oil when less than 24 hrs old or 8 daily doses of 200 μg during the first week of life. They were killed when 77-80 weeks old. It was reported that no evidence of carcinogenicity was obtained (Roe et al., 1968) [The Working Group noted the inadequate reporting of the experiment].
TABLE 2. TUMOUR INCIDENCES IN MICE AND RATS GIVEN GRADED DOSES OF CHLOROFORM BY GAVAGE

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>DOSE (mg/kg bw)</th>
<th>SEX</th>
<th>NUMBER OF ANIMALS</th>
<th>INITIAL</th>
<th>FINAL</th>
<th>NUMBER OF TUMOUR-BEARING ANIMALS/NUMBER OF ANIMALS EXAMINED HISTOLOGICALLY</th>
<th>KIDNEY</th>
<th>LIVER</th>
<th>THYROID</th>
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<tr>
<td>H6C3Fl mice</td>
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<td>100</td>
<td>M</td>
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<td>F</td>
<td>50</td>
<td>0/45</td>
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<td>Matched controls</td>
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<td>Corn oil</td>
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<td></td>
<td>M</td>
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- a No biological significance attached to findings
- b Dosage increased to final levels after 18 weeks
- c Carcinomas
- d 2 carcinomas + 2 adenomas
- e Dosage reduced to final levels after 22 weeks
- f 7 adenomas + 1 carcinoma
- g 10 carcinomas + 3 adenomas
- h 7 adenomas + 3 carcinomas
- i 10 carcinomas + 3 adenomas + 2 carcinomas
(c) **Intraperitoneal administration**

Mouse: Groups of 20 male A/St mice, 6-8 weeks old, were given thrice weekly i.p. injections of 80, 200 or 400 mg/kg bw chloroform in tricaprylin for 8 weeks, except for those given the highest dose, which received only 2 injections per week. All survivors were killed 24 weeks after the first injection. No increase in the incidence of lung tumours was observed in comparison with tricaprylin-injected controls (Theiss et al., 1977) [The Working Group noted the limitations of a negative result obtained in this test system; see also General Remarks on the Substances Considered, p. 34].

3.2 Other relevant biological data

(a) **Experimental systems**

**Toxic effects**

The acute toxicity of chloroform is species-, strain-, sex- and age-dependent. Thus, the acute oral LDS0s in young and older adult male Sprague-Dawley rats are 1336 and 1188 mg/kg bw, whereas in 14-day-old animals it is 445 mg/kg bw (Kimura et al., 1971). The single oral LD50 in male mice varied from 120 mg/kg bw in DBA/2J mice to 490 mg/kg bw in C57BL/6J mice (Hill et al., 1975).

Males of many mouse strains are susceptible to renal tubular necrosis, whereas females are not similarly affected. The response to chloroform increased with age of the mice. Strains C3H, C3Hf, A and HR were susceptible, and strains C57BL, C57L, C57BR/cd and ST resistant, to exposure (Deringer et al., 1953).

Liver damage was the cause of death of rats and mice after acute administration of chloroform (Brown et al., 1974a; Doyle et al., 1967). An early dilatation of the granular endoplasmic reticulum, with detachment of the ribosomes, was observed in the livers of treated rats (Scholler, 1968). In rats, rabbits and guinea-pigs exposed to 125, 250 or 425 mg/m³ (25, 50 or 85 ppm) chloroform in air, and in dogs exposed to 25 ppm, for 7 hrs/day on 5 days/week for 6 months, histopathological alterations in the liver and kidney, higher mortality and changes in organ weights were observed; centrilobular granular degeneration was seen in rat liver. These effects appeared to be reversible in rats given only 25 ppm (Torkelson et al., 1976).

**Embryotoxicity and teratogenicity**

Doses of 20, 50 or 126 mg/kg bw/day were given to rats on days 6-15 of gestation, and 20, 35 or 50 mg/kg bw/day to rabbits on days 6-18 of gestation; reduced birth weights were observed with the highest dose levels in both species. There was no evidence of teratogenicity in either species with any dose level (Thompson et al., 1974b).
Rats were exposed to subanaesthetic doses of chloroform: 150, 500 and 1500 mg/m³ (30, 100 and 300 ppm), in air by inhalation for 7 hrs per day on days 6-15 of gestation. The 100 ppm dose caused a low incidence of acardiac foetuses with imperforate anus. All doses of chloroform were foetotoxic and retarded development (Schwetz et al., 1974).

It was reported in an abstract that chloroform caused increased foetal mortality and decreased foetal weight, but no teratogenic effects were observed when pregnant rats were exposed to 20.1 ± 1.2 g/m³ during days 7-14 of gestation (Dilley et al., 1977).

Absorption, distribution, excretion and metabolism

Chloroform is rapidly absorbed and distributed to all organs, with relatively high concentrations in nervous tissue (Von Oettingen, 1964). After intraduodenal injection of ¹⁴C-chloroform to rats, 70% of the chloroform was found unchanged in the expired air and 4% as ¹⁴CO₂ during 24 hrs. At least 75% of the radioactivity was excreted in the expired air in 18 hrs; the liver and, to a much lesser extent, the kidney were the main organs in which CO₂ was formed (Paul & Rubinstein, 1963). Male mice had the greatest amounts of radioactivity in the kidney, while female mice had more radioactivity in the liver (Taylor et al., 1974).

The metabolism of chloroform has been reviewed (Charlesworth, 1976; Hathway, 1974). When ¹⁴C-chloroform was administered orally to mice rats and monkeys, radioactivity was found in expired air. Most of the dose was excreted unchanged by monkeys, as ¹⁴CO₂ by mice, and as both by rats. Three metabolites were detected in the urine of rats and mice, one of which was identified as urea (Brown et al., 1974b; Taylor et al., 1974).

Various treatments that affect hepatic drug-metabolizing enzymes alter the hepatotoxicity of chloroform, indicating that a metabolite of chloroform may be responsible for the liver necrosis (McLean, 1970; Scholler, 1970). After administration of ¹⁴C-chloroform, there was extensive covalent ¹⁴C-binding to liver and kidney proteins; this paralleled the extent of necrosis in control and treated mice (Ilett et al., 1973). In similar experiments, binding in the kidneys of mice of two strains was related to their susceptibility to kidney lesions (Vesell et al., 1976). Other factors, such as the availability of glutathione (Brown et al., 1974a), concentration of cytochrome P450 and oxygen tension (Sipes et al., 1977; Uehleke & Werner, 1975) affected the extent of covalent binding and of hepatic centrilobular damage.

In phenobarbital-treated rats, liver necrosis was observed only with doses of chloroform high enough to decrease levels of reduced glutathione in liver (Docks & Krishna, 1976). In vitro, covalent binding of radioactivity from ¹⁴C-chloroform to microsomal macromolecules
is inhibited by cysteine (Pohl et al., 1977). The finding of 2-oxothiazolidine-4-carboxylic acid in incubates was strong evidence for formation of phosgene; the reactive metabolite phosgene is formed by mixed-function oxidation of chloroform to trichloromethanol following dehydrochlorination (Mansuy et al., 1977; Pohl et al., 1977, 1979).

Mutagenicity and other related short-term tests

In assays with Salmonella typhimurium TA1535 and TA1538 and with Escherichia coli K12, chloroform was not mutagenic in the presence of microsomal preparations from mouse, rabbit or rat liver (Uehleke et al., 1976, 1977).

(b) Humans

Chloroform exposure has repeatedly been fatal to man. Rapid death was attributed to cardiac arrest and delayed death to liver and kidney damage (Challen et al., 1958; Matsuki & Zsigmond, 1974). Symptoms of chloroform exposure include respiratory depression, coma, renal damage and liver damage as measured by elevated serum enzyme levels (Storms, 1973). In 8 volunteers, 20-68% of an oral dose of 500 mg $^{13}$C-chloroform was expired unchanged in the air; in 2 subjects, 48-50% of the dose was eliminated in the expired air as $^{13}$CO$_2$ (Fry et al., 1972). Blood concentrations and kinetics of chloroform after anaesthesia were described by Smith et al. (1973).

For the occurrence of chloroform in human tissues, see section 2.2 (e).

3.3 Case reports and epidemiological studies

Hepatomegaly was demonstrated in 17/68 workers exposed regularly to chloroform for 1-4 years, in 5/39 workers with past exposure to chloroform, in 2/23 workers with hepatitis but no exposure to chloroform (positive controls) and in 2/164 workers with no hepatitis and no exposure to chloroform. Of the 17 cases with hepatomegaly, 4 had toxic hepatitis and 14 had fatty degeneration of the liver. No liver cancers were found (Bomski et al., 1967) [The Working Group noted that this study is uninformative with regard to the carcinogenicity of chloroform, due to small numbers, disproportionate number of current employees and short follow-up time since first exposure].

1The Working Group was aware of a mortality study in progress on anaesthetists employed when chloroform was in use as an anaesthetic (IARC, 1978d).
4. Summary of Data Reported and Evaluation

4.1 Experimental data

Chloroform was tested in three experiments in mice and in one in rats by oral administration. It produced hepatomas and hepatocellular carcinomas in mice, malignant kidney tumours in male rats and tumours of the thyroid in female rats. Chloroform was also tested in one experiment by subcutaneous injection and in one by intraperitoneal injection in mice: these experiments were considered to be inadequate.

Chloroform is foetotoxic; it was not mutagenic in the bacterial systems tested.

1Subsequent to the meeting of the Working Group, the Secretariat became aware of the results of 3 studies, in which mice, rats and dogs were administered toothpaste containing chloroform by gavage or in gelatin capsules on 6 days per week for 80 weeks (mice and rats) or 7½ years (dogs), followed by observation periods ranging from 15-24 weeks. No treatment-related increase in the incidence of tumours was observed in rats receiving 60 mg/kg bw/day chloroform (Palmer et al., 1979) or in dogs receiving 15 or 30 mg/kg bw/day (Heywood et al., 1979). In mice, benign and malignant tumours of the kidney occurred in 8/38 male ICI mice administered 60 mg/kg bw/day chloroform, but no such tumours occurred in females given that dose, or in males and females receiving 17 mg/kg bw/day or in controls. In a second experiment in mice, 7 benign and 2 malignant tumours of the kidney occurred among 49 male CFLP (ICI-redefined) mice given 60 mg/kg bw/day chloroform in toothpaste base compared with 6 benign kidney tumours among 237 male mice given the toothpaste base without chloroform. In a third experiment, groups of C57BL, CBA, CF/1 or ICI male mice received 60 mg/kg bw/day chloroform in toothpaste base or toothpaste base alone; 2 additional groups of male ICI mice received 60 mg/kg bw/day chloroform in arachis oil or arachis oil alone. Two benign and 3 malignant tumours of the kidney occurred among 47 ICI male mice given chloroform in toothpaste base, and 3 benign and 9 malignant tumours of the kidney occurred among 48 ICI male mice given chloroform in arachis oil. One benign tumour of the kidney occurred in each group of respective controls. No kidney tumours occurred in treated C57BL or CBA mice; and no increased incidence of malignant kidney tumours was seen in CF/1 male mice (1/48 treated and 2/45 controls) (Roe et al., 1979).
4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The past use of chloroform as an anaesthetic and its present use in drugs and cosmetic products, as an insecticidal fumigant and as an industrial solvent indicate that widespread human exposure occurs. This is confirmed by many reports of its presence in air, water and foods.

4.3 Evaluation

There is sufficient evidence that chloroform is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard chloroform as if it presented a carcinogenic risk to humans.
5. References


Eschenbrenner, A.B. & Miller, E. (1945) Induction of hepatomas in mice by repeated oral administration of chloroform, with observations on sex differences. J. natl Cancer Inst., 5, 251-255


Fujii, T. (1977) Direct aqueous injection gas chromatography-mass spectrometry for analysis of organohalides in water at concentrations below the parts per billion level. J. Chromatogr., 139, 297-302


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Morita, M. (1976) Chlorination and chlorinated organic materials (Jap.). *Yosui To Haisui*, 18, 143-149 [Chem. Abstr., 85, 148872m]


Rudali, G. (1967) Oncogenic activity of some halogenated hydrocarbons used in therapeutics (Fr.). UICC Monogr. Ser., 7, 138-143


CHLOROFORM


US Environmental Protection Agency (1976b) Extension of period for submission of rebuttal evidence and comments with regard to presumption against registration and continued registration of pesticide products containing chloroform (trichloromethane). Fed. Regist., 41, 22297

US Food & Drug Administration (1976a) Human Drugs Containing Chloroform, April, 635,000, Rockville, MD


1,2-DICHLOROETHANE

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: 1,2-Dichloroethane

Synonyms: 1,2-Bichloroethane; α,β-dichloroethane; sym-
dichloroethane; dichloroethylene; EDC; ENT 1,656; ethylene
chloride; ethylene dichloride; glycol dichloride

Trade names: Brocide; Dutch liquid; Dutch oil; Freon 150

1.2 Structural and molecular formulae and molecular weight

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\end{align*}
\]

\[C_2H_5Cl_2 \quad \text{Mol. wt: 98.9}\]

1.3 Chemical and physical properties of the pure substance

From Hardie (1964), unless otherwise specified

(a) **Description:** Clear, colourless, oily liquid (Hawley, 1971; Patterson *et al.*, 1976)

(b) **Boiling-point:** 83.5°C

(c) **Melting-point:** -35.4°C

(d) **Density:** \(d^{20} 1.253\)

(e) **Refractive index:** \(n^2_0 1.4449\)

(f) **Spectroscopy data:** Infra-red, Raman, nuclear magnetic
resonance and mass spectral data have been tabulated
(Grasselli & Ritchey, 1975).
(g) **Solubility:** Slightly soluble in water (0.869 g/100 ml at 20°C); soluble in most organic solvents

(h) **Volatility:** Vapour pressure is 64 mm at 20°C.

(i) **Vapour density:** 3.4 (air = 1) (National Fire Protection Association, 1972)

(j) **Stability:** Stable at ordinary temperatures when dry; at > 600°C, decomposes to vinyl chloride (see IARC, 1979a), hydrogen chloride and acetylene. In the presence of air, moisture and light, at ordinary temperatures, darkens in colour. Resistant to oxidation (Hawley, 1971)

(k) **Reactivity:** Can be hydrolysed to ethylene glycol in the presence of water at 160-175°C, 15 atm, or in the presence of alkali at 140-250°C, 40 atm. Both chlorine atoms are reactive. Does not corrode metal (Hawley, 1971)

(l) **Conversion factor:** 1 ppm in air is equivalent to 4 mg/m³.

1.4 Technical products and impurities

1,2-Dichloroethane is available in drums or tank cars as technical and spectrophotometric grades (Hawley, 1971). One manufacturer's specifications for a technical-grade product are as follows: water, 0.03% max; alkalinity (as NaOH) 0.0005% max; acidity (as HCl) 0.0002% max; free halogens, none; residue on evaporation, 0.01% max; boiling-range at 760 mm, within a 1.5°C range including 83.5°C.

1,2-Dichloroethane produced in Japan is reported to contain poly-chlorinated ethanes as impurities.

When used as a fumigant, 1,2-dichloroethane is usually mixed with carbon tetrachloride in a ratio of 3:1 to reduce the fire hazard (Martin & Worthing, 1977).
2. Production, Use, Occurrence and Analysis

A review article on 1,2-dichloroethane has been published (Hardie, 1964).

(a) Production and use

1,2-Dichloroethane was the first chlorinated hydrocarbon to be synthesized: it was first produced in 1795 by the chlorination of ethylene by Delman et al. (Prager et al., 1918). Since late 1970, all of the 1,2-dichloroethane produced in the US has been made by the chlorination or oxychlorination (a catalysed reaction with air and hydrogen chloride) of ethylene (Approximately 3.17 kg of 1,2-dichloroethane are produced per kg of ethylene consumed). It is currently produced primarily by chlorination, but an increasing percentage is being produced by oxychlorination. 1,2-Dichloroethane has also been produced as a by-product in the chlorohydrin process for the manufacture of ethylene oxide, which involves the conversion of ethylene to ethylene chlorohydrin by reacting it with hypochlorous acid; the chlorohydrin is converted to the oxide by dehydrochlorination with slaked lime (Approximately 0.1 kg of 1,2-dichloroethane may be produced for each kg of ethylene oxide). Ethylene oxide is no longer produced by this method in the US.

In Japan, all commercial production of 1,2-dichloroethane is based upon the chlorination of ethylene.

Commercial production of 1,2-dichloroethane in the US was first reported in 1922 (US Tariff Commission, 1923). In 1976, 13 US producers reported a total production of 3600 million kg (US International Trade Commission, 1977); however, this is likely to be an underestimate, since some 1,2-dichloroethane that is produced is not separated (and therefore not reported) by some producers. US exports in 1976 amounted to 208 million kg (US Department of Commerce, 1977); imports are not reported separately but are believed to be negligible in all years except 1974, when an estimated 34 million kg were imported.

1,2-Dichloroethane is produced at an annual rate in excess of 100 million kg in the Benelux countries, the Federal Republic of Germany, France, Italy, the UK, Scandinavia, Spain, and eastern Europe. Austria and Switzerland each produce less than 100 thousand kg annually.

1,2-Dichloroethane was first produced commercially in Japan in 1965. In 1976, 18 producers reported a total production of 1800 million kg; imports were 89 million kg, and no exports were reported.
(b) Use

Use of 1,2-dichloroethane in the US in 1976 was as follows:
production of vinyl chloride, 81.6%; production of 1,1,1-trichloro-
ethane, 3.3%; production of ethyleneamines, 2.8%; production of tetra-
chloroethylene, 2.3%; production of trichloroethylene, 2.0%; as a
lead scavenger, 1.9%; production of vinylidene chloride, 1.8%; mis-
cellaneous applications, 0.1%; and exports, 4.2%.

About 4000 million kg 1,2-dichloroethane were used in the US for
the production of vinyl chloride in 1976. About 96% of the vinyl
chloride made in that year was used for the production of vinyl chloride
homopolymer and copolymer resins. The remainder was used for the
production of 1,1,1-trichloroethane and as a comonomer with vinylidene
chloride in the production of resins (For more detailed information on
the uses of vinyl chloride and polyvinyl chloride, see IARC 1979a).

In 1976, 165 million kg 1,2-dichloroethane were used in the US in
the production of 1,1,1-trichloroethane (For information on the uses
of 1,1,1-trichloroethane, see monograph, p. 515); approximately 139
million kg were used to make ethyleneamines; 115 million kg were used
for the production of tetrachloroethylene (For information on the uses
of tetrachloroethylene, see monograph, p. 491); 99 million kg were used
for the production of trichloroethylene (For information on the uses
of trichloroethylene, see monograph, p. 545); and 89 million kg were used
for the production of vinylidene chloride (For information on the uses
of vinylidene chloride, see IARC, 1979b).

1,2-Dichloroethane is used as a lead-scavenging agent in petrol to
transform the combustion products of lead alkyls to more easily vapour-
ized forms. It is a major ingredient of many petrol antiknock mixtures.
About 92 million kg were used for this purpose in the US in 1976.

Miscellaneous applications for 1,2-dichloroethane, which consumed
7.3 million kg in 1976, include: various solvent applications; use as
a fumigant for grain, upholstery and carpets; and as a chemical inter-
mediate for the manufacture of polysulphide elastomers and ethylene-
imine.

No data on its use in Europe were available.

In Japan, 90% of 1,2-dichloroethane is used for the production of
vinyl chloride and 10% as an industrial solvent and a chemical inter-
mediate.

1,2-Dichloroethane is registered for agricultural use in the US in
various formulations with other fumigants for the postharvest fumigation
of grain and for use in orchards, agricultural premises and mushroom
houses (US Environmental Protection Agency, 1969).
1,2-DICHLOROETHANE

This substance was evaluated at the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. It was noted that there is little direct information on the amount of residues appearing in commercial samples or in food reaching the consumer; however, the following residue levels were recommended as guidelines: in raw cereals at point of entry into a country or when supplied for milling, provided that the commodity is freely exposed to air for a period of at least 24 hrs after fumigation before sampling, 50 mg/kg; in milled cereal products that are to be subjected to baking or cooking, 10 mg/kg; in bread and other cooked cereal products, 0.1 mg/kg (WHO, 1972).

In the US, 1,2-dichloroethane is exempted from the requirement of a tolerance when used as a fumigant after harvest for the following grains: barley, corn, oats, popcorn, rice, rye, sorghum and wheat (US Environmental Protection Agency, 1976). The basis for this exemption and similar exemptions in Australia and Canada is that no hazard will remain when the food reaches the consumer (WHO, 1972).

1,2-Dichloroethane has been cited by the US Environmental Protection Agency as a candidate for action through the rebuttable presumption against registration (RPAR) (see General Remarks on Substances Considered, p. 31) process because of possible carcinogenicity and mutagenicity (Anon., 1978a).

The US Occupational Safety and Health Administration's health standards for air contaminants require that an employee's exposure to 1,2-dichloroethane not exceed 200 mg/m³ (50 ppm) in the workplace air in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977). In April 1976, the US National Institute for Occupational Safety and Health recommended that occupational exposure to ethylene dichloride not exceed 20 mg/m³ (5 ppm), determined as a time-weighted average exposure for up to a 10-hr work day in a 40-hr work week, and 60 mg/m³ (15 ppm) as a peak concentration (National Institute for Occupational Safety & Health, 1976a). That Institute has recently proposed that these values be lowered to 1 ppm and 2 ppm, respectively (Anon., 1978b).

2.2 Occurrence

1,2-Dichloroethane is not known to occur as a natural product.

(a) Air

Chlorinated hydrocarbons, including 1,2-dichloroethane, have been detected in urban air at levels of 0.04-38 µg/m³ (0.01-9.4 ppb) (Okuno et al., 1974). A level of 300 µg/m³ has been detected near a vinyl chloride plant (Kretzschmar et al., 1976).
In 1974, total annual US emissions of 1,2-dichloroethane to the ambient air were estimated to have been 74 million kg (representing about 1.8% of total reported production). The individual sources of these emissions were: (1) manufacture of end-products, primarily vinyl chloride, 38.6 million kg; (2) manufacture of 1,2-dichloroethane, 26.3 million kg; (3) use as a solvent, 6.4 million kg; and (4) storage and distribution, 2.7 million kg (Patterson et al., 1976).

(b) Water

As part of a US Environmental Protection Agency study, the National Organics Reconnaissance Survey for Halogenated Organics sampled finished drinking-water supplies in 80 US cities. 1,2-Dichloroethane was found in the waters of 28 cities at level of 0-6 \( \mu \text{g/l} \) (Symons et al., 1975).

In a more recent study, surface water samples taken near heavily industrialized sites across the US were examined for all contaminants present. Levels of 1,2-dichloroethane greater than 1 \( \mu \text{g/l} \) were detected at 53 of 204 sites (Ewing et al., 1977).

1,2-Dichloroethane has also been detected in: (1) tap-water, at levels of 8 \( \mu \text{g/l} \) and 61 mg/l; (2) river-water, at a level of 0.7 \( \mu \text{g/l} \) (Eurocop-Cost, 1976); (3) raw and finished drinking-water (Shackelford & Keith, 1976); and (4) tap-water in Japan, at a level of 0.9 \( \mu \text{g/l} \) (Fujii, 1977).

(c) Humans

1,2-Dichloroethane has been found in expired air at levels of 0-0.8 \( \mu \text{g/hr} \) (Conkle et al., 1975).

(d) Occupational exposure

A 1974 National Occupational Hazard Survey estimated that workers primarily exposed to 1,2-dichloroethane were those in hospitals, blast furnaces, steel mills and air transportation industries (National Institute for Occupational Safety & Health, 1977a).

(e) Other

1,2-Dichloroethane has been detected in waste products that had been dumped in the North Sea from vinyl chloride production plants in Europe (Jensen et al., 1975).

2.3 Analysis

Methods used for the analysis of 1,2-dichloroethane in environmental samples are listed in Table 1.
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<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fumigant mixtures</td>
<td>Inject directly</td>
<td>GC</td>
<td>Horwitz (1975)</td>
<td></td>
</tr>
<tr>
<td><strong>Air</strong></td>
<td>Trap on activated charcoal or porous polymer packing (Chromosorb 101), desorb by heating, retrap in line on GC column</td>
<td>GC/FID</td>
<td>Working range, 160 µg/m³-160 mg/m³ (40 ppb-40 ppm)</td>
<td>Parkes et al. (1976)</td>
</tr>
<tr>
<td></td>
<td>Trap on porous polymer (Tenax), desorb by heating, retrap in line on GC column</td>
<td>GC/FID</td>
<td>Parsons &amp; Mitzner (1975)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trap in pyridine, add sodium hydroxide solution, heat</td>
<td>Spectrophotometry (415 nm)</td>
<td>400 mg/m³ (100 ppm) (v/v, 20°C, 760 mm)</td>
<td>Gage et al. (1962)</td>
</tr>
<tr>
<td></td>
<td>Trap on charcoal, extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Working range, 195-819 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977b)</td>
</tr>
<tr>
<td><strong>Direct</strong></td>
<td>Laser absorption spectroscopy, 9-11 nm</td>
<td></td>
<td>Alone: 944 mg/m³ (236 ppm); in gas mixture: 4000 mg/m³ (1000 ppm)</td>
<td>Green &amp; Steinfeld (1976)</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td>Photolization NS</td>
<td>28 mg/m³ (7 ppm)</td>
<td>Driscoll &amp; Warneck (1973)</td>
<td></td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Inject directly</td>
<td>GC/FID</td>
<td>90 µg/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td></td>
<td>Sparge (helium), retrap on GC column</td>
<td>GC/Hall</td>
<td>0.2 µg/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-----------------</td>
<td>--------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Municipal, artesian deionized,</td>
<td>Sparge (helium), trap on para-2,6-diphenyl phenylene oxide, desorb by heating, retrap in line on GC column</td>
<td>GC/MS</td>
<td></td>
<td>Dowty et al. (1975)</td>
</tr>
<tr>
<td>charcoal filtered water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Sparge (helium), trap on adsorbant, GC, microcoulometry desorb by heating, retrap in line (halide-specific mode) on GC column</td>
<td></td>
<td>0.1 µg/l</td>
<td>Symons et al. (1975)</td>
</tr>
<tr>
<td>Food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grains</td>
<td>Grind in dry ice, boil in acid, trap volatile fumigant in cold solvents</td>
<td>GC/ECD</td>
<td>4 mg/kg</td>
<td>Malone (1969, 1970)</td>
</tr>
<tr>
<td>Spice oleoresins</td>
<td>Dilute (ethanol), add internal standard (1,2-dichloropropane)</td>
<td>GC, microcoulometry</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
</tbody>
</table>

Abbreviations: GC - gas chromatography; FID - flame-ionization detection; ECD - electron capture detection; MS - mass spectrometry; Hall - Hall conductivity detection
A collaborative study was carried out to determine the efficiency of activated charcoal as a trapping agent for organic vapours in air (Reckner & Sachdev, 1975).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 50 male and 50 female 5 week-old B6C3Fl mice were administered technical-grade 1,2-dichloroethane in corn oil by gavage on 5 consecutive days per week for 78 weeks. High-dose males received 150 mg/kg bw/day for 8 weeks and then 200 mg/kg bw/day for 70 weeks, followed by 13 weeks without treatment. High-dose females received 250 mg/kg bw/day for 8 weeks, 400 mg/kg bw/day for 3 weeks and 300 mg/kg bw for 67 weeks, followed by 13 weeks without treatment. Low-dose males received 75 mg/kg bw/day for 8 weeks and 100 mg/kg bw/day for 70 weeks, followed by 12 weeks without treatment. Low-dose females received 125 mg/kg bw/day for 8 weeks, 200 mg/kg bw/day for 3 weeks and 150 mg/kg bw/day for 67 weeks, followed by 13 weeks without treatment. The time-weighted average doses were 195 and 299 mg/kg bw/day for high-dose males and females and 97 and 149 mg/kg bw/day for low-dose males and females. A group of 20 male and 20 female mice that received corn oil alone served as matched vehicle controls. Another group of 60 male and 60 female mice that received the same vehicle served as pooled vehicle controls. Of high-dose males, 50% survived at least 84 weeks, and 42% survived until the end of the study; 72% (36/50) of high-dose female mice died between weeks 60 and 80. In the low-dose groups, 52% (26/50) of males survived less than 74 weeks, and 68% (34/50) of females survived until the end of the study. In the vehicle control groups, 55% (11/20) of males and 80% (16/20) of females survived until the end of the study. Almost all organs, and any tissue containing visible lesions, were examined histologically. The numbers of animals with tumours and the total numbers of tumours were significantly greater in male and female mice treated with the higher dose level, and in female mice treated with the low dose, than in controls. Increased incidences of the following neoplasms were observed: mammary adenocarcinomas, uterine adenocarcinomas, endometrial stromal neoplasms of the uterus, and squamous-cell carcinomas of the forestomach in females; lung adenomas and malignant histiocytic lymphomas in males and females; and hepatocellular carcinomas in male mice (see Table 2). A group of 20 male

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1The Working Group was aware of studies in progress to assess the carcinogenicity of 1,2-dichloroethane by skin application in mice and by oral administration in rats (IARC, 1978).
### TABLE 2. ORAL ADMINISTRATION OF 1,2-DICHLOROETHANE TO MICE AND RATS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF ANIMALS EXAMINED HISTOPATHOLOGICALLY</th>
<th>NO. OF ANIMALS WITH TUMOURS</th>
<th>TOTAL NO. OF TUMOURS</th>
<th>TUMOUR TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HERPETOCELLULAR CARCINOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MALIGNANT HISTOCYTIC LYMPHOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LUNG ADENOMAS + CARCINOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FORESTOMACH SQUAMOUS-CELL CARCINOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S.C. FIBROSARCOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HUMAN ADENOCARCINOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UTERINE ADENOCARCINOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UTERINE ENDOMETRIAL STROMAL SARCOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RENAL ANGIOSARCOMAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(SEVERAL ORGANS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mice</th>
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</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td>Pooled vehicle controls</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Matched vehicle controls</td>
<td>19</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Low-dose</td>
<td>46</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>High-dose</td>
<td>47</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td>Pooled vehicle controls</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Matched vehicle controls</td>
<td>20</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Low-dose</td>
<td>50</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>High-dose</td>
<td>48</td>
<td>29</td>
<td>15</td>
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<table>
<thead>
<tr>
<th>Rats</th>
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<th></th>
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<th>Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td>Pooled vehicle controls</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Matched vehicle controls</td>
<td>20</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Low-dose</td>
<td>50</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>High-dose</td>
<td>50</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td>Pooled vehicle controls</td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Matched vehicle controls</td>
<td>20</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Low-dose</td>
<td>50</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>High-dose</td>
<td>50</td>
<td>33</td>
<td>4</td>
</tr>
</tbody>
</table>

---

*a 1 mouse had 1 adenoma and 1 adenocarcinoma

*b 2 rats had 1 fibroadenoma and 1 adenocarcinoma
and 20 female untreated matched controls was included, but it was not considered in the statistical analyses of tumour incidence (National Cancer Institute, 1978).

**Rat:** Groups of 50 male and 50 female Osborne Mendel rats, 9 weeks old, were administered technical-grade 1,2-dichloroethane in corn oil by gavage on 5 consecutive days per week for 78 weeks. High and low doses were 100 and 50 mg/kg bw/day for 7 weeks, 150 and 75 mg/kg bw/day for 10 weeks, and 100 and 50 mg/kg bw/day for 18 weeks, respectively, followed by cycles of 1 treatment-free week and 4 weeks under treatment with the same doses (100 and 50 mg/kg bw/day) for 43 weeks (34 weeks under treatment and 9 treatment-free weeks). The time-weighted average doses were 95 and 47 mg/kg bw/day for high- and low-dose males and females. A group of 20 male and 20 female rats received corn oil alone and were used as matched vehicle controls; another group of 60 male and 60 female rats received the same vehicle and were used as the pooled vehicle control group. The last high-dose male rat died during week 23 of the observation period following administration of the chemical, and the last high-dose female rat died during week 15 of the observation period. Low-dose rats were observed for 32 weeks after administration. Mortality was increased in the high-dose groups: 50% of males were dead by week 55 and 50% of females by week 57; by week 75, 84% of males and 80% of females were dead. In the low-dose group, 52% of the males survived over 82 weeks, and 50% of the females survived over 85 weeks. All treated and control animals were examined histologically. The total number of tumours was significantly greater than that in controls only in female rats treated with the high dose; however, a significant increase in the number of squamous-cell carcinomas of the forestomach in male rats and of mammary gland adenocarcinomas and fibroadenomas in female rats treated with the high dose was observed. An increase in the incidence of haemangiosarcomas in animals of both sexes was also noted, but it was statistically significant only in males (see Table 2). A group of 20 male and 20 female untreated matched controls was included, but it was not considered in the statistical analyses of tumour incidence (National Cancer Institute, 1978).

**Intraperitoneal administration**

**Mouse:** Groups of 20 male A/St mice, 6-8 weeks old, were given thrice weekly i.p. injections of 20, 40 or 100 mg/kg bw 1,2-dichloroethane in tricaprylin for 8 weeks. All survivors were killed 24 weeks after the first injection. No significant increase in the incidence of lung tumours was observed compared with that in tricaprylin-treated controls (Theiss et al., 1977) [The Working Group noted the limitations of a negative result obtained with this test system; see also General Remarks on Substances Considered, p. 34].
3.2 Other relevant biological data

(a) Experimental systems

The toxicity and metabolism of 1,2-dichloroethane have been reviewed (WHO, 1970; National Institute for Occupational Safety & Health, 1976b; Von Oettingen, 1964).

Toxic effects

The single oral LD$_{50}$ in rats is 700 mg/kg bw (McCollister et al., 1956); the inhalational LD$_{50}$ in rats is 4000 mg/m$^3$ (1000 ppm) in air for a 4-hr exposure (Carpenter et al., 1949). Rats exposed to various concentrations in air showed central nervous system depression, anaesthesia and coma (Von Oettingen, 1964). Acute exposure caused disseminated haemorrhagic lesions, mainly in the liver; chronic exposure caused degeneration of the liver and tubular damage and necrosis of the kidneys (McCollister et al., 1956). Necrosis of the corneal endothelium was seen in dogs after s.c. injection of 1,2-dichloroethane (Kuwabara et al., 1968).

No data on the embryotoxicity or teratogenicity of 1,2-dichloroethane were available.

Absorption, distribution, excretion and metabolism

Following i.p. injection of 50-170 mg/kg bw $^{14}$C-1,2-dichloroethane to mice, 10-42% was expired unchanged or 12-15% as CO$_2$, depending upon the dose; most of the remainder was excreted in the urine, primarily as chloroacetic acid, S-carboxymethylcysteine and thiodiacetic acid. The metabolism of 1,2-dichloroethane to chloroacetic acid proceeds possibly via chloroacetaldehyde to 2-chloroethanol (Yllner, 1971). Little dechlorination of 1,2-dichloroethane was found to occur in rat and rabbit liver preparations in vitro (Bray et al., 1952; Van Dyke & Wineman, 1971).

Studies in vitro and in isolated perfused rat liver indicate that 1,2-dichloroethane, in the presence of glutathione and rat liver cytosol or glutathione-S-transferases A and C, forms a chemically reactive sulphur-half mustard intermediate. It has been proposed that the active compound is S-chloroethyl glutathione (Rannug & Beije, 1979; Rannug et al., 1978).

The similarity of the toxic effects of ethylene chlorohydrin (2-chloroethanol) and 1,2-dichloroethane (Ambrose, 1950; Hayes et al., 1973; Miller et al., 1970) suggests that poisoning by 1,2-dichloroethane is due at least in part to its metabolic products.
Mutagenicity and other related short-term tests

1,2-Dichloroethane is mutagenic in *Salmonella typhimurium* TA1530, TA1535 and TA100, presumably causing base-pair substitution mutations (Bignami et al., 1977; Brem et al., 1974; McCann et al., 1975; Rannug et al., 1978); the mutagenic effect was enhanced by addition of cytosol and glutathione (Rannug et al., 1978; Rannug & Beije, 1979). It was ineffective in inducing somatic crossing-over and non-disjunction in *Aspergillus nidulans* (Bignami et al., 1977).

Ehrenberg et al. (1974) reported an increase in mutation frequency in barley (*Hordeum vulgare*) when kernels were treated for 24 hrs at 20°C with 30.3 mM 1,2-dichloroethane. It caused no chromosome breaks in *Allium* root tips or in human lymphocytes, nor did it induce lysogeny in *Escherichia coli* K39 (λ) (Kristoffersson, 1974).

1,2-Dichloroethane induced sex-linked recessive lethals in *Drosophila melanogaster* when larvae or adult males were treated; the frequency of these mutations was dose related (Rapoport, 1960). Exposure of virgin *Drosophila melanogaster* females to 1,2-dichloroethane vapours in air (7 mg in a 1.5-litre dessicator for 4 or 8 hours) led to an increase in the frequency of sex-linked recessive lethals; an increase in the frequency of sex-chromosome non-disjunction was seen after the 8-hr treatment (Shakarnis, 1969). In a subsequent study using a radioresistant stock of *Drosophila melanogaster* and treatment for up to 6 hrs with 10 ml of a 0.07% solution of 1,2-dichloroethane in the gas phase, Shakarnis (1970) confirmed the effect of the compound in inducing sex-linked recessive lethals; non-disjunction was not observed, however.

Chloroacetaldehyde, a postulated metabolite of 1,2-dichloroethane, is mutagenic in *Salmonella typhimurium* TA100 (McCann et al., 1975; see IARC, 1979c).

(b) Humans

The toxic effects of 1,2-dichloroethane in humans have been reviewed recently. Deaths due to ingestion and inhalation of the solvent have been attributed to circulatory and respiratory failure (National Institute for Occupational Safety & Health, 1976b).

In many cases of acute poisoning, hyperaemia and haemorrhagic lesions have been observed throughout the body; Martin et al. (1968) attributed these to a reduction in the level of blood clotting factors and to thrombocytopenia.

Repeated exposures to 1,2-dichloroethane in the occupational environment have been associated with anorexia, nausea, abdominal pain, irritation of the mucous membranes, dysfunction of liver and kidney and neurological disorders (Byers, 1943; Delplace et al., 1962; Watrous, 1947).
3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

1,2-Dichloroethane was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced benign and malignant tumours of the lung and malignant lymphomas in animals of both sexes, hepatocellular carcinomas in males and mammary and uterine adenocarcinomas in females. In rats, it produced carcinomas of the forestomach in male animals, benign and malignant mammary tumours in females and haemangiosarcomas in animals of both sexes. It was inadequately tested by intraperitoneal administration in mice.

1,2-Dichloroethane is mutagenic in Salmonella typhimurium, Drosophila melanogaster and Hordeum vulgare. It can form a reactive chloroethyl sulphide intermediate in the presence of rat liver enzymes.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production of 1,2-dichloroethane and its use as a lead scavenging agent in petrol, as a fumigant and as a chemical intermediate suggest that widespread human exposure occurs. This is confirmed by many reports of its occurrence in the general and working environments.

4.3 Evaluation

There is sufficient evidence that 1,2-dichloroethane is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard 1,2-dichloroethane as if it presented a carcinogenic risk to humans.
5. References


Fujii, T. (1977) Direct aqueous injection gas chromatography-mass spectrometry for analysis of organohalides in water at concentrations below the parts per billion level. J. Chromatogr., 139, 297-302


1,2-DICHLOROETHANE


IARC (1979c) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 19, Some Monomers, Plastics and Synthetic Elastomers, and Acrolein, Lyon, p. 396


1,2-DICHLOROETHANE


Shakarnis, V.F. (1969) 1,2-Dichloroethane induced chromosome non-disjunction and recessive sex-linked lethal mutation in Drosophila melanogaster (Russ.). Genetika, 5, 89-95


WHO (1970) Toxicological evaluation of some extraction solvents and certain other substances. WHO/Food/Add/70. 39, pp. 91-93


DICHLOROMETHANE

Two reviews on dichloromethane are available (Berkowitz, 1978; Mercier, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 75-09-2

Chem. Abstr. Name: Dichloromethane

Synonyms: Methane dichloride; methylene bichloride; methylene chloride; methylene dichloride

Trade names: Aerothene MM; Freon 30; Narkotil; Solaesthin; Solmethylene

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{CH}_2\text{Cl}_2 & \quad \text{Mol. wt: 84.9} \\
\end{align*}
\]

1.3 Chemical and physical properties of the pure substance

From Hawley (1977), unless otherwise specified

(a) Description: Colourless liquid

(b) Boiling-point: 40.1°C

(c) Freezing-point: -97°C

(d) Density: \(d^{15}_{4} 1.335\)

(e) Refractive index: \(n^2_D 1.4244\)

(f) Spectroscopy data: \(\lambda_{\text{vap}} < 200\) nm; infra-red, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).
(g) Solubility: Soluble in water (2 g/100 g water at 20°C), phenols, aldehydes, ketones, glacial acetic acid, triethyl phosphate, acetoacetic ester, formamide and cyclohexylamine; miscible in all proportions with commercial chlorinated solvents, diethyl ether and ethanol (Hardie, 1964).

(h) Volatility: Vapour pressure is 400 mm at 24.1°C (Perry & Chilton, 1973).

(i) Stability: Nonflammable and nonexplosive in air; no appreciable decomposition at room temperature when in contact with common metals. Prolonged heating with water at 180°C results in formation of formic acid, methyl chloride, methanol, hydrochloric acid and some carbon monoxide (Hardie, 1964)

(j) Reactivity: Reacts at normal temperatures with aluminium and alloys of potassium and sodium; at elevated temperatures in contact with water, it corrodes iron, some stainless steels, copper, nickel and certain other metals and alloys; readily chlorinated to chloroform and carbon tetrachloride in the presence of chlorination catalysts (Hardie, 1964)

(k) Conversion factor: 1 ppm in air is equivalent to 3.5 mg/m³.

1.4 Technical products and impurities

In the US, standard grade dichloromethane has the following typical specifications: a clear, water-white liquid, free of suspended matter; specific gravity, 25°C/25°C, 1.319–1.323; acidity, 5 mg/kg max; non-volatile residue, 10 mg/kg max; free halogen, none; and a 100% distillation range of 39.5–40.5°C.

Commercial grades of dichloromethane may contain 0.0001–1% of added stabilizers, such as phenol, hydroquinone, para-cresol, resorcinol, thymol, l-naphthol or amines. A representative commercial sample contains not more than the following impurities: water, 200 mg/kg; acid (as HCl), 5 mg/kg; and chloroform, 2500 mg/kg (Hardie, 1964).

In Japan, dichloromethane has a purity of 99–100%.
2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Dichloromethane was first prepared in 1840 by Regnault by chlorinating methyl chloride in sunlight (Hardie, 1964). It is currently produced commercially in the US either by: (1) chlorination of methyl chloride (which is obtained from reaction of methanol and hydrogen chloride) or (2) by direct chlorination of methane. Approximately 65% of that produced in 1976 involved the chlorination of methyl chloride, in which chloroform and carbon tetrachloride are obtained as coproducts.

In Japan, approximately 73% of dichloromethane is produced by chlorination of methane and about 27% by chlorination of methyl chloride.

Commercial production of dichloromethane in the US was first reported in 1934 (US Tariff Commission, 1936). In 1976, 5 US companies reported a total production of 244 million kg (US International Trade Commission, 1977). Imports in that year were 19.1 million kg, with 47.9% from the Federal Republic of Germany, 31.2% from Belgium, 10.6% from Japan, 7.6% from The Netherlands and 2.7% from France (US Department of Commerce, 1977a). Exports were 38.2 million kg, to the following countries (percent of total exports): The Netherlands (33.6), Canada (25.3), Mexico (8.4), Brazil (7.9), Japan (6.1), Republic of South Africa (6.1), Australia (5.4), Venezuela (3.0), Sweden (1.2) and at least 5 other countries (30) (US Department of Commerce, 1977b).

Dichloromethane is believed to be produced in the following European countries (number of producers): Belgium (1), the Federal Republic of Germany (3), France (4), Italy (2), The Netherlands (3), Spain (1), and the UK (1).

It has been produced commercially in Japan since about 1944. In 1976, 4 companies produced an estimated 24.6 million, and 3 million kg were exported.

(b) Use

In 1976, dichloromethane was used in the US as follows: paint removers, 44%; solvents (degreasing), 25%; aerosol propellants, 19%; and other applications, 12%.

Of all organic paint removers, those based on dichloromethane are the most widely used (Downing, 1967). Typical paint-stripping compositions that have dichloromethane as the major component may also contain paraffins, glacial acetic acid, formic acid, alcohols, acetone and a sulphonated detergent (Hardie, 1964).
Dichloromethane is used for degreasing engine parts in the motor transportation, railway and aircraft industries (Gosselin et al., 1976). It is a component of diphase chlorinated solvents, the upper phase of which is water to reduce evaporation of the dichloromethane (Spring, 1967). With other chlorinated solvents, dichloromethane is replacing trichloroethylene for use in metal degreasing because of restrictions concerning photochemically reactive materials and, more recently, concern about the carcinogenicity of trichloroethylene (Anon., 1976).

Aerosol applications for dichloromethane include insecticides, hair sprays, shampoos, paints and others. It has been predicted that use as aerosols, as replacements for fluorocarbons, could become the second most important market for dichloromethane (Anon., 1976).

Miscellaneous applications of dichloromethane include use as a solvent in certain pharmaceutical applications and in the extraction of naturally-occurring heat-sensitive substances, such as edible fats, cocoa, butter, caffeine and the beer flavouring in hops. It is also used as a solvent in the manufacture of photographic film and synthetic fibre (Hardie, 1964), as a component of fire-extinguishing compositions and as an insecticidal fumigant. Virtually all caffeine extraction for the production of decaffeinated coffee in the US is now carried out with dichloromethane instead of trichloroethylene.

No data on its use in Europe were available.

In 1976, it was used in Japan as follows: solvent, 40%; blowing agent for urethane, 20%; paint remover, 18%; and other 22%.

Dichloromethane is registered for use in the US as an insecticide for commodity fumigation of a variety of grains (US Environmental Protection Agency, 1969); and an estimated 45.4 thousand kg dichloromethane were used in 1975 in the US as a commodity and space fumigant. It is exempted from the requirement of a tolerance for residues when used as a fumigant after harvest for barley, corn, oats, popcorn, rice, rye, sorghum and wheat and for the postharvest fumigation of citrus fruits (US Environmental Protection Agency, 1976).

The US Food and Drug Administration (FDA) permits the presence of dichloromethane in the following foods: (1) in spice oleoresins as a residue after spice extraction, at a level no greater than 30 mg/kg; (2) in hops extract, at a level no greater than 2.2%; and (3) in coffee as a residue from its use as a solvent in caffeine extraction, at a level no greater than 10 mg/kg. The FDA also allows its use in adhesives and in the production of polycarbonate resins intended for use in producing, manufacturing, packaging, processing, preparing or holding food (US Food & Drug Administration, 1977).
Permissible levels of dichloromethane in the working environment have been established in various countries. The US Occupational Safety and Health Administration's health standards require that an employee's exposure to dichloromethane at no time exceed 1740 mg/m$^3$ (500 ppm) in any 8-hr work shift of a 40-hr work week, with an acceptable ceiling concentration of 3500 mg/m$^3$ (1000 ppm), and not exceed 7000 mg/m$^3$ (2000 ppm) for more than 5 min in any 2 hrs (US Occupational Safety & Health Administration, 1977). The 8-hr time-weighted average value in The Federal Republic of Germany is 1750 mg/m$^3$ (500 ppm); in the German Democratic Republic and Czechoslovakia, 500 mg/m$^3$ (144 ppm); and in Sweden, 350 mg/m$^3$ (100 ppm). The acceptable ceiling concentration in the USSR is 50 mg/m$^3$ (14 ppm) (Winell, 1975).

The US National Institute for Occupational Safety and Health has recommended that occupational exposure to dichloromethane not exceed 261 mg/m$^3$ (75 ppm), determined as a time-weighted average for up to a 10-hr work day of a 40-hr work week, in the absence of exposure to carbon monoxide above a time-weighted average of 31.5 mg/m$^3$ (9 ppm) for up to a 10-hr work day (National Institute for Occupational Safety & Health, 1976).

2.2 Occurrence

Dichloromethane is formed during the chlorination of water.

(a) Air

Dichloromethane was one of 12 chlorinated hydrocarbons detected in urban air, at levels of 0.035-32.9 µg/m$^3$ (0.01-9.4 ppb) (Okuno et al., 1974); it has been detected at levels of <17.5 ng/m$^3$ (5 ppt) in rural air samples (Grimsrud & Rasmussen, 1975). A level of 121 ng/m$^3$ (35 ppt) was detected in the troposphere (Cox et al., 1976). It has also been detected in air in which cigarette smoke was present (Holzer et al., 1976).

(b) Water

Dichloromethane is formed during the chlorination of water. A survey in the US indicated that 1% of raw-water supplies and 8% of finished-water supplies contained it, with a mean concentration in finished water of <1 µg/l. Nine out of 10 US water supplies surveyed in one study contained dichloromethane; the highest concentration was 1.6 µg/l (Safe Drinking Water Committee, 1977). Dichloromethane was detected in the municipal drinking-water in 2 locations at a level of <5 µg/l, and in bottled water (Dowty et al., 1975; Saunders et al., 1975). In another location, dichloromethane was detected in drinking-water at a level of 0.3 µg/l (Fujii, 1977).

The concentrations of dichloromethane detected at various stages of treatment in a sewage-treatment plant were 8.2 µg/l in the influent before
treatment, 2.9 µg/l in the effluent before chlorination and 3.4 µg/l in the effluent after chlorination (Bellar et al., 1974).

Published reports of the detection of dichloromethane in river and lake water as well as in effluent from paper mills and chemical and latex manufacturing plants at various US locations have been tabulated (Shackelford & Keith, 1976).

(c) Humans

Dichloromethane was detected in the expired air of 5/8 male human subjects at levels of 0.12-340 µg/hr (Conkle et al., 1975).

(d) Occupational exposure

On the basis of health hazard evaluations of various US companies conducted in 1973 and 1974, dichloromethane exposure concentrations in a variety of jobs were as follows (in ppm): servicing diesel engines, 11 ppm; spray-painting booths, 1-74 ppm; chemical plant, 0-5520 ppm, 8-hr time-weighted average, 875 ppm; plastic tank construction, a few ppm; ski manufacture, 0-36 ppm; cleaning foam heads, 3-29 ppm; cleaning nozzles in plastics manufacture, 5-37 ppm (National Institute for Occupational Safety & Health, 1976).

In a 1973 study of occupational exposure to propellants used in hair spray in a hairdresser's in Wilmington, DE, it was determined that beauticians were exposed to a daily mean background concentration of <3.5-7 mg/m³ (≤1-2 ppm) dichloromethane. Air samples taken 1-2 min after a hairdresser had completed spraying a hair-do contained 3.5-455 mg/m³ (1-130 ppm) dichloromethane (Hoffman, 1973).

(e) Other

Dichloromethane was detected in 15/17 spice oleoresins from one manufacturer and in 3 from another as follows (mg/kg): allspice (68), black pepper (23), capsicum (31 and 4), cassia (83), celery (33), cinnamon (24), coriander (24), ginger (10 and 7), marjoram (48), nutmeg (63), paprika (14), rosemary (41), sage (29), thyme (36) and turmeric (59 and 1) (Page & Kennedy, 1975).

2.3 Analysis

The collection of dichloromethane from air, using silica gel, activated charcoal, porous polymer beads and liquids, and its analysis, using colorimetry, gas chromatography, infra-red spectrometry and photo-detector analysis, have been reviewed (National Institute for Occupational Safety & Health, 1976).
Methods used for the analysis of dichloromethane in environmental samples are listed in Table 1.

Gas chromatography-mass spectrometric methods have been proposed to determine dichloromethane in air and water (Coleman et al., 1976; Grimsrud & Rasmussen, 1975). Other methods include the use of gas chromatography-thermal conductivity detection (Naumova & Belova, 1976), colorimetry (Tyras & Blochowicz, 1974) and photoionization-mass spectrometry (Driscoll & Warneck, 1973).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Intraperitoneal administration

Mouse: Groups of 20 male A/St mice, 6-8 weeks old, received reagent-grade dichloromethane in tricaprylin at doses of 160, 400 and 800 mg/kg bw (found in preliminary toxicity tests to be the maximum tolerated dose, i.e., that tolerated by all of 5 mice that received 6 i.p. injections over a 2-week period). Each dose was injected intraperitoneally thrice weekly for a total of 16-17 injections (total doses, 2720, 6800 and 12,800 mg/kg bw in the respective groups). After 24 weeks, 18, 5 and 12 animals in the three groups were still alive; these were killed and their lungs examined for tumours and compared with 15 survivors out of 20 vehicle-treated controls. In the treated mice, 0.9, 0.8 and 0.5 lung tumours per mouse were observed, which were not significantly different from the 0.27 observed in controls injected with tricaprylin (Theiss et al., 1977) [The Working Group noted the poor survival of treated animals and the limitations of negative results obtained with this test system; see also General Remarks on Substances Considered, p. 34].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The LD$_{50}$ by i.p. injection in mice is 2000 mg/kg bw (Klaassen & Plaa, 1966); the LC$_{50}$ by inhalation in mice is 56 g/m$^3$ (16,200 ppm) (Svirbely et al., 1947).  

$^{1}$The Working Group was aware of studies in progress to assess the carcinogenicity of dichloromethane in rats and hamsters by inhalation, and in mice and rats by oral administration (IARC, 1978a).
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair-spray aerosol</td>
<td>Analyse directly</td>
<td>GC/TCD</td>
<td></td>
<td>Schubert &amp; Ketel (1972)</td>
</tr>
<tr>
<td><strong>Air</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td>Trap on charcoal, extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Working range, 1700-7100 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977)</td>
</tr>
<tr>
<td></td>
<td>Inject sample directly, using diglycerol as GC stationary phase</td>
<td>GC/MS</td>
<td>0.7 μg/m³ (0.2 ppb)</td>
<td>Fujii (1977)</td>
</tr>
<tr>
<td></td>
<td>Inject directly</td>
<td>GC/FID</td>
<td>10 mg/m³</td>
<td>Kuptsova et al. (1976)</td>
</tr>
<tr>
<td>Standard mixtures in air</td>
<td>Adsorb on Chromosorb 101, desorb by heating, retrap in line on GC column</td>
<td>GC/ECD</td>
<td>14 μg/m³-35 mg/m³ (0.4 ppb-40 ppm; v/v)</td>
<td>Parkes et al. (1976)</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industrial discharge to atmosphere</td>
<td>Trap in evacuated glass pipette containing glacial acetic acid, react with alkali and pyridine</td>
<td>Spectrophotometry 530 nm</td>
<td></td>
<td>Prikhod’ko et al. (1974)</td>
</tr>
<tr>
<td><strong>Chlorinated drinking-water</strong></td>
<td>Transfer volatile to gaseous phase by bubbling nitrogen through sample, concentrate</td>
<td>GC/FID</td>
<td>0.1 μg/l</td>
<td>Bellar et al. (1974)</td>
</tr>
<tr>
<td></td>
<td>Gas strip volatile, trap on Tenax-GC, desorb by heating, retrap in line on GC column</td>
<td>GC/FID</td>
<td>ppb range</td>
<td>Kuo et al. (1977)</td>
</tr>
<tr>
<td></td>
<td>Cool to 40°C, extract (pentane)</td>
<td>GC/FID</td>
<td>1-10 mg/l</td>
<td>Dietz &amp; Traud (1973)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
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<tr>
<td>Chlorinated drinking-water</td>
<td>Sparge, trap in line on GC column</td>
<td>GC/Hall</td>
<td>0.1 µg/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td>Soil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sediments</td>
<td>Mix with water, cool to 4°C, extract (pentane)</td>
<td>GC/FID</td>
<td></td>
<td>Dietz &amp; Traud (1973)</td>
</tr>
<tr>
<td>Food</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spice oleoresins</td>
<td>Vacuum distill (toluene), wash (water)</td>
<td>GC/ECD</td>
<td>1 mg/kg</td>
<td>Page &amp; Kennedy (1975)</td>
</tr>
<tr>
<td>Biological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Equilibrate with air in closed vessel, inject directly</td>
<td>GC/FID</td>
<td></td>
<td>Tremel-Cabic et al. (1974)</td>
</tr>
<tr>
<td>Blood</td>
<td>Weigh capsule containing sample, break in line, vaporize, flush onto column with carrier gas</td>
<td>GC/FID</td>
<td>1 mg/kg</td>
<td>Laham &amp; Potvin (1976)</td>
</tr>
</tbody>
</table>

Abbreviations: GC/TCD - gas chromatography/thermal conductivity detection; FID - flame-ionization detection; MS - mass spectrometry; ECD - electron capture detection; Hall - Hall conductivity detection
Dichloromethane affects mainly the central nervous system (National Institute for Occupational Safety & Health, 1976); hepatotoxic effects were observed in mice only with single lethal doses (Gehring, 1968). No renal dysfunction was detected in mice; slight calcification of the tubules was seen in dogs (Klaassen & Plaa, 1966, 1967). In mice, continuous inhalation of 17.5 g/m³ (5000 ppm) caused swelling of the rough endoplasmic reticulum, transient severe fatty changes in the liver and necrosis in isolated hepatocytes (Weinstein et al., 1972).

**Embryotoxicity and teratogenicity**

Groups of rats and mice were exposed by inhalation for 7 hrs daily on days 6-15 of gestation to 4.4 g/m³ in air (1250 ppm) dichloromethane; no effects were observed on the average number of implantation sites per litter, litter size, incidence of foetal resorptions, foetal sex ratios or foetal body measurements. No treatment-related increase in the incidence of skeletal or visceral malformations was observed (Schwetz et al., 1975).

**Absorption, distribution, excretion and metabolism**

The highest levels of radioactivity in rats following exposure by inhalation to 1935 mg/m³ ¹⁴C-dichloromethane were found in the fat, liver, kidney and adrenals. Two hours after exposure, the concentration in fat had decreased by more than 90% and the concentration in liver by 25% (Carlsson & Hultengren, 1975).

*In vivo* and *in vitro* studies indicate that dichloromethane is metabolized to CO (Carlsson & Hultengren, 1975; Fodor et al., 1973; Kubic et al., 1974) by microsomal mono-oxygenase(s) (Hogan et al., 1976).

**Mutagenicity and other related short-term tests**

Dichloromethane was mutagenic in *Salmonella typhimurium* TA100 and TA98, both in the presence and absence of a liver microsomal activation system (Jongen et al., 1978).

(b) **Humans**

Fatalities have been associated with acute or prolonged exposure to dichloromethane (Moskowitz & Shapiro, 1952; Stewart & Hake, 1976). It acts primarily on the central nervous system (National Institute for Occupational Safety & Health, 1976), causing narcosis (Irish, 1963). Long-term occupational exposure to dichloromethane causes damage to the liver and central nervous system (Hanke et al., 1974; Weiss, 1967).

After a 2-hr exposure, about 50% of inhaled dichloromethane is taken up into the bloodstream (Astrand, 1975); it is also absorbed
through the skin (Steward & Dodd, 1964). It is eliminated mainly in expired air (Riley et al., 1966).

Inhalation of 0.18-3.5 g/m$^3$ (500-1000 ppm) in air for 1-2 hrs resulted in the formation of significant amounts of carboxyhaemoglobin (Stewart & Hake, 1976; Stewart et al., 1972).

3.3 Case reports and epidemiological studies

No case reports or adequate epidemiological studies were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Dichloromethane was tested in only one experiment in male mice by intraperitoneal injection. This experiment was considered to be inadequate, although the results suggested an increased incidence of lung tumours.

Dichloromethane is mutagenic in Salmonella typhimurium.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and use of dichloromethane mainly as a solvent over the past several decades and its recovery from air and drinking-water indicate that widespread human exposure occurs.

4.3 Evaluation

The available data do not permit an evaluation of the carcinogenicity of dichloromethane to be made.

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1The Working Group was aware of a retrospective cohort study in progress on workers employed in a fibre production process using dichloromethane as a solvent (IARC, 1978b).
5. References


Dietz, F. & Traud, J. (1973) Gas chromatographic determination of low-molecular-weight chlorohydrocarbons in water samples and sediments (Germ.). Vom Wasser, 41, 137-155


Fujii, T. (1977) Direct aqueous injection gas chromatography-mass spectrometry for analysis of organohalides in water at concentrations below the parts per billion level. J. Chromatogr., 139, 297-302

Gehring, P.J. (1968) Hepatotoxic potency of various chlorinated hydrocarbon vapours relative to their narcotic and lethal potencies in mice. Toxicol. appl. Pharmacol., 13, 287-298


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Safe Drinking Water Committee (1977) Drinking Water and Health, Washington DC, National Academy of Sciences, p. 743


DICHLOROMETHANE


HEXACHLOROETHANE

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 67-72-1

Chem. Abstr. Name: Hexachloroethane

Synonyms: Carbon hexachloride; hexachloroethane; 1,1,1,2,2,2-hexachloroethane; hexachloroethylene; perchloroethane

Trade names: Avlothane; Distokal; Distopan; Distopin; Egitol; Falkitol; Fasciolin; Mottenhexe; Phenohep

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{C} & \quad \text{C} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

\[\text{C}_2\text{Cl}_6\quad \text{Mol. wt: 236.7}\]

1.3 Chemical and physical properties of the pure substance

From Weast (1976), unless otherwise specified

(a) **Description:** Colourless crystals with a camphor-like odour (Hawley, 1977)

(b) **Boiling-point:** 185°C (sublimes) (Hawley, 1977)

(c) **Melting-point:** 186.8-187.4°C (sealed tube)

(d) **Spectroscopy data:** Infra-red, Raman and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(e) **Solubility:** Insoluble in water, soluble in ethanol, diethyl ether, benzene, chloroform and oils (Windholz, 1976)
(f) **Volatile**: Vapour pressure is 1 mm at 32.7°C (Perry & Chilton, 1973).

(g) **Stability**: Nonflammable (Hardie, 1964); at temperatures > 185°C, may give carbon tetrachloride and tetrachloroethylene (van Oss, 1972)

(h) **Reactivity**: Generally inert chemically (Hardie, 1964)

1.4 **Technical products and impurities**

The specifications for technical hexachloroethane produced in Japan are as follows: melting-point, 184-187°C; purity, 98.5% min; water content, 0.03% max; ash, 0.05% max; acid (as HCl), 0.01% max.

2. **Production, Use, Occurrence and Analysis**

2.1 **Production and use**

(a) **Production**

Hexachloroethane was prepared by heating carbon tetrachloride with copper powder to 120°C (Prager et al., 1918). The commercial process of manufacture is the chlorination of tetrachloroethylene in the presence of ferric chloride at 100-140°C (Hardie, 1964).

Hexachloroethane was first produced commercially in the US in 1921 (US Tariff Commission, 1922); it was last reported in the US in 1967, when one company reported production of an undisclosed amount (see preamble, p. 16) (US Tariff Commission, 1969). US imports of hexachloroethane in 1976 were 730 thousand kg, with 380 thousand kg from the UK and 350 thousand kg from France (US Department of Commerce, 1977).

Annual production by one company in Spain is estimated to be 700 thousand kg, 500 thousand kg of which are exported.

Hexachloroethane was first produced commercially in Japan in 1955. Annual production of 300–500 thousand kg by one company continued until 1975, when it was discontinued. Japanese requirements for the chemical, which have been relatively constant in recent years, have since been filled by imports, which amounted to about 300 thousand kg in 1976. Formulations containing the chemical are also believed to have been imported.
Hexachloroethane is used in the US in the following applications: (1) as a constituent of candles and grenades for the generation of 'smoke' or 'fog'; (2) a degassing agent for magnesium; (3) a component of extreme pressure lubricants; (4) an ignition suppressant in combustible liquids; (5) a moth repellent; (6) a plasticizer for cellulose esters; (7) an anthelminthic in veterinary medicine; (8) an accelerator in rubber; (9) a retardant in fermentation processes; (10) a component of submarine paints; (11) an additive to fire-extinguishing fluids; and (12) as a constituent of various fungicidal and insecticidal formulations. With the possible exception of use for smoke generation, only limited quantities of hexachloroethane are used in these applications (Hardie, 1964).

Smoke is produced by igniting a mixture of hexachloroethane and zinc dust; fairly volatile zinc chloride is evolved which then condenses in the form of smoke (Van Oss, 1972).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to hexachloroethane not exceed an 8-hr time-weighted average of 10 mg/m³ (1 ppm) in the working atmosphere in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977).

No data on its use in Europe were available.

The major use of hexachloroethane in Japan is for degassing in the aluminium casting industry. Small amounts are also used for smoke generation.

2.2 Occurrence

Hexachloroethane is not known to occur as a natural product.

(a) Water

Hexachloroethane has been found in 1 river-water sample, 8 samples of finished drinking-water, and in the effluent water from 1 chemical plant and 1 chlorinated sewage treatment plant in the US (Shackelford & Keith, 1976). It has been detected in river-water and tap-water, at a level of 4.4 µg/l, and in the effluent from a US chemical plant, at a level of 8.4 µg/l (Eurocop-Cost, 1976). It was detected in only one sample of surface waters collected from 204 sites near heavily industrialized areas (Ewing et al., 1977).

Hexachloroethane has also been detected in effluent waters from kraft paper mills, at levels of < 1 µg/l (Keith, 1976) and in drinking-
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>Adsorb on charcoal, extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Useful range, 5-25 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977b)</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea and fresh-water</td>
<td>Extract (pentane), dry, inject aliquot</td>
<td>GC/ECD</td>
<td>Useful range, 0.01-10 µg/l</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Waste-water</td>
<td>Separate neutral and acidic compounds, extract alkaline solution (chloroform)</td>
<td>GC/FID</td>
<td></td>
<td>Keith (1976)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Extract (tetralin or chloroform)</td>
<td>GC/FID</td>
<td>0.04 µg/l</td>
<td>Keith et al. (1976)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC/MS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap-water</td>
<td>Adjust pH and dechlorinate, drain on XAD2 macroreticular resin, elute with ether, collect and dry eluant</td>
<td>GC/MS</td>
<td></td>
<td>Suffet et al. (1976)</td>
</tr>
<tr>
<td>Surface-water</td>
<td>Sample at 60°C, strip (nitrogen gas), GC/MS trap on Tenax GC, desorb by heating, retap in line on GC column</td>
<td>GC/MS</td>
<td>1 µg/l</td>
<td>Ewing et al. (1977)</td>
</tr>
<tr>
<td>Water</td>
<td>Standard solutions in water only</td>
<td>UV at 240 nm</td>
<td>Useful range, 5-25 mg/l</td>
<td>Simonov et al. (1971)</td>
</tr>
</tbody>
</table>

Abbreviations: GC/ECD - gas chromatography/electron capture detection; FID - flame-ionization detection; MS - mass spectrometry; UV - ultra-violet spectrometry
A 1974 National Occupational Hazard Survey indicated that workers primarily exposed to hexachloroethane are those in paperboard mills (National Institute for Occupational Safety & Health, 1977a).

2.3 Analysis

Methods used for the analysis of hexachloroethane in environmental samples are listed in Table 1.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female 5-week-old B6C3F1 mice were administered a solution of technical-grade hexachloroethane (purity 98%) in corn oil by gavage on 5 consecutive days a week for 78 weeks. High- and low-dose animals received 1000 and 500 mg/kg bw/day; after 8 weeks, these doses were increased to 1200 and 600 mg/kg bw/day, respectively, and these were maintained for the remaining 70 weeks. The time-weighted average doses were 1179 and 590 mg/kg bw/day, respectively. Animals were killed and necropsied 13 weeks after the last dose. Groups of 20 male and 20 female mice that served as vehicle controls were given corn oil alone for 78 weeks and killed after 90 weeks; another group of 20 male and 20 female untreated control mice were also killed after 90 weeks. In males, survival was unexpectedly low in control and low-dose animals: only 5/20 of the vehicle controls, 1/20 of the untreated controls and 7/50 of the low-dose mice survived until the end of the test, compared with 29/50 of the high-dose mice. In females, 34/50 high-dose, 40/50 low-dose, 16/20 vehicle controls and 17/20 untreated controls survived until the end of the test. The numbers of tumour-bearing animals/animals examined histopathologically were: in males, 3/17 untreated controls, 4/20 vehicle controls, 17/50 low-dose and 34/49 high-dose animals; in females, 5/18 untreated controls, 8/20 vehicle controls, 32/50 low-dose and 26/49 high-dose animals. A significant increase was observed in the incidence of hepatocellular carcinomas: in males examined histologically, 1/18 untreated controls, 3/20 vehicle controls (3/19 lived for more than 41 weeks), 15/50 low-dose animals (15/46 lived for more than 41 weeks) and 31/49 high-dose animals (31/48 lived for more than 41 weeks). In females examined histologically, the respective incidences of hepatocellular
carcinomas were: 0/18 untreated controls, 2/20 vehicle controls, 20/50 low-dose and 15/49 high-dose animals (National Cancer Institute, 1978).

Rat: Groups of 50 male and 50 female 7-week-old Osborne-Mendel rats were administered technical-grade hexachloroethane in corn oil by gavage on 5 consecutive days a week. High- and low-dose animals received 500 and 250 mg/kg bw/day for 22 weeks, followed by 11 cycles of 4 weeks of treatment and 1 week treatment-free. The animals were then maintained for a further 34 weeks on a standard diet without treatment. Time-weighted average doses were 423 and 212 mg/kg bw/day, respectively. Groups of 20 animals of each sex used as vehicle controls were administered corn oil alone; groups of 20 males and 20 females served as untreated controls. In males, 38% of the high-dose and 48% of the low-dose animals lived for more than 90 weeks; and 16% of high-dose and 20% of low-dose animals survived until the end of test, compared with 48% of high-dose and 54% of low-dose females. The numbers of animals with tumours/animals examined histopathologically were: in males, 10/20 untreated controls, 9/20 vehicle controls, 17/49 low-dose and 11/50 high-dose animals; in females, 15/20 untreated controls, 14/20 vehicle controls, 33/50 low-dose and 20/49 high-dose animals. Kidney tumours were observed in 6 males and 1 female given the low dose and in 3 females given the high dose, compared with 1 in male vehicle controls and 2 in untreated female controls (National Cancer Institute, 1978).

3.2 Other relevant biological data

(a) Experimental systems

The i.p. LD50 of hexachloroethane in mice is 4.5 mg/kg bw; maximal lethality was observed after 4 days (Baganz et al., 1961).

Hexachloroethane depresses the central nervous system (Bywater, 1955) and causes hepatic dysfunction and damage (Fowler, 1969). A single oral dose of 2.5 g/kg bw reduces hepatic microsomal mono-oxygenase activities in rats by 50% (Vainio et al., 1976).

Orally administered hexachloroethane is absorbed and appears rapidly in the systemic circulation. It is distributed widely throughout the body, the highest concentrations being found in fat, the lowest in muscle (Fowler, 1969).

When 500 mg/kg 14C-hexachloroethane were fed to rabbits, only 5% of the radioactivity was excreted in the urine after 3 days, as di- and trichloroethanol, mono-, di- and trichloroacetic acid and oxalic acid. Between 14 and 24% of the dose was expired unchanged or as CO2, tetrachloroethylene and 1,1,2,2-tetrachloroethane; the rest was retained in the carcass (Jondorf et al., 1957). In sheep, a small portion of the dose was excreted in the bile (Fowler, 1969). Dechlorination
occurs in homogenates of rabbit liver (Bray *et al*., 1952). Formation of pentachloroethane and tetrachloroethylene was observed in sheep and in slices of sheep liver (Fowler, 1969).

No data on the embryotoxicity, teratogenicity or mutagenicity of hexachloroethane were available.

(b) Humans

No data were available to the Working Group.

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Hexachloroethane was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced malignant liver tumours in males and females. In rats, no statistically significant excess of tumours was observed; however, a few renal tumours, rarely seen in untreated animals, were found.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The production and many uses of hexachloroethane for over 50 years, and its occurrence in water and air, indicate that human exposure occurs.

4.3 Evaluation

There is limited evidence that hexachloroethane is carcinogenic in experimental animals.
5. References

Baganz, H., Perkow, W., Lim, G.T. & Meyer, F. (1961) Studies on the toxicity of alkylated and chlorinated ethanes and ethenes (Germ.). Arzneimittel-Forsch., 11, 902-905


Bureau International Technique des Solvants Chlorés (1976) Standardization of methods for the determination of traces of some volative chlorinated aliphatic hydrocarbons in air and water by gas chromatography. Anal. chem. acta, 82, 1-17


1,1,2,2-TETRACHLOROETHANE

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: 1,1,2,2-Tetrachloroethane

Synonyms: Acetylene tetrachloride; dichloro-2,2-dichloroethane; tetrachloroethane; sym-tetrachloroethane

Trade names: Acetosal; Bonoform; Cellon; Westron

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{H} & \quad \text{C} \quad \text{C} \quad \text{H} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[\text{C}_2\text{H}_2\text{Cl}_4\quad \text{Mol. wt: 167.9}\]

1.3 Chemical and physical properties of the pure substance

From National Institute for Occupational Safety & Health (1976), unless otherwise specified

(a) Description: Colourless, corrosive liquid with a chloroform-like odour (Hawley, 1977)

(b) Boiling-point: 146.3°C

(c) Melting-point: -36°C

(d) Density: \(d^2_{20} 1.596\)

(e) Spectroscopy data: Infra-red, Raman, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(f) Refractive index: \(n^2_D 1.4918\) (Hawley, 1977)
(g) **Solubility**: Sparingly soluble in water (0.29 g/100 ml at 25°C); soluble in methanol, ethanol, benzene, diethyl ether, petroleum ether, carbon tetrachloride, chloroform, carbon disulphide, dimethylformamide and oils (Windholz, 1976)

(h) **Vapour density**: Vapour pressure is 5 mm at 21°C.

(i) **Vapour density**: 5.79 (air = 1)

(j) **Stability**: Nonflammable (Hawley, 1977). In the absence of air, moisture and light, it is stable, even at high temperatures. When exposed to air, it degrades slowly to trichloroethylene and traces of phosgene (Hardie, 1964).

(k) **Reactivity**: Unaffected by strong acids at ordinary and moderate temperatures, but converted to glyoxal sulphate by fuming sulphuric acid. In weak alkali, trichloroethylene is produced, and in strong alkali, explosive dichloroacetylene is formed. Metals, in the presence of steam, convert it to 1,2-dichloroethylene (Hardie, 1964).

(l) **Conversion factor**: 1 ppm in air is equivalent to 6.87 mg/m³.

1.4 Technical products and impurities

No data were available to the Working Group.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

1,1,2,2-Tetrachloroethane was first prepared in 1869 by Bethelot and Jungfleisch (Hardie, 1964) by the reaction of acetylene with excess antimony pentachloride (Frager et al., 1918). It is produced commercially by the reaction of acetylene with chlorine. Other patented processes involve the chlorination of 1,2-dichloroethylene and the two-stage chlorination of 1,2-dichloroethane (Hardie, 1964).

Commercial production of 1,1,2,2-tetrachloroethane in the US was first reported in 1921 (US Tariff Commission, 1922). For many years, large quantities of this chemical were produced and consumed captively in
the production of trichloroethylene, but separate production data were never reported; however, an estimated 222 million kg 1,1,2,2-tetrachloroethane were produced in the US in 1967 for this purpose. This figure is believed to have decreased to about 17 million kg by 1974, and in 1976, only one US company reported the production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977).

No data on its production in Europe were available. It is not produced commercially in Japan. Two companies in Canada and one in Argentina produce 1,1,2,2-tetrachloroethane as an intermediate in the manufacture of trichloroethylene.

(b) Use

The principal use for 1,1,2,2-tetrachloroethane is as an intermediate in the production of trichloroethylene from acetylene. Other relatively minor uses are as an insecticide and as a solvent (Hardie, 1964).

In 1967, an estimated 85% (189 million kg) of the total 222 million kg trichloroethylene produced in the US was made via 1,1,2,2-tetrachloroethane as an intermediate. By 1974, however, the amount had decreased to about 8% (17 million kg) of the total 217 million kg produced.

1,1,2,2-Tetrachloroethane is registered by the US Environmental Protection Agency as a mothproofing agent for textiles. Its use as a fumigant for control of white fly in greenhouses (Hardie, 1964) and as a grain fumigant (van Oss, 1972) has been reported, but these uses are not currently registered in the US.

Miscellaneous uses, based on its solvent properties, include extraction of ruthenium compounds from aqueous solutions and use as a reaction solvent for chlorination reactions (Hardie, 1964).

No data on its use in Europe and Japan were available.

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to 1,1,2,2-tetrachloroethane not exceed an 8-hr time-weighted average of 35 mg/m³ (approx. 5 ppm) in the working atmosphere during any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977). The corresponding standard in the Federal Republic of Germany is 7 mg/m³ (1 ppm) and in the German Democratic Republic, 10 mg/m³ (1.5 ppm); the acceptable ceiling concentration in the USSR is 5 mg/m³ (0.7 ppm) (Winell, 1975).

In early 1977, the US National Institute for Occupational Safety and Health recommended that occupational exposure to 1,1,2,2-tetrachloro-
ethane be controlled so that no employee is exposed to the chemical at a concentration greater than 6.87 mg/m³ (1 ppm) of air by volume, determined as a time-weighted average concentration in the workplace air, for up to a 10-hr work day in a 40-hr work week (National Institute for Occupational Safety & Health, 1977a).

2.2 Occurrence

1,1,2,2-Tetrachloroethane is not known to occur as a natural product.

(a) Air

Various chlorinated hydrocarbons, including 1,1,2,2-tetrachloroethane, have been detected in urban atmospheres in Japan, at levels of 0.07-64 μg/m³ (0.01-9.4 ppb) (Okuno et al., 1974).

(b) Water

1,1,2,2-Tetrachloroethane has been found in 3 samples of finished drinking-water and in samples of effluent from 3 chemical plants and one sewage treatment plant in the US (Shackelford & Keith, 1976). It has been detected in tap-water, at a level of 0.11 μg/l, and in effluent from a chemical production plant, at a level of 2.2 mg/l. An unspecified isomer of tetrachloroethane has been determined in tap-water at a level of 0.01 μg/l (Eurocop-Cost, 1976).

(c) Food

Tetrachloroethane (unspecified isomer) has been detected in the volatile flavour components of boiled beef (MacLeod & Coppock, 1976).

(d) Occupational exposure

Occupational exposure to 1,1,2,2-tetrachloroethane in the US, Japan, India, Italy and Czechoslovakia has been reviewed (National Institute for Occupational Safety & Health, 1976).

A 1974 National Occupational Hazard Survey estimated that workers primarily exposed to 1,1,2,2-tetrachloroethane are those in the toiletry preparations, industrial controls and electric service industries (National Institute for Occupational Safety & Health, 1977b).

(e) Other

1,1,2,2-Tetrachloroethane has been detected in vinyl chloride waste products dumped into the North Sea (Jensen et al., 1975), and an unspecified isomer has been detected in commercial solvent cleaners used in the electronics industry (Lin et al., 1975).
2.3 Analysis

Sampling and analytical methods to determine 1,1,2,2-tetrachloroethane in the environment have been reviewed (National Institute for Occupational Safety & Health, 1976). Methods used for the analysis of 1,1,2,2-tetrachloroethane in environmental samples are listed in Table 1.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 50 male and 50 female 5-week-old B6C3F1 hybrid mice were administered technical-grade 1,1,2,2-tetrachloroethane in corn oil by gavage on 5 days per week. Initially, high-dose animals received 200 mg/kg bw/day, and low-dose animals received 100 mg/kg bw/day; however, after 18 weeks these doses were increased to 300 and 150 mg/kg bw/day, respectively. Test animals were maintained at these levels for 3 weeks, followed by 5 weeks at 400 and 200 mg/kg bw/day and 52 weeks at 300 and 150 mg/kg bw/day. The measured, time-weighted average doses were 142 (low-dose) and 284 (high-dose) mg/kg bw/day. Animals were killed and necropsied 12 weeks after the last dose. Groups of 20 male and 20 female mice that served as matched controls were given corn oil alone for 78 weeks and killed after 91 weeks; another group of 20 male and 20 female control mice were fed the standard diet for 90 weeks. By 90 weeks, only 1 male that received the high dose was still alive, whereas 34% of females lived to that time. Histopathology was performed on all organ systems in 98% or more of animals entered into the experiment. In males, hepatocellular carcinomas occurred in 2/19 untreated controls, in 1/18 vehicle-treated controls, in 13/50 low-dose animals and in 44/49 high-dose animals; in females, the respective incidences were 0/19, 0/20, 30/48 and 43/47 (National Cancer Institute, 1978).

Rat: Groups of 50 male and 50 female 7-week-old Osborne-Mendel rats were administered technical-grade 1,1,2,2-tetrachloroethane in corn oil by gavage on 5 days per week. High-dose animals received 100 mg/kg bw/day; in males, this was increased after 14 weeks to 130 mg/kg bw/day for 18 weeks followed by 9 cycles of 4 weeks at this dose and 1 week treatment-free for 45 weeks (total, 78 weeks); in females, the dose was reduced after 25 weeks to 80 mg/kg bw/day for 7 weeks followed by the cyclic treatment at this dose level for 45 weeks. Low-dose males received 50 mg/kg bw/day for 14 weeks and 65 mg/kg bw for 64 weeks; females received 50 mg/kg bw/day for 25 weeks and 40 mg/kg bw/day for 53 weeks. All groups were then maintained for a further 32 weeks on a
**TABLE 1. METHODS FOR THE ANALYSIS OF 1,1,2,2-TETRACHLOROETHANE**

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Air</strong></td>
<td>Trap on charcoal, extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Useful range, 16-70 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977c)</td>
</tr>
<tr>
<td><strong>Ambient</strong></td>
<td>Trap in Brecheafl flask fitted with rubber septum, sample with gas syringe</td>
<td>GC/ECD</td>
<td></td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td>Cool in water, extract (pentane)</td>
<td>GC/FID</td>
<td>0.01-0.1 mg/l</td>
<td>Dietz &amp; Traud (1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC/ECD</td>
<td>0.01-0.1 mg/l</td>
<td></td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Inject directly</td>
<td>GC/ECD</td>
<td>7 μg/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Adjust pH, dechlorinate, adsorb on ionic exchangers, elute ether, or liquid-liquid extraction, or headspace sampling</td>
<td>GC/MS</td>
<td></td>
<td>Suffet et al. (1976)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Extract (pentane), dry</td>
<td>GC/ECD</td>
<td>0.035 μg/l</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td><strong>Sediments</strong></td>
<td>Cool sample at 4°C, mix with water, extract (pentane)</td>
<td>GC/FID</td>
<td>0.01-0.1 mg/l</td>
<td>Dietz &amp; Traud (1973)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC/ECD</td>
<td>0.01-0.1 μg/l</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** GC/FID - gas chromatography/flame-ionization detection; ECD - electron capture detection; NS - mass spectrometry
standard diet without treatment. Time-weighted average doses were 62 mg/kg bw/day and 108 mg/kg bw/day in males and 43 and 76 mg/kg bw/day in females. Groups of 20 animals of each sex used as matched controls were administered corn oil alone; groups of 20 males and 20 females served as untreated controls. Weight gain was consistently lower in high-dose groups than in low-dose and control groups; and 50% of high-dose males, 40% of high-dose females, 50% of low-dose males and 58% of low-dose females lived for more than 105 weeks. Histopathology of all organ systems was performed on 98% or more of the animals entered into the study. The incidences of tumours in treated and vehicle control rats were not significantly different for any tumour type; however, 2 of 49 males treated with the high dose developed hepatocellular carcinomas and another had a neoplastic nodule of the liver (time of appearance unspecified), compared with 0/20 vehicle controls (National Cancer Institute, 1978).

(b) Intraperitoneal administration

Mouse: Groups of 20 male A/St mice, 6-8 weeks old, were given thrice weekly i.p. injections of 1,1,2,2-tetrachloroethane in tricaprylin at doses of 80 mg/kg bw (5 injections), 200 mg/kg bw (18 injections) or 400 mg/kg bw (16 injections). All survivors (10, 15 and 5 at the 3 doses, respectively) were killed 24 weeks after the first injection. The average numbers of lung tumours per mouse were 0.3, 0.5 and 1.0, which were not significantly different from the 0.27 observed in tricaprylin-injected controls (Theiss et al., 1977) [The Working Group noted the poor survival of treated animals and the limitations of a negative result obtained with this test system; see also General Remarks on Substances Considered, p. 34].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The oral LD$_{50}$ of 1,1,2,2-tetrachloroethane in rats is 250 mg/kg bw (Gohlke et al., 1977); the i.p. LD$_{50}$ in mice is 820 mg/kg bw (Takeuchi, 1966).

In dogs and mice, the compound causes central nervous system depression and is highly hepatotoxic (Bolman & Mann, 1931; Plaa et al., 1958; Tomokuni, 1969). Marked changes in lipid and adenosine triphosphate levels were observed in the livers of mice after 3 hrs' exposure by inhalation to 41 mg/m$^3$ (600 ppm) 1,1,2,2-tetrachloroethane in air; the changes were similar to those caused by carbon tetrachloride (Tomokuni, 1969). A single oral dose of 437 mg/kg bw to rats reduced hepatic benzo(a)pyrene-hydroxylase and para-nitroanisole-O-demethylase levels by 50% after 24 hrs; uridine 5'-diphosphate-glucuronyltransferase
activity was reduced to a lesser extent (Vainio et al., 1976).

**Embryotoxicity and teratogenicity**

Treatment of AB-Jena and DBA mice with 300–400 mg/kg bw/day tetrachloroethane during organogenesis produced embryotoxic effects and a low incidence of malformations (encephaly, cleft palate, anophthalmia, fused ribs and vertebrae). The effects were related to dose and period of treatment (Schmidt, 1976).

**Absorption, distribution, excretion and metabolism**

$^{14}$C-1,1,2,2-Tetrachloroethane injected intraperitoneally to mice is metabolized rapidly: less than 4% was expired unchanged, half of the dose was expired as CO$_2$ and minute amounts as tri- and tetrachloroethylene. About 30% was excreted in the urine, and 16% remained in the body. The urine contained di- and trichloroacetic acid, trichloroethanol, oxalic acid and small amounts of glyoxylic acid and urea. About 50% of the radioactivity in the urine was unaccounted for. The author (Yllner, 1971) concluded that 1,1,2,2-tetrachloroethane is metabolized as follows:

```
CHCl$_2$CHCl$_2$  < 5%  > 57%
    /   \
   /     \
CCL$_2$:CHCl  < 0.5%  CCl$_2$:CCl$_2$
       /         /
CCL$_3$CH$_2$OH  CCL$_3$COOH  HOOC-COOH
       /   \
       /     \
       CHCl$_2$COOH  CH$\text{CHO}$COOH  CO$_2$
       /   \
       /     \
       CH$_2$NH$_2$COOH
```

**Mutagenicity and other related short-term tests**

1,1,2,2-Tetrachloroethane was mutagenic in *Salmonella typhimurium* strains TA1530 and TA1535, showing a linear increase in reversion frequency with increasing concentration; negative results were obtained in strain TA1538. It also inhibited the growth of DNA polymerase-deficient (*pol A$^{-}$) *Escherichia coli*; the ratio of the areas of inhibition of *pol A$^{-}$:*pol A$^{+}$ was 1.88 with a concentration of 10 µl/plate (Brem et al., 1974).

**(b) Humans**

The toxicity of 1,1,2,2-tetrachloroethane has been reviewed (Browning, 1953; Lobo-Mendonça, 1963; National Institute for Occupational Safety & Health, 1976). Numerous deaths due to its ingestion,
inhalation and cutaneous absorption have been recorded. The solvent affects primarily the central nervous system and the liver and caused polyneuritis and paralysis (Browning, 1953; Hamilton & Hardie, 1974). Of 380 workers exposed to the solvent 133 (35%) exhibited tremor and other nervous symptoms (Lobo-Mendonça, 1963). Accidental and occupational exposure produced liver damage, ranging from severe fatty degeneration to necrosis and acute atrophy, which was frequently fatal, and gastrointestinal disorders; toxic effects were also observed in the haematopoetic system (Horiguchi et al., 1964; Lobo-Mendoça, 1963).

About 97% of inhaled 1,1,2,2-tetrachloroethane was retained in the lungs 1 hr after exposure (Morgan et al., 1970).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

1,1,2,2-Tetrachloroethane was tested in one experiment in mice and in one in rats by oral administration. In male and female mice, it produced hepatocellular carcinomas. Although a few hepatocellular carcinomas were observed in male rats, no significant increase in the incidence of tumours was observed in animals of either sex. The compound was inadequately tested in one experiment in mice by intraperitoneal injection.

1,1,2,2-Tetrachloroethane is mutagenic in Salmonella typhimurium and has teratogenic effects in mice.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production of 1,1,2,2-tetrachloroethane, particularly as an intermediate for other halogenated hydrocarbons, since the early 1920s indicates that exposure of both workers and the general population occurs. This is confirmed by reports of its occurrence in air, water and certain industrial effluents.

4.3 Evaluation

There is limited evidence that 1,1,2,2-tetrachloroethane is carcinogenic in experimental animals.
5. References


Lin, L.-C., Wang, C.-B. & Hsieh, C.-C. (1975) Highly toxic substances found in local industrial removers by GC-MS spectrometry (Chin.). Hua Hsueh, 4, 123-125 [Chem. Abstr., 87, 10796z]


National Cancer Institute (1978) Bioassay of 1,1,2,2-Tetrachloroethane for Possible Carcinogenicity, DHEW Publication No. (NIOH) 78-827, Washington DC, US Department of Health Education, & Welfare

National Institute for Occupational Safety & Health (1976) Criteria for a Recommended Standard ... Occupational Exposure to 1,1,2,2-Tetrachloroethane, DHEW (NIOSH) Publication No. 77-121, Cincinnati, OH. Available from Washington DC, US Government Printing Office


Takeuchi, Y. (1966) Experimental studies on the toxicity of 1,1,1,2-tetrachloroethane compared with 1,1,2,2-tetrachloroethane and 1,1,1-trichloroethane (Jap.). Jpn. J. ind. Health, 8, 371-374


TETRACHLOROETHYLENE

Two reviews on tetrachloroethylene are available (Berkowitz, 1979; National Institute for Occupational Safety & Health, 1976).

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: Tetrachloroethane

Synonyms: Carbon bichloride; carbon dichloride; ethylene tetrachloride; per; perc; perchlor; perchlorehylene; perchlorehylene; perk; tetrachlorethylene; 1,1,2,2-tetrachloroethylene

Trade names: Ankilostin; Antisal 1; Dee-Solv; Didakene; Dow-Per; ENT 1860; Fedal-Un; Nema; Perclene; Percosolv; Perklone; PerSec; Tetlen; Tetracap; Tetraleno; Tetravec; Tetroguer; Tetropil

1.2 Structural and molecular formulae and molecular weight

\[ \text{Cl}\text{C} = \text{C}\text{Cl} \]

\[ \text{Cl} \text{C} = \text{C}\text{Cl} \]

\[ \text{C}_2\text{Cl}_4 \]

Mol. wt: 165.8

1.3 Chemical and physical properties of the pure substance

From Hawley (1977), unless otherwise specified

(a) Description: Colourless liquid

(b) Boiling-point: 121°C

(c) Freezing-point: -22.4°C
(d) **Density**: $d_{20}^{20} = 1.625$

(e) **Refractive index**: $n_D^{25} = 1.5029$

(f) **Spectroscopy data**: Infra-red, Raman and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(g) **Solubility**: Practically insoluble in water (0.015 g/100 ml water at 25°C) (Hardie, 1964); miscible with ethanol, diethyl ether and oils in all proportions.

(h) **Vizility**: Vapour pressure is 20 mm at 26.3°C (Perry & Chilton, 1973).

(i) **Stability**: Nonflammable; decomposes slowly in contact with water to yield trichloroacetic and hydrochloric acids. At 700°C in contact with active carbon, it decomposes to hexachloroethane and hexachlorobenzene (Hardie, 1964).

(j) **Reactivity**: Oxidized by strong oxidizing agents (sulphuric and nitric acids, sulphur trioxide); reaction with excess hydrogen in the presence of reduced nickel catalyst produces total decomposition to hydrogen chloride and carbon (Hardie, 1964).

(k) **Conversion factor**: 1 ppm in air is equivalent to 6.78 mg/m³.

### 1.4 Technical products and impurities

Tetrachloroethylene is available in the US in the following grades: purified, technical, USP, spectrophotometric (Hawley, 1977) and dry-cleaning. The technical and dry-cleaning grades both meet specifications for technical grade and differ only in the amount of stabilizer added to prevent decomposition. Stabilizers are believed to include amines or mixtures of epoxides and esters. Typical analysis of the commercial grades is as follows: appearance, clear and free of suspended matter; specific gravity, 20°C/20°C, 1.624; nonvolatile residue, 0.0003%; free chlorine, none; moisture, no cloud at -5°C; 100% distillation range, 120.8-121.6°C.

USP grade contains not less than 99.0% and no more than 99.5% tetrachloroethylene, the remainder consisting of ethanol; it is available in the US in 0.2, 0.5, 1.0, 2.5 and 5 ml capsules intended for internal drug use (US Pharmacopeial Convention, Inc., 1975).
In Japan, tetrachloroethylene is available as a technical product with the following specifications: nonvolatile matter, 0.002% max; acidity (as HCl), 0.0001% max; and pH, 6.8.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

Tetrachloroethylene was first prepared in 1821 by Faraday by thermal decomposition of hexachloroethane (Hardie, 1964). The original commercial method of producing tetrachloroethylene involved a four-step process based on acetylene and chlorine as the raw materials. By July 1975, only one US plant with about 3% of total tetrachloroethylene capacity was using this process. Currently, the majority of tetrachloroethylene produced in the US is made by the oxyhydrochlorination, chlorination and/or dehydrochlorination of other hydrocarbons or chlorinated hydrocarbons. The raw materials include 1,2-dichloroethane (see monograph, p. 429), methane, ethane, propane, propylene, propylene dichloride and various other chlorinated materials such as 1,1,2-trichloroethane (see monograph, p. 533). An estimated 60% of the tetrachloroethylene produced in the US in 1974 was prepared from 1,2-dichloroethane, and about 40% from methane, ethane and propane.

In western Europe, tetrachloroethylene is produced by oxychlorination processes and by propylene chlorination.

In Japan, an estimated 60% of tetrachloroethylene is produced by chlorination of 1,2-dichloroethane and 40% by chlorination of methane and propane.

In 1972, worldwide demand for tetrachloroethylene was estimated to be 600 million kg.

It has been produced commercially in the US since 1925 (Hardie, 1964). In 1976, 9 US companies reported a total production of 304 million kg (US International Trade Commission, 1977). US imports in that year were 23.3 million kg, from the following countries (percent of total): France (34), Belgium (21), Italy (18), Japan (11), Canada (10), The Netherlands (4), and the Federal Republic of Germany (2) (US Department of Commerce, 1977a); exports were 22 million kg, and went to the following countries (percent of total): Mexico (38), the Federal Republic of Germany (18), The Netherlands (14), Belgium (9), Canada (5) and at least 5 other countries (16) (US Department of Commerce, 1977b).
Total annual production of tetrachloroethylene in western Europe is 250-500 million kg; the Federal Republic of Germany, France, Italy and the UK are the major producing countries, and Austria, Scandinavia, Spain, Switzerland and Benelux are minor producing regions. Annual production of tetrachloroethylene in eastern Europe is estimated to be 50-100 million kg.

Tetrachloroethylene has been produced commercially in Japan since 1952. In 1977, 8 companies produced an estimated 54.7 million kg; exports were 2.6 million kg in that year, none was imported.

(b) Use

In 1976, tetrachloroethylene was used in the US as follows: textile industry, 68%; industrial metal cleaning, 15%; chemical intermediate, 14%; and other applications, 3%.

Tetrachloroethylene is used in the textile industry for dry-cleaning and for processing and finishing. It is nonflammable, easily recoverable for reuse, does not hydrolyse appreciably, and can be used on all fabrics. In 1975, 70% of the dry-cleaners in the US used tetrachloroethylene, and it constituted over 65% of the total dry-cleaning solvent usage. In 1974, 18-27 million kg tetrachloroethylene were used for textile processing and finishing in the US.

It is used in both cold cleaning and vapour degreasing of metals; in 1974, about 80% of the total used in the US for metal cleaning was in vapour degreasing.

It is used as a chemical intermediate in the synthesis of Fluorocarbon 113 (1,1,2-trichloro-1,2,2-trifluoroethane), Fluorocarbon 114 (1,2-dichloro-1,1,2,2-tetrafluoroethane), Fluorocarbon 115 (chloropentafluoroethane), and Fluorocarbon 116 (hexafluoroethane).

Tetrachloroethylene is also used as a heat-exchange fluid, and as a drug against hookworms and some nematodes (National Institute for Occupational Safety & Health, 1978; US Pharmacopeial Convention, Inc., 1975).

In western Europe, use of tetrachloroethylene is as follows: dry-cleaning, 70-95%; metal cleaning and extraction, 5-15%; chemical intermediate, 0-10%; and other, 0-5%. Its use in Japan in 1977 was: dry-cleaning, 50%; metal cleaning, 21%; solvent and miscellaneous uses, 29%.

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to tetrachloroethylene not exceed an 8-hr time-weighted average of 670 mg/m³ (100 ppm) in the working atmosphere during an 8-hr work
TETRACHLOROETHYLENE

shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977). The corresponding standard in the Federal Republic of Germany is 670 mg/m³; in the German Democratic Republic, 300 mg/m³; in Sweden, 200 mg/m³; and in Czechoslovakia, 250 mg/m³; the acceptable ceiling concentration in the USSR is 10 mg/m³ (Winell, 1975).

2.2 Occurrence

Tetrachloroethylene is not known to occur as a natural product.

(a) Air

About 85% of the tetrachloroethylene used annually in the US is lost to the atmosphere; in 1974, this amount was estimated to be 250 million kg (Fuller, 1976).

Numerous US studies have reported tetrachloroethylene in air [concentrations in parts per trillion (ppt¹), unless otherwise specified]:

1. in rural air in central Michigan (30-50) (Russell & Shadoff, 1977);
2. in locations in California, including Los Angeles (673.3), Palm Springs (278.1), Badger Pass (30.7), Menlo Park (201.9) (Singh, 1976), Stanford Hills (38.3), Point Reyes (43.1) (Singh et al., 1977), Pasadena (1.3-4.2 ppb²), West San Gabriel Valley to Manhattan Beach (< 0.01-3.8 ppb) and the Los Angeles Basin (0.37-3.84 ppb) (Simmonds et al., 1974);
3. in New Brunswick, New Jersey (0.5 ppb) (Lillian et al., 1976);
4. in rural south-eastern Washington state (20) (Grimsrud & Rasmussen, 1975); and
5. in various other locations (reported as mean concentrations), including Seagirt, New Jersey (0.32 ppb); New York City, New York (4.5 ppb), Sandy Hook, New Jersey (0.39 ppb), Delaware City, Delaware (0.24 ppb), Baltimore, Maryland (0.18 ppb), Wilmington, Ohio (0.15 ppb), White Face Mountains, New York (0.07 ppb) and Bayonne, New Jersey (1.63 ppb) (Lillian et al., 1975).

In a UK study, tetrachloroethylene was detected in the air at the following locations (ppb): Runcorn Works perimeter (15-40), Runcorn Heath (0.2-5), Liverpool/Manchester suburban area (< 0.1-10), Moel Famau, Flintshire (< 0.1-2.5), Rannoch Moor, Argyllshire (0.3-1), and Forest of Dean, Monmouthshire (3) (Pearson & McConnell, 1975). In an air-sampling study conducted in central Exmoor and the moorlands of North Wales, tetrachloroethylene concentrations were found to range from 8-57 ng/m³; in air over the north-east Atlantic Ocean between Cap Blanc and Lands End 1-9 ng/m³ were detected (Murray & Riley, 1973). Tetrachloroethylene was also detected in the air over Adrigole, County Cork, Eire, at a level of 27.6 ppt (Cox et al., 1976).

¹ 1 ppt in air is equivalent to 6.78 ng/m³.
² 1 ppb in air is equivalent to 6.78 µg/m³.
(b) Water

Tetrachloroethylene may be formed in small quantities during chlorination of water: samples from 8 of 10 water utilities contained 0.07-0.46 µg/l (Safe Drinking Water Committee, 1977). It has also been detected in the municipal drinking-water at a number of localities [Bertsch et al., 1975; (0.5 µg/l) Eurocop-Cost, 1976; (< 5 µg/l) Saunders et al., 1975].

Rainwater has been found to contain up to 0.15 µg/l tetrachloroethylene. Average and maximum concentrations in sea-water were 0.12 µg/l and 2.6 µg/l and the maximum concentration in sediments 4.8 µg/l (Pearson & McConnell, 1975). Surface water from the Atlantic Ocean contained 0.2-0.8 ng/l tetrachloroethylene (Murray & Riley, 1973). It has also been detected in rivers and in subterranean water (Dowty et al., 1975; Eurocop-Cost, 1976; Zürcher & Giger, 1976); and in commercial deionized charcoal-filtered water (Dowty et al., 1975).

Tetrachloroethylene was detected in the influent to a sewage treatment plant at a level of 6.2 µg/l, in the effluent before chlorination, at 3.9 µg/l, and in the effluent after chlorination, at 4.2 µg/l (Bellar et al., 1974). It has also been detected in the effluents from chemical production plants, an oil refinery and textile plants and in lake water (Shackelford & Keith, 1976).

(c) Food

Tetrachloroethylene has been detected in dairy produce (0.3-13 µg/kg), meat (0.9-5 µg/kg), oils and fats (0.01-7 µg/kg), beverages (2-3 µg/kg), fruit and vegetables (0.7-2 µg/kg), fresh bread (1 µg/kg) (McConnell et al., 1975) and commercially available rendered fats and meat-and-bone meal (Ingr, 1976).

(d) Marine organisms

Tetrachloroethylene residues were detected in specific organs of the following fish (concentrations expressed as µg/kg on a dry-weight basis): 3 species of molluscs (0-176), eel (1-43), cod (0-8), coalfish (0-6), dogfish (0-13), and bib (0-27) (Dickson & Riley, 1976).

In another study, tetrachloroethylene residues were reported as follows (concentrations expressed as µg/kg of wet tissue): in 14 species of invertebrates (0.05-15), 3 species of marine algae (13-20), 15 species of fish (0-41), the organs and eggs of 8 species of sea and freshwater birds (0.7-39), and the organs of 2 species of mammals (0-19) (Pearson & McConnell, 1975).
(e) **Humans**

Tetrachloroethylene has been detected in post-mortem human tissue samples, at levels of less than 0.5-29.2 μg/kg (wet tissue) (McConnell *et al.*, 1975), and in expired air, at levels of 0.022-12 μg/hr/subject (Conkle *et al.*, 1975).

(f) **Occupational exposure**

Tetrachloroethylene was detected in the air of industrial installations at a concentration of 2 mg/m$^3$ (0.3 ppm) (Kiparisova & Stepanenko, 1976). Concentrations measured in dry-cleaning plants varied from 20-300 mg/m$^3$ (3-45 ppm) (Engels *et al.*, 1975).

2.3 **Analysis**

The determination of chlorinated hydrocarbons, including tetrachloroethylene, in ambient and alveolar air, workplace atmospheres, blood and urine has been reviewed (Walter *et al.*, 1976). Methods used for the analysis of tetrachloroethylene in environmental samples are listed in Table 1.

Grimsrud & Rasmussen (1975) report that difficulty in removing tetrachloroethylene from the carrier gas system limits the value of gas chromatography/mass spectrometry methods. This method was used by Coleman *et al.* (1976) to quantify halocarbons, including tetrachloroethylene, in drinking-water.

Carbon dioxide laser absorption spectrometry can be used to detect tetrachloroethylene in prepared samples of air pollutants, with a limit of detection of 9.5 μg/m$^3$ (1.4 ppb) (Schnell & Fischer, 1975).

3. **Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans**

3.1 **Carcinogenicity studies in animals**

(a) **Oral administration**

Mouse: Groups of 50 male and 50 female B6C3F1 mice, approximately 5 weeks old at the beginning of treatment, were administered tetrachloroethylene (USP grade) in corn oil by gavage on 5 consecutive days per week for 78 weeks. High-dose males received 900 mg/kg bw/day for 11 weeks,

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1 The Working Group was aware of studies in progress to assess the carcinogenicity of tetrachloroethylene in mice and rats by oral administration and in mice by skin application (IARC, 1978a).
### Table 1. Methods for the Analysis of Tetrachloroethylene

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Extraction/Clean-Up</th>
<th>Detection</th>
<th>Limit of Detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encapsulated liquids</td>
<td>Dilute (ethanol)</td>
<td>IR</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Cough syrups</td>
<td>Dilute (ethanol) if necessary</td>
<td>IR</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td>Sample on charcoal, extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Useful range, 655-2749 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Determine directly, enrich</td>
<td>GC</td>
<td>15 mg/m³</td>
<td>Krynska et al. (1976)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap on Chromosorb 101, desorb by heating, retrap in line on GC column</td>
<td>GC</td>
<td>2.5 mg/m³, 3.4 µg/m³ (0.5 ppb)</td>
<td>Parkes et al. (1976)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Sample in glass watch flask fitted with rubber septum, sample with gas syringe</td>
<td>GC/ECD</td>
<td>1 µg/m³</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td></td>
<td>0.2 µg/m³ (30 ppt)</td>
<td>Russell &amp; Shadoff (1977)</td>
</tr>
<tr>
<td>Drinking- &amp; sewage water</td>
<td>Bubble nitrogen through sample, concentrate</td>
<td>GC/FID; GC/MS</td>
<td>0.1 µg/l</td>
<td>Bellar et al. (1974)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Extract (pentane), dry</td>
<td>GC/ECD</td>
<td>25 ng/l</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Analyse directly</td>
<td>GC/ECD</td>
<td>0.5 µg/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Analyse directly</td>
<td>GC/ECD</td>
<td>8 µg/l</td>
<td>Nicholson &amp; Meresz (1975)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>-------------------</td>
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</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oil and liquid</td>
<td>Heat sample, use headspace</td>
<td>GC/FID</td>
<td></td>
<td>Drexler &amp; Osterkamp (1977)</td>
</tr>
<tr>
<td>paraffin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobacco smoke</td>
<td>Trap on Tenax GC and Carbopack</td>
<td>GC/FID; GC/MS</td>
<td></td>
<td>Holzer et al. (1976)</td>
</tr>
<tr>
<td></td>
<td>BHT coated with 5 and 25% OV-101</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>silicon fluid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IR - infra-red spectrometry; GC/FID - gas chromatography/flame-ionization detection; ECD - electron capture detection; MS - mass spectrometry
1100 mg/kg bw/day for 67 weeks followed by 12 weeks without treatment; high-dose females received 600 mg/kg bw/day for 11 weeks and 800 mg/kg bw/day for 67 weeks. Respective doses in low-dose animals were 450 and 550 mg/kg bw/day in males and 300 and 400 mg/kg bw/day in females. Time-weighted average doses were 536 and 1072 mg/kg bw/day in males and 386 and 772 mg/kg bw/day in females. Groups of 20 male and 20 female mice were either untreated or received corn oil alone. All surviving mice were killed 90 weeks after the start of the experiment. The times at which 50% of animals were still alive were 90 weeks for control animals of both sexes, 78 weeks for low-dose males, 43 weeks for high-dose males, 62 weeks for low-dose females and 50 weeks for high-dose females. The shorter lifespan in treated animals was due to early toxicity and high incidences of hepatocellular carcinomas in animals of both sexes: hepatocellular carcinomas occurred in 2/17 untreated control males, 2/20 vehicle control males, 32/49 low-dose males and 27/48 high-dose males; in females, the respective incidences were 2/20, 0/20, 19/48 and 19/48. Metastases were found in 1 untreated control male, in 3 low-dose males, in 1 low-dose female and in 1 high-dose female (National Cancer Institute, 1977).

Rat: Groups of 50 male and 50 female 7-week-old Osborne-Mendel rats were treated with tetrachloroethylene (USP grade) in corn oil by gavage on 5 days a week for 78 weeks. High-dose animals received 1000-1400 mg/kg bw/day, and low-dose animals 500-700 mg/kg bw/day. All surviving animals were then observed until 110 weeks after the start of treatment. The time-weighted average doses were 471 and 941 mg/kg bw/day in low- and high-dose males and 474 and 949 mg/kg bw/day in low- and high-dose females. Dose-related mortality was observed in animals of both sexes after 30 weeks. Groups of 20 male and 20 female untreated rats or vehicle-treated rats served as controls. The times at which 50% of animals were still alive were 44 weeks for high-dose males, 66 weeks for high-dose females, 66 weeks for control groups, over 88 weeks for low-dose males and 102 weeks for low-dose females. No increases in tumour incidences were observed. Toxic nephropathy was observed in treated rats that died as early as week 20 (National Cancer Institute, 1977) [The Working Group noted the poor survival of treated animals].

(b) Inhalation and/or intratracheal administration

Rat: In a study reported as an abstract, groups of 96 male and 96 female Sprague-Dawley rats were exposed by inhalation to 2 or 4 g/m³ (300 or 600 ppm) tetrachloroethylene in air for 6 hrs per day on 5 days a week for 12 months, followed by observation up to 30 months. No statistically significant difference in tumour incidence between treated and control animals was found (Rampy et al., 1977) [The Working Group noted the incomplete reporting of the experiment and the short duration of the exposure].
(c) Intraperitoneal administration

Mouse: Groups of 20 male A/St mice, 6-8 weeks old, were given thrice weekly i.p. injections of 80 mg/kg bw (14 injections), 200 mg/kg bw (24 injections) or 400 mg/kg bw (48 injections) tetrachloroethylene in tricaprylin. All survivors (15, 17, 18 mice in the three groups, respectively) were killed 24 weeks after the first injection. The average number of lung tumours per mouse was not increased compared with that in controls that received tricaprylin alone (Theiss et al., 1977) [The Working Group noted the limitations of negative results obtained with this test system; see also General Remarks on Substances Considered, p. 34].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The toxic effects of tetrachloroethylene have been reviewed (Von Oettingen, 1964).

The oral LD$_{50}$ of tetrachloroethylene in mice is 6.4-8 g/kg bw (Kohne, 1940), 8.85 and 10.8 g/kg bw; it was less toxic in oily solution than when undiluted (Dybing & Dybing, 1946). The inhalational LC$_{50}$ in mice (4 hrs) is 35 g/m$^3$ (5200 ppm) (Friberg et al., 1953), and the i.p. LD$_{50}$ is 4.7 g/kg bw (Klaassen & Plaa, 1966). In rats, the oral LD$_{50}$ is 13 g/kg bw (Smyth et al., 1969). For rabbits, the minimum lethal dose (24 hrs) after s.c. injection is 2.2 g/kg bw; in dogs, the minimum lethal dose (30 min) after i.v. injection is 85 mg/kg bw (Barsoum & Saad, 1934). The i.p. LD$_{50}$ in dogs is 3.5 g/kg bw (Klaassen & Plaa, 1967).

The minimal narcotic concentration of tetrachloroethylene for mice is 20 g/m$^3$ (2950 ppm) (Lazarew, 1929). Single exposure of rats to 13.6 g/m$^3$ (2000 ppm) for 5 hrs caused no loss of consciousness (Rowe et al., 1952). Lamson et al. (1929) reported the narcotic concentration for dogs as 62 g/m$^3$ (9900 ppm).

Thirteen exposures to 17 g/m$^3$ (2500 ppm) tetrachloroethylene vapours for 7 hrs daily was fatal to the majority of rats (Rowe et al., 1952). The average maximum tolerated oral dose of tetrachloroethylene over a period of 78 weeks was 941 mg/kg bw/day in male Osborne-Mendel rats, 949 mg/kg bw/day in females, 1072 mg/kg bw/day in male B6C3Fl mice, and 722 mg/kg bw/day in females (National Cancer Institute, 1977).

Repeated exposure to vapours has produced a variety of pathological changes in the liver, ranging from fatty degeneration to necrosis in rats, rabbits and guinea-pigs (Rowe et al., 1952). Repeated exposure of male
Sprague-Dawley rats to 4 g/m³ (600 ppm) vapour for 6 hrs/day on 5 days/week for 12 months resulted in reversible toxic effects in the liver (Pegg et al., 1978). Oral doses of 0.3 g/kg bw produced degenerative changes and extensive atrophy of the liver in dogs (Hall & Shillinger, 1925).

Oral doses of tetrachloroethylene have lesser effects on the kidney: only a nearly lethal dose (4 g/kg bw) caused swelling of the convoluted tubules and hydropic degeneration in male mice (Klaassen & Plaa, 1966; Plaa & Larson, 1965). I.p. doses of 1.6-2.3 g/kg bw tetrachloroethylene caused slight calcification of the tubules of the kidneys in dogs (Klaassen & Plaa, 1967).

Embryotoxicity and teratogenicity

Groups of rats and mice were exposed by inhalation for 7 hrs daily on days 6-15 of gestation to 2 g/m³ in air (300 ppm) tetrachloroethylene; no effects were observed on the average number of implantation sites per litter, litter size, incidence of foetal resorptions, foetal sex ratios or foetal body measurements. No treatment-related increase in the incidence of skeletal or visceral malformations was observed (Schwetz et al., 1975).

Absorption, distribution, excretion and metabolism

Tetrachloroethylene is readily absorbed through the lungs and to some extent from the gastrointestinal tract (Von Oettingen, 1964). Fats and oils facilitate its absorption from the intestine after oral administration to dogs (Lamson et al., 1929). Skin absorption of tetrachloroethylene in mice is low in relation to that of a series of chlorinated ethanes and ethylenes (Tsuruta, 1975).

The half-life of expiration of ³⁶Cl-labelled tetrachloroethylene in rats was about 7 hrs, regardless of dose or route of application (Pegg et al., 1978).

Mice excreted about 90% of an inhaled dose of 1300 mg/kg bw ¹⁴C-labelled tetrachloroethylene: 70% in the expired air, 20% in the urine and < 0.5% in the faeces. The metabolites identified in the urine were trichloroacetic acid (52% of total urinary activity), oxalic acid (11%) and traces of dichloroacetic acid (Yllner, 1961). In contrast, Daniel (1963) found only 2% of an oral dose of about 1000 mg/kg bw ³⁶Cl-tetrachloroethylene in the urine of rats; trichloroacetic acid (0.6%) and inorganic chloride were the only metabolites detected.

When ¹⁴C-labelled tetrachloroethylene was administered to adult male rats by gavage or by inhalation, approximately 70% of the body burden was expired as unchanged compound, 26% as CO₂ in expired air and as nonvolatile metabolites in urine and faeces and 3-4% remained in the carcass (Pegg et al., 1978).
The hepatotoxicity of tetrachloroethylene was enhanced in rats treated with Aroclor 1254. Pretreatment of rats with phenobarbital or Aroclor 1254 orally considerably increased the urinary excretion of trichloro compounds after oral administration of tetrachloroethylene in oil (Moslen et al., 1977).

In rat liver perfusion experiments, tetrachloroethylene was converted into trichloroacetic acid, the only metabolite detected (Bonse et al., 1975).

The presence of an epoxide intermediate (oxirane) has been proposed in the metabolism of tetrachloroethylene on the basis of its oxidative metabolism (Henschler & Bonse, 1977).

Mutagenicity and other related short-term tests

Results reported in an abstract suggest that tetrachloroethylene is mutagenic in plate tests in Salmonella typhimurium TA100. In a host-mediated assay in mice, using Salmonella typhimurium TA1950, TA1951 and TA1952, there was a significant increase in the number of revertants with doses equivalent to the LD$_{50}$ and to half the LD$_{50}$, but this was not dose-related (Černá & Kypěnová, 1977).

Tetrachloroethylene did not induce mutations to prototrophy at the gal, arg and nad loci in Escherichia coli K12 and had no effect on forward mutation frequency in the methytryptophan resistance system at a nontoxic concentration of 0.9 mM (liquid tests) (Greim et al., 1975).

There was no induction of chromosomal aberrations in bone-marrow cells of mice that had received either single (half LD$_{50}$) or 5 daily i.p. injections (one-sixth LD$_{50}$) of the chemical (Černá & Kypěnová, 1977).

(b) Humans

The effects of inhalation of various concentrations have been reviewed; these include irritation of the mucous membranes, skin irritation (Von Oettingen, 1964) and lung oedema (Patel et al., 1977). The neurological effects of tetrachloroethylene on dry-cleaners have also been reviewed (Tuttle et al., 1977).

Chronic exposure to tetrachloroethylene vapours caused irritation of the respiratory tract, nausea, headache, sleeplessness, abdominal pains and constipation (Chmielewski et al., 1976; Coler & Rossmiller, 1953; Stewart et al., 1970; Von Oettingen, 1964). Pathological findings (liver cirrhosis, hepatitis and nephritis) are rare (Stewart, 1969). Other reports of intoxications and fatalities due to tetrachloroethylene have been made (Eberhardt & Freundt, 1966; Larsen et al.,
Therapeutic administration of tetrachloroethylene as an anthelminthic has occasionally produced side effects (Von Oettingen, 1964). A case of 'obstructive jaundice' in a 6-week old infant has been attributed to tetrachloroethylene in breast milk. During her pregnancy, the mother had frequently visited her husband at his work place in a dry-cleaning plant. Liver function tests and serum transaminase levels in the parents were normal (Bagnell & Ellenberger, 1977).

Tetrachloroethylene vapours and liquid can be absorbed through the skin (Hake & Stewart, 1977; Stewart & Dodd, 1964) and through the lungs (Stewart et al., 1961). Inhaled tetrachloroethylene is excreted very slowly: its biological half-life is 3-5 days, depending on the length of exposure (Stewart et al., 1970). The half-life of tetrachloroethylene in alveolar air after dermal absorption of the liquid was approximately 8 hrs (Stewart & Dodd, 1964). After exposure to 0.7 g/m³ (100 ppm) in air for 8 hrs, the concentrations in the alveolar air decreased exponentially, with an initial expiration half-life of 25-30 min (Fernandez et al., 1976). The total body half-life was calculated to be 71.5 hrs (Guberan & Fernandez, 1974).

Inhalation of tetrachloroethylene is followed by a long-lasting excretion of metabolites in the urine (Ikeda & Imamura, 1973). Tetrachloroethylene is metabolized very slowly, and determination of its urinary metabolites can therefore not be taken as a satisfactory measure of exposure. Male volunteers exposed to 0.6 g/m³ (87 ppm) tetrachloroethylene vapours in air for 3 hrs excreted about 1.8% of the dose in the urine as trichloroacetic acid in 67 hrs (Ogata et al., 1971). At concentrations well below 678 mg/m³ (100 ppm), both trichloroacetic acid and trichloroethanol concentrations in the urine reach a plateau (Ikeda, 1977).

Of 200 workers exposed to tetrachloroethylene vapours, 35% had more than 10 mg/l trichloroacetic acid in their urine. About half the subjects with these levels of urinary trichloroacetic acid had some symptoms of poisoning (Münzer & Heder, 1972).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

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1The Working Group was aware of a mortality study in progress on dry-cleaning workers exposed to tetrachloroethylene (IARC, 1978b).
4. Summary of Data Reported and Evaluation

4.1 Experimental data

Tetrachloroethylene was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced hepatocellular carcinomas in animals of both sexes. The experiment in rats was considered to be inadequate. Tetrachloroethylene was also inadequately tested by inhalation exposure in rats and by intraperitoneal injection in mice.

Tetrachloroethylene was not mutagenic in Escherichia coli and was negative in cytogenetic tests in mice.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and use of tetrachloroethylene over the past several decades, particularly for dry-cleaning purposes, indicate that widespread human exposure occurs. This is confirmed by many reports of its occurrence in air, water, fish and food samples.

4.3 Evaluation

There is limited evidence that tetrachloroethylene is carcinogenic in mice.

1Subsequent to the meeting of the Working Group, the Secretariat became aware of a study of 330 deceased laundry and dry-cleaning workers who had been exposed to carbon tetrachloride, trichloroethylene and tetrachloroethylene. An excess of lung, cervical and skin cancers and a slight excess of leukaemias and liver cancers were observed (Blair et al., 1979). In an abstract, Blair et al. (1978) described a clinical report of 5 cases of chronic lymphocytic leukaemia in a family that operated a dry-cleaning business.
5. References


Bureau International Technique des Solvents Chlorés (1976) Standardization of methods for the determination of traces of some volatile chlorinated aliphatic hydrocarbons in air and water by gas chromatography. Anal. chim. acta, 82, 1-17


Eberhardt, H. & Freundt, K.J. (1966) Perchloroethylene poisoning (Germ.). Arch. Toxikol., 21, 338-351


TETRACHLOROETHYLENE


Rampy, L.W., Quast, J.F., Leong, B.K.J. & Gehring, P.J. (1977) Results of long-term inhalation toxicity studies on rats of 1,1,1-trichloroethane and perchloroethylene formulations (Abstract). In: International Congress on Toxicology, Toronto, Canada, 1977, p. 27


Safe Drinking Water Committee (1977) Drinking Water and Health, Washington DC, National Academy of Sciences, p. 769


TETRACHLOROETHYLENE


1,1,1-TRICHLOROETHANE

One review on 1,1,1-trichloroethane is available (Mercier, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: 1,1,1-Trichloroethane

Synonyms: Chloroethene; chlorotene; chlorothene; methyl chloroform; methyltrichloromethane; trichloroethane; α-trichloroethane

Trade names: Aerothene TT; Chlorten; Chlorothane NU; Chlorothene NU; Chlorothene VG; Inhibisol; α-T

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{Cl} & \quad \text{H} \\
\text{Cl} & \quad \text{C} - \text{C} - \text{H} \\
\text{Cl} & \quad \text{H}
\end{align*}
\]

\[\text{C}_2\text{H}_3\text{Cl}_3 \quad \text{Mol. wt: 133.4}\]

1.3 Chemical and physical properties of the pure substance

From Aviado et al. (1976), unless otherwise specified

(a) Description: Colourless liquid (Hardie, 1964)

(b) Boiling-point: 74.1°C

(c) Melting-point: -32.6°C (Hardie, 1964)

(d) Density: \(d^{25} 1.336\)

(e) Refractive index: \(n^D_{20} 1.4370\) (Grasselli & Ritchey, 1975)
Spectroscopy data: Infra-red, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

Solubility: Practically insoluble in water (0.03 g/100 g of water at 25°C); soluble in acetone, benzene, carbon tetrachloride, methanol, diethyl ether and carbon disulphide.

Vapour pressure is 103 mm at 20°C.

Stability: Nonflammable; decomposes at high temperatures (> 360°C) or at ambient temperatures in the presence of water and metals, liberating hydrogen chloride; oxidized by atmospheric oxygen at high temperatures, forming phosgene (Hardie, 1964).

Reactivity: Reacts with an aqueous suspension of calcium hydroxide, forming 1,1-dichloroethylene; reacts with chlorine in sunlight to give 1,1,1,2-tetrachloroethane and small quantities of penta- and hexachloroethane (Hardie, 1964).

Conversion factor: 1 ppm in air is equivalent to 5.4 mg/m³.

Technical products and impurities

1,1,1-Trichloroethane is available commercially in the US in technical and solvent grades, which differ only in the amount of stabilizer added to prevent corrosion of metal parts. Stabilized grades contain 3-8% stabilizer, such as nitromethane, N-methylpyrrole, 1,4-dioxane, butylene oxide, 1,3-dioxolane and secondary butyl alcohols. Typical specifications are as follows: a clear, water-white liquid; specific gravity, 25°C/25°C, 1.300-1.320; nonvolatile residue, 0.001% max; water content, 100 mg/kg max; acidity (as HCl), 0.001% max; 100% distillation range, 72-88°C; pH, 6.0-7.5; and acid acceptance (as NaOH), 0.165% min.

Specifications for reagent grade 1,1,1-trichloroethane are as follows; boiling-range of a 100 ml sample, the difference between the temperature observed when 1 ml and 95 ml have distilled does not exceed 16°C; specific gravity, 1.312-1.321; acidity (as HCl), 0.001% max; residue on evaporation, 0.001% (US Pharmacopeial Convention, Inc., 1975).
Technical grade 1,1,1-trichloroethane available in Japan has the following specifications: distillation range, 70-88°C; acidity (as HCl), 0.001% max; nonvolatile matter, 0.001% max; moisture content, 0.01% max.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(a) Production

1,1,1-Trichloroethane was first prepared in 1840 by the reaction of chlorine with 1,1-dichloroethane (Prager et al., 1918). It is produced commercially in the US by chlorination of vinyl chloride derived from 1,2-dichloroethane; hydrochlorination of vinylidene chloride derived from 1,2-dichloroethane; or thermal chlorination of ethane. Of the total US capacity for 1,1,1-trichloroethane manufacture, 90% is based on 1,2-dichloroethane-derived intermediates.

1,1,1-Trichloroethane is produced in Japan by chlorination of vinyl chloride.

Commercial production of 1,1,1-trichloroethane in the US was first reported in 1946 (US Tariff Commission, 1947). In 1976, total production by the 4 producing companies amounted to 287 million kg (US International Trade Commission, 1977); imports were negligible. US exports of 1,1,1-trichloroethane in 1974 were 32 million kg.

Total annual western European production of 1,1,1-trichloroethane is 120-200 million kg: the Federal Republic of Germany produces more than 100 million kg; France and the UK produce 10-50 million kg; and Austria, Benelux, Italy, Scandinavia, Spain and Switzerland each produce less than 100 thousand kg. Annual production in eastern Europe is estimated to be less than 100 thousand kg.

In 1976, 5 Japanese companies produced an estimated 60 million kg of 1,1,1-trichloroethane; exports were 5 million kg, and none was imported.

(b) Use

In 1974, use of 1,1,1-trichloroethane in the US was as follows: cold cleaning of metals, 37%; vapour degreasing, 34%; chemical intermediate for vinylidene chloride (see IARC, 1979), 23%; and other applications, 6%.

1,1,1-Trichloroethane is widely used as a cleaning solvent because of its nonflammability and solvent properties. It is used as a cold
cleaning solvent for electric motors, generators, switchgear and electronic apparatus, and has also begun to compete with Fluorocarbon 113 (1,1,2-trichloro-1,2,2-trifluoroethane) in high-purity cleaning applications, such as missile parts, semiconductors and high-vacuum equipment.

Stabilized 1,1,1-trichloroethane (see section 1.4) protects against corrosion and is stable under conditions of vapour degreasing. Between 1971 and 1974, use of this compound for vapour degreasing grew at an average annual rate of 21%.

In 1974, approximately 47% of the vinylidene chloride produced in the US was derived from 1,1,1-trichloroethane (for information on uses of vinylidene chloride, see IARC, 1979).

The largest other use for 1,1,1-trichloroethane is in aerosols, in which it acts both as a vapour-pressure depressant (making it a good propellant) and as a solvent and carrier for many of the active ingredients used in aerosols. It has been estimated that 14 aerosol products and 45 nonaerosol products containing 10-100% 1,1,1-trichloroethane were available to US consumers in 1969 (Aviado et al., 1976).

Several million kg of 1,1,1-trichloroethane per year are used in adhesives as a resin solvent. It is also used as a lubricant carrier to inject graphite, grease and other lubricants; and it is used alone and in cutting oil formulations as a coolant and lubricant for drilling and tapping alloy and stainless steels. 1,1,1-Trichloroethane is also used to develop printed circuit boards and as a solvent in drain cleaners, shoe polishes, spot cleaners, insecticide formulations and printing inks. It is used in motion picture film cleaning, in stain repellents for upholstery fabrics, for wig cleaning, and in textile processing and finishing.

In western Europe, 1,1,1-trichloroethane is used as follows: vapour degreasing, 30%; cold cleaning of metals, 30%; solvent for manufactured products (such as adhesives), 30%; and other uses, 10%.

In 1976, 1,1,1-trichloroethane was used in Japan as follows: cleaning solvent for metals, 77%; spot removers, 10%, and other uses, 13%.

1,1,1-Trichloroethane is approved by the US Food and Drug Administration (FDA) as a constituent of adhesives used as components of articles intended for use in packaging, transporting or holding food (US Food and Drug Administration, 1977a). On 16 December, 1977, the FDA ruled that an approved new drug application is required, as of 16 January 1978, to market any aerosol drug product containing 1,1,1-trichloroethane and intended to be inhaled either directly or indirectly (US Food & Drug Administration, 1977b).
Also in the US, 1,1,1-trichloroethane is exempted from the requirement of a tolerance for residues: (1) when used as a solvent in pesticide formulations applied to growing crops and raw agricultural commodities after harvest; (2) when used as a solvent in pesticide formulations used on animals, when it comprises not more than 25% of the formulation; and (3) when used in the postharvest fumigation of citrus fruits (US Environmental Protection Agency, 1976).

The US Occupational Safety and Health Administration's standards for exposure to air contaminants require that an employee's exposure to 1,1,1-trichloroethane not exceed an 8-hr time-weighted average of 1900 mg/m³ (350 ppm) in the workplace air in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977). The corresponding standard in the Federal Republic of Germany is 1080 mg/m³ (200 ppm); that in the German Democratic Republic and Czechoslovakia, 500 mg/m³ (92 ppm); and that in Sweden, 540 mg/m³ (100 ppm). In the USSR, the acceptable ceiling concentration is 20 mg/m³ (3.7 ppm) (Winell, 1975).

2.2 Occurrence

1,1,1-Trichloroethane is not known to occur as a natural product.

(a) Air

1,1,1-Trichloroethane has been detected in air samples taken: (1) over the Los Angeles Basin, at an average concentration of 2 µg/m³ (0.37 ppb¹) (Simmonds et al., 1974); (2) in ambient air over New Brunswick, New Jersey, at a level of 4.5 µg/m³ (0.83 ppb) (Lillian et al., 1976); (3) in air samples in Stanford Hills, California, at a level of 422 ng/m³ (77.6 ppt²) (average), and Point Reyes, California, at a level of 492 ng/m³ (90 ppt) (average) (Singh et al., 1977); (4) in rural air samples taken in central Michigan, at levels of 500-700 ng/m³ (80-120 ppt) (Russell & Shadoff, 1977); (5) in rural air samples taken in southeastern Washington state, at a level of 545 ng/m³ (100 ppt) (Grimsrud & Rasmussen, 1975); and (6) in the following locations (mean concentration in ppb): Seagirt, New Jersey (0.10); New York City, New York (0.61); Sandy Hook, New Jersey (0.15); Delaware City, Delaware (0.10); Baltimore, Maryland (0.12); Wilmington, Ohio (0.097); White Face Mountains, New York (0.067); and Bayonne, New Jersey (1.59) (Lillian et al., 1975).

1,1,1-Trichloroethane has also been detected in ambient air over Tokyo, at an average concentration of 4.3 µg/m³ (0.8 ppb) (Ohta et al., 1976); in air in South Africa, at a level of 132 ng/m³ (24.4 ppt); and in Eire, at a level of 350 ng/m³ (64.8 ppt) (Cox et al., 1976).

¹ 1 ppb is equivalent to 5.4 µg/m³ of air.

² 1 ppt is equivalent to 5.4 ng/m³ of air.
In a UK study, 1,1,1-trichloroethane was detected in air at the following locations (in ppb): Runcorn Works perimeter (~16); Runcorn Heath (6.2-11); Liverpool/Manchester suburban area (<0.1-6); Moel Famau, Flintshire (2-4); Rannoch Moor, Argyllshire (1-1.5); and Forest of Dean, Monmouthshire (2.8) (Pearson & McConnell, 1975).

(b) Water

1,1,1-Trichloroethane has been detected in finished drinking-water (Dowty et al., 1975) and was one of 72 compounds found in the drinking-water supplies of 5 US cities (Coleman et al., 1975).

Rainwater collected in UK was reported to contain up to 90 ng/l 1,1,1-trichloroethane, and municipal waters contained up to 300 ng/l combined carbon tetrachloride and 1,1,1-trichloroethane. The maximum concentration of 1,1,1-trichloroethane found in sea-water was 3.3 μg/l, and the average concentration in combination with carbon tetrachloride was 0.25 μg/l. Marine sediments contained up to 5 μg/kg 1,1,1-trichloroethane and carbon tetrachloride combined (Pearson & McConnell, 1975).

1,1,1-Trichloroethane has been measured in crude sewage at a level of 16.5 μg/l, in effluent from a biological treatment plant at a level of 9 μg/l, and in chlorinated biological effluent at a level of 8.5 μg/l (Eurocop-Cost, 1976).

(c) Food and drink

In a UK study of 12 food items, 1,1,1-trichloroethane residues were found in meat (3-6 μg/kg), oils and fats (5-10 μg/kg), tea (7 μg/kg), fruit and vegetables (1-4 μg/kg) and fresh bread (2 μg/kg) (McConnell et al., 1975).

(d) Marine organisms

1,1,1-Trichloroethane was detected in the following marine organisms (concentration in μg/kg): 14 species of invertebrates (0.03-34); 3 species of algae (9.4-35, including carbon tetrachloride); in the flesh or organs of 9 species of fish (1-26) and 7 species of fish (0.7-47, including carbon tetrachloride); in the organs or eggs of 8 species of sea- and freshwater birds (1.1-43, including carbon tetrachloride); and in the organs of 2 species of mammals (0.3-30, including carbon tetrachloride) (Pearson & McConnell, 1975).

(e) Humans

1,1,1-Trichloroethane has been detected in human expired air, at levels of 0.03-140 μg/hr/subject (Conkle et al., 1975).
2.3 Analysis

Analytical methods to determine halogenated hydrocarbons, including 1,1,1-trichloroethane, in air using gas chromatography and in blood and urine using infra-red spectrometry have been reviewed (Walter et al., 1976). The identification and analysis of 1,1,1-trichloroethane in air, sewage sludge and paint using gas chromatography have also been reviewed (Franklin Institute Research Laboratories, 1975).

Methods used for the analysis of 1,1,1-trichloroethane in environmental samples are listed in Table 1.

Environmental air samples have been analysed by gas chromatography (Lillian et al., 1976) or gas chromatography/mass spectrometry after trapping by a cryogenic technique (Tyson, 1975).

Laser absorption spectroscopy at 9-11 μm has been used to determine 1,1,1-trichloroethane in air samples either alone, with a limit of detection of 29 mg/m³ (5.3 ppm), or in a mixture of gases, with a limit of detection of 50 mg/m³ (9.2 ppm) (Green & Steinfeld, 1976).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 50 male and 50 female B6C3F1 mice, 5 weeks of age, were given technical-grade 1,1,1-trichloroethane containing about 3% para-dioxane and 2% minor impurities in corn oil by gavage on 5 days per week for 78 weeks. Initially, the high and low doses for both male and female mice were 4000 and 2000 mg/kg bw/day; during the 10th week of the study, these doses were increased to 5000 and 2500 mg/kg bw/day; at week 20 they were increased to 6000 and 3000 mg/kg bw/day and maintained at these levels to the end of the study. Time-weighted average doses for the high- and low-dose mice were 5615 and 2807 mg/kg bw/day, respectively. A group of 20 male and 20 female untreated mice were used as controls; no vehicle-control animals were used. In males, 10/20 of the matched controls, 21/50 of the low-dose group, and 25/50 of the high-dose group had died within 1 year after the start of the experiment; in females, the corresponding figures were 1/20, 9/50 and

1The Working Group was aware of studies in progress to assess the carcinogenicity of 1,1,1-trichloroethane in mice by i.p. injection and in mice and rats by oral administration (IARC, 1978).
<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>LIMIT OF DETECTION</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerosols</td>
<td>Analyse directly</td>
<td>GC/MS</td>
<td></td>
<td>Sheinin et al. (1975)</td>
</tr>
<tr>
<td>Air</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td>Trap (charcoal), extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Working range, 904-3790 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977)</td>
</tr>
<tr>
<td>Rural</td>
<td>Trap (porous polymer beads), desorb by heating, retrap in line on GC column</td>
<td>GC/ECD; GC/MS</td>
<td>Working range, 160-700 ng/m³ (30-130 ppt)</td>
<td>Russell &amp; Shadoff (1977)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>Trap in Drechsel flask fitted with rubber septum, sample with gas syringe</td>
<td>GC/ECD</td>
<td>0.5 ng/l</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Water</td>
<td>Sparge (helium), trap on polymer column, desorb by heating, retrap in line on GC column</td>
<td>GC/MS</td>
<td></td>
<td>Coleman et al. (1976) Dowty et al. (1975)</td>
</tr>
</tbody>
</table>

Abbreviations: GC/FID - gas chromatography/flame-ionization detection; ECD - electron capture detection; MS - mass spectrometry
20/50. At 90 weeks, 15 low-dose males, 11 high-dose males, 23 low-dose females and 13 high-dose females were still alive. All animals were killed at 95 weeks. Almost all organs, and all tissues with macroscopically visible lesions, were examined histologically. Three out of 49 males in the high-dose group developed liver-cell adenomas and one a hepatocellular carcinoma. No liver tumours occurred in controls (National Cancer Institute, 1977) [The Working Group noted the poor survival of the treated animals].

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, 7 weeks of age, received technical-grade 1,1,1-trichloroethane containing 3% para-dioxane and 2% minor impurities in corn oil by gavage on 5 days a week for 78 weeks at two dose levels: 750 mg/kg bw/day and 1500 mg/kg bw/day. A group of 20 male and 20 female untreated rats served as matched controls. The animals were killed 110 weeks after the start of treatment. Both males and females given the test chemical exhibited early mortality when compared with untreated controls: only 3% of treated rats survived to termination of the experiment. A few tumours not considered to be related to treatment were observed (National Cancer Institute, 1977) [The Working Group noted the poor survival of the treated animals].

(b) Inhalation and/or intratracheal administration

Rat: Results of a study reported as an abstract indicate that in groups of 96 male and 96 female Sprague-Dawley rats exposed to vapours of 9.5 and 4.7 g/m³ (1750 and 875 ppm) 1,1,1-trichloroethane in air for 6 hrs per day on 5 days a week for 12 months, followed by observation up to 30 months, no increased incidence of tumours was observed (Rampy et al., 1977) [The Working Group noted the incomplete reporting of the experiment].

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

The toxicity of 1,1,1-trichloroethane has been reviewed (Aviado et al., 1976; Stewart, 1968).

The oral LD₅₀ of 1,1,1-trichloroethane in mice and rats is about 11 g/kg bw (Torkelson et al., 1958); the i.p. LD₅₀ in mice is 5 g/kg bw (Klaassen & Plaa, 1966). After inhalation of 98 g/m³ (18,000 ppm) for 3 hrs, 15/21 rats died (Adams et al., 1950).

1,1,1-Trichloroethane causes central nervous system depression in rats. Liver damage has been reported in rats only after exposure to nearly lethal doses (Adams et al., 1950). Continuous inhalation for
14 weeks caused hepatotoxicity in mice (McNutt et al., 1975). Inhalation of 1,1,1-trichloroethane was found to increase hepatic drug metabolism in rats (Lal et al., 1969).

**Embryotoxicity and teratogenicity**

Groups of rats and mice were exposed by inhalation for 7 hrs daily on days 6-15 of gestation to 4.7 g/m³ in air (875 ppm) 1,1,1-trichloroethane; no effects were observed on the average number of implantation sites per litter, litter size, incidence of foetal resorptions, foetal sex ratios or foetal body measurements. No treatment-related increase in the incidence of skeletal or visceral malformations was observed (Schwetz et al., 1975).

**Absorption, distribution, excretion and metabolism**

In mice and rats, 1,1,1-trichloroethane is absorbed through the lungs, gastrointestinal tract and skin (Stewart, 1968; Tsuruta, 1975). After inhalation in mice it was found in brain and kidney at approximately equal concentrations and in liver at higher concentrations (Holmberg et al., 1977). In rats, more than 98% of the absorbed dose was rapidly expired unchanged; 0.5% was converted to CO₂. Much of the remainder was excreted as the glucuronide of 2,2,2-trichloroethanol in the urine (Hake et al., 1960). Small amounts of trichloroacetic acid were found in the urine of rats (Eben & Kimmerle, 1974). Unlike 1,1,2,2-tetrachloroethane or the isomer 1,1,2-trichloroethane, 1,1,1-trichloroethane is not dechlorinated in vitro in the presence of hepatic microsomes, NADPH and O₂ (Van Dyke & Wineman, 1971).

**Mutagenicity and other related short-term tests**

1,1,1-Trichloroethane was mutagenic in Salmonella typhimurium strain TA100, with or without a microsomal activation system (Simmon et al., 1977).

**(b) Humans**

At least 30 fatalities have been associated with exposure to 1,1,1-trichloroethane, mostly due to deliberate inhalation or to accidental occupational exposures. Death was due to suffocation; the lungs showed acute oedema and congestion (Bass, 1970; Caplan et al., 1976; Stahl et al., 1969). Exposure to 1.36–2.7 g/m³ (250–500 ppm) of the solvent impairs psychophysiological functions (Gamberale & Hultengren, 1973). Generally, the toxic effects of 1,1,1-trichloroethane in humans are similar to those in animals (Stewart, 1968; Torkelson et al., 1958).

1,1,1-Trichloroethane may be absorbed through the lungs, gastrointestinal tract or skin (Fukabori et al., 1977; Stewart, 1968) and is excreted unchanged via the lungs for many hours after exposure.
1,1,1-TRICHLOROETHANE

(Astrand et al., 1973; Stewart et al., 1961). A small percentage is metabolized to 2,2,2-trichloroethanol and trichloroacetic acid and excreted in the urine (Fukabori et al., 1976; Seki et al., 1975; Stewart, 1968).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

1,1,1-Trichloroethane was tested in one experiment in mice and in one in rats by oral administration and in one experiment by inhalation exposure in rats. Although a few liver tumours were observed in male mice, these experiments were considered to be inadequate.

1,1,1-Trichloroethane is mutagenic in Salmonella typhimurium.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production of this compound and its use as a chemical intermediate and in metal cleaning operations over several decades suggest that widespread human exposure occurs. This is confirmed by many reports of its occurrence in the general environment.

4.3 Evaluation

The available data do not permit an evaluation of the carcinogenicity of 1,1,1-trichloroethane to be made.
5. References


Bureau International Technique des Solvants Chlorés (1976) Standardization of methods for the determination of traces of some volatile chlorinated aliphatic hydrocarbons in air and water by gas chromatography. Anal. chim. acta., 82, 1-17


Gehring, P.J. (1968) Hepatotoxic potency of various chlorinated hydrocarbon vapours relative to their narcotic and lethal potencies in mice. Toxicol. appl. Pharmacol., 13, 287-298


Rampy, L.W., Quast, J.F., Leong, B.K.J. & Gehring, P.J. (1977) Results of long-term inhalation toxicity studies on rats of 1,1,1-trichloroethane and perchloroethylene formulations (Abstract) In: Proceedings of the International Congress of Toxicology, Toronto, Canada, 1977, p. 27


1,1,2-TRICHLOROETHANE

1. Chemical and Physical Data

1.1 Synonyms and trade names


Chem. Abstr. Name: 1,1,2-Trichloroethane

Synonyms: Ethane trichloride; β-trichloroethane; 1,2,2-trichloroethane; vinyl trichloride

Trade name: β-T

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{Cl} & \quad \text{C} \quad \text{C} \quad \text{Cl} \\
\text{H} & \quad \text{H}
\end{align*}
\]

\( \text{C}_2\text{H}_3\text{Cl}_3 \quad \text{Mol. wt: 133.4} \)

1.3 Chemical and physical properties of the pure substance

From Hardie (1964), unless otherwise specified

(a) Description: Colourless liquid

(b) Boiling-point: 113.5°C

(c) Melting-point: -37°C

(d) Density: \( d^2_0 \) 1.4411

(e) Refractive index: \( n^2_0 \) 1.47064

(f) Spectroscopy data: Infra-red, Raman, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).
(g) **Solubility:** Soluble in water (0.45 g/100 ml water at 20°C); miscible with chlorinated solvents and soluble in other common organic solvents

(h) **Vapour pressure** is 16.7 mm at 20°C.

(i) **Stability:** Stable in air at ordinary temperatures; in the absence of air or water it is stable up to about 110°C; in the presence of water, hydrolysis occurs at its boiling-point.

(j) **Reactivity:** Dehydrochlorinates to 1,1-dichloroethylene when heated with aqueous caustic soda; reaction with an aqueous lime suspension yields a mixture of 1,1- and 1,2-dichloroethylene; can be chlorinated in the vapour phase to 1,1,1,2-tetrachloroethane

(k) **Conversion factor:** 1 ppm in air is equivalent to 5.45 mg/m³.

1.4 **Technical products and impurities**

In the US, 1,1,2-trichloroethane is available as a technical grade product, which may be stabilized (identity of stabilizers unknown). It typically meets the following specifications: a colourless liquid, free of suspended matter and sediment; distillation range at 760 mm, 110.0-115.5°C; specific gravity, 25°C/25°C, 1.427-1.437; water content, 200 mg/kg max; acidity (as HCl), 100 mg/kg max; and non-volatile residue, 20 mg/kg max.

2. **Production, Use, Occurrence and Analysis**

2.1 **Production and use**

(a) **Production**

1,1,2-Trichloroethane was first prepared in about 1840 by Regnault by the reaction of chloroethylene with antimony pentachloride (Hardie, 1964; Prager et al., 1918). It is produced in the US either by reaction of acetylene gas with a mixture of hydrogen chloride and chlorine in the presence of a catalyst or by chlorination of ethylene followed by chlorination of the 1,2-dichloroethane intermediate. Most 1,1,2-trichloroethane produced in the US is made by the chlorination of ethylene (Hardie, 1964).
In Japan, 1,1,2-trichloroethane is produced by chlorination of ethylene.

Commercial production of 1,1,2-trichloroethane in the US was first reported during 1941-1943 (US Tariff Commission, 1945). In 1976, only one US company reported commercial production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977); however, an additional US company produces it as an intermediate in vinlylidene chloride production. Data on US imports and exports were not available.

No data on its production in Europe were available. It has been produced commercially in Japan since 1951. In 1976, 3 companies produced approximately 36 million kg; none was imported or exported.

(b) Use

1,1,2-Trichloroethane is used in the US as an intermediate in the production of vinlylidene chloride, as a solvent and as a component of adhesives.

An estimated 77 million kg vinlylidene chloride (see IARC, 1979) were produced and isolated in the US in 1974, and approximately 53% of this was made from 1,1,2-trichloroethane. Vinlylidene chloride is also produced by one US company as an unisolated chemical intermediate in the production of 1,1,1-trichloroethane; and in 1976, an estimated 50 million kg were produced from 1,1,2-trichloroethane.

A very little 1,1,2-trichloroethane is used as a solvent (Hardie, 1964).

No data on its use in Europe were available. In Japan, 1,1,2-trichloroethane is used captively in vinlylidene chloride production.

1,1,2-Trichloroethane is approved by the US Food and Drug Administration as a constituent of adhesives used as components of articles intended for use in packaging, transporting or holding food (US Food & Drug Administration, 1977).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to 1,1,2-trichloroethane not exceed an 8-hr time-weighted average of 45 mg/m³ (10 ppm) in the workplace air in any 8-hr work shift of a 40-hr work week (US Occupational Safety & Health Administration, 1977).
2.2 Occurrence

1,1,2-Trichloroethane is not known to occur as a natural product.

(a) Water

1,1,2-Trichloroethane was one of 72 compounds detected in drinking-water supplies sampled in 5 US cities (Coleman et al., 1976). It has been detected in other drinking-water samples at levels of < 0.1-8.5 μg/l (Safe Drinking Water Committee, 1977) and 0.45 μg/l (Eurocop-Cost, 1976). It has also been detected in industrial effluent discharges, at a level of 5.4 mg/l (Eurocop-Cost, 1976).

In an estimated 75 million kg of chlorinated aliphatic hydrocarbons (also known as EDC-tar) formed as by-products during polyvinyl chloride production and dumped at sea, 1,1,2-trichloroethane constituted about 40% of the weight of one distillate (Rosenberg et al., 1975).

(b) Occupational exposure

A 1974 National Occupational Hazard Survey indicated that workers primarily exposed to 1,1,2-trichloroethane were those in the blast furnace and steel mill, telephone communication, engineering and scientific instrument manufacturing industries (National Institute for Occupational Safety & Health, 1977a).

2.3 Analysis

A sampling and analytical method recommended by the US National Institute for Occupational Safety and Health for determining 1,1,2-trichloroethane in workplace atmospheres is based on collection on charcoal, desorption in carbon disulphide, followed by analysis by gas chromatography with flame ionization detection for a validated range of 26-111 mg/m³ in air (National Institute for Occupational Safety & Health, 1977b).

Gas chromatography-mass spectrometry has been used to determine 1,1,2-trichloroethane in ambient air, with a limit of detection of 27 ng/m³ (5 ppt) (Grimsrud & Rasmussen, 1975) and in drinking-water by sparging, trapping from the sparge gas and analysing from the trap in-line, with a limit of detection at the μg/l (ppb) level (Coleman et al., 1976).
3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3F1 mice, 5 weeks of age, received technical-grade 1,1,2-trichloroethane in corn oil by gavage on 5 consecutive days a week for 78 weeks. The experiment was terminated after an additional 12 weeks of observation, at a total of 90 weeks. High-dose and low-dose animals received, respectively, 300 and 150 mg/kg bw/day for 8 weeks, and then 400 and 200 mg/kg bw/day for 70 weeks, followed by 12-13 weeks without treatment. The time-weighted average doses were 390 and 195 mg/kg bw/day. Groups of 20 male and 20 female mice either received corn oil alone and served as matched vehicle controls or remained untreated and served as matched untreated controls. At least 50% of the male mice in each group were alive at week 86; 50% of the female mice were still alive after 81, 58, 89 and 90 weeks in the high-dose, low-dose, vehicle control and untreated control groups, respectively. The incidence of hepatocellular carcinomas was increased significantly (P < 0.01) in all treated groups: in males, 2/17 (12%) untreated controls, 2/20 (10%) vehicle controls, 18/49 (37%) low-dose animals and 37/49 (76%) high-dose animals; in females, 2/20 (10%) untreated controls, 0/20 vehicle controls, 16/48 (33%) low-dose animals and 40/45 (89%) high-dose animals. Adrenal phaeochromocytomas were present in 8/48 (17%) high-dose males and in 12/43 (28%) high-dose females, but in no other groups (National Cancer Institute, 1978).

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, 6 weeks old, received technical-grade 1,1,2-trichloroethane in corn oil by gavage on 5 consecutive days a week for 78 weeks. High-dose and low-dose groups received, respectively, 70 and 35 mg/kg bw/day for 20 weeks, then 100 and 50 mg/kg bw/day for 58 weeks and were then left untreated for the subsequent 34-35 weeks. The time-weighted average doses were 92 and 46 mg/kg bw/day. Groups of 20 male and 20 female rats either received corn oil alone and served as matched vehicle controls or remained untreated and served as untreated matched controls. At least 50% of the male rats in the high-dose, low-dose and untreated control groups survived more than 96 weeks; 50% of females in the high-dose, low-dose and untreated control groups survived more than 105 weeks. Vehicle control groups had unexpectedly poor survival, with only 5% (1/20) of males and 20% (4/20) of females still alive at the end of the treatment period.

1The Working Group was aware of a completed but as yet unpublished study in mice given 1,1,2-trichloroethane by i.p. injection (IARC, 1978).
study; the authors did not, therefore, include them in statistical comparisons. No statistically significant increase in tumour incidence was found, for any type of tumour, either in males or in females (see Table 1) (National Cancer Institute, 1978).

3.2 Other relevant biological data

(a) Experimental systems

The oral LD$_{50}$ of 1,1,2-trichloroethane in rats is 835 mg/kg bw (Smyth et al., 1969); the i.p. LD$_{50}$ in mice is 500 mg/kg bw (Klaassen & Plaa, 1966).

1,1,2-Trichloroethane depresses the central nervous system, is hepatotoxic and induces kidney damage in mice (Gehring, 1968; Klaassen & Plaa, 1966; Plaa & Larson, 1965; Plaa et al., 1958). It is less hepatotoxic than chloroform or carbon tetrachloride but more hepatotoxic than 1,1,1-trichloroethane, trichloroethylene or dichloromethane (Gehring, 1968; Klaassen & Plaa, 1966). In mice, hepatic dysfunction is observed at the LD$_{10}$; higher doses cause centrilobular necrosis (Klaassen & Plaa, 1966). It is a skin irritant in guinea-pigs (Kronevi et al., 1977).

No data on the embryotoxicity or teratogenicity of 1,1,2-trichloroethane were available.

Following an i.p. dose of 0.1-0.2 g/kg bw $^{14}$C-1,1,2-trichloroethane to mice, 73-87% was found in the urine and 16-22% was expired (40% unchanged and 60% as CO$_2$); 1-3% of the dose remained in the animal. Three metabolites were identified in the urine: chloroacetic acid, S-carboxymethylcysteine and thiodiacetic acid; small amounts of glycolic acid, 2,2-dichloroethanol, 2,2,2-trichloroethanol, oxalic acid and trichloroacetic acid were also found, suggesting that the metabolism of 1,1,2-trichloroethane proceeds via the formation of chloroacetaldehyde (Yilner, 1971).

The enzymic dechlorination of 1,1,2-trichloroethane in vitro depends on the presence of hepatic microsomes, NADPH and oxygen and was inducible by in vivo treatment with phenobarbital and benzo[a]pyrene (Van Dyke & Wineman, 1971).

1,1,2-Trichloroethane (20, 40 and 60 µmol/plate) was not mutagenic in a plate assay with *Salmonella typhimurium* strain TA1535 with or without a microsomal activation system (Rannug et al., 1978).

(b) Humans

1,1,2-Trichloroethane has a narcotic action at low concentrations and has an irritant effect on the eyes and the mucous membranes of the
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<th>TOTAL NO. OF TUMOURS</th>
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respiratory tract. When in contact with the skin it produces cracking and erythema. Long-term exposure to the vapour produces chronic gastric symptoms, fat deposition in the kidneys and damage to the lungs (Hardie, 1964).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

1,1,2-Trichloroethane was tested in one experiment in mice and in one in rats by oral administration. It produced hepatocellular carcinomas and adrenal phaeochromocytomas in mice of both sexes. The study in rats gave inconclusive results.

1,1,2-Trichloroethane was not mutagenic in Salmonella typhimurium.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production of 1,1,2-trichloroethane over several decades, primarily for use as an intermediate in the manufacture of vinylidene chloride, indicates that occupational exposure occurs. Reports of its occurrence in the environment indicate that the general population is also exposed.

4.3 Evaluation

There is limited evidence that 1,1,2-trichloroethane is carcinogenic in mice.
5. References


Gehring, P.J. (1968) Hepatotoxic potency of various chlorinated hydrocarbon vapours relative to their narcotic and lethal potencies in mice. Toxicol. appl. Pharmacol., 13, 287-298


Kronevi, T., Wahlberg, J. & Holmberg, B. (1977) Morphological lesions in guinea pigs during skin exposure to 1,1,2-trichloroethane. Acta pharmacol. toxicol., 41, 298-305


Safe Drinking Water Committee (1977) Drinking Water and Health, Washington DC, National Academy of Sciences, pp. 775-777


Yllner, S. (1971) Metabolism of 1,1,2-trichloroethane-1,2-\textsuperscript{14}C in the mouse. Acta pharmacol. toxicol., 30, 248-256
TRICHLOROETHYLENE

This compound was considered by a previous Working Group, in February 1976 (IARC, 1976a). Since that time new data have become available and these have been incorporated into the monograph and taken into account in the present evaluation.

Two reviews on trichloroethylene are available (Lyman, 1978; Mercier, 1977).

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 79-01-6

Chem. Abstr. Name: Trichloroethylene

Synonyms: Acetylene trichloride; 1-chloro-2,2-dichloroethylene; 1,1-dichloro-2-chloroethylene; ethinyl trichloride; ethylene trichloride; TCE; Tri; trichlorethylene; 1,1,2-trichloroethylene

Trade names: Algylen; Anamenth; Benzinol; Blacosolv; Blancosolv; Cecolene; Chlorilen; Chlorylea; Chlorylen; Chorylen; Circosolv; Crawhaspol; Densinfluat; Dow-Tri; Dukeron; Fleck-Flip; Flock Flip; Fluate; Gemalgene; Germalgene; Lanadin; Lethurin; Narcogen; Narkogen; Narkosoid; Nialk; Perma-A-Chlor; Perm-A-Clor; Petzinol; Philex; Threthylene; Trethylene; Triad; Trial; Triasol; Trichloran; Trichloren; Triclene; Tri-Clene; Trieline; Trielin; Triklone; Trilen; Trilene; Triline; Trimar; Triol; TRI-plus; TRI-plus M; Vestrol; Vitran; Westrosol

1.2 Structural and molecular formulae and molecular weight

\[
C_2HCl_3 \quad \text{Mol. wt: } 131.4
\]
1.3 Chemical and physical properties of the pure substance

From Weast (1976), unless otherwise specified

(a) **Description**: Colourless liquid (Irish, 1963)

(b) **Boiling-point**: 87°C

(c) **Melting-point**: -73°C

(d) **Freezing-point**: -86.8°C (Irish, 1963)

(e) **Density**: $d^0_{20} 1.4642$

(f) **Refractive index**: $n^0_D 1.4773$

(g) **Spectroscopy data**: $\lambda_{\text{vap}} < 200$ nm; infra-red, Raman, nuclear magnetic resonance and mass spectral data have been tabulated (Grasselli & Ritchey, 1975).

(h) **Solubility**: Miscible with water (0.1% w/v at 20°C) (Irish, 1963); miscible with acetone, ethanol, diethyl ether, chloroform and oils (Lloyd et al., 1975)

(i) **Vapour density**: 4.54 (air = 1) (Irish, 1963)

(j) **Vapour density**: 4.54 (air = 1) (Irish, 1963)

(k) **Stability**: Nonflammable; when pure and containing a stabilizer, it is stable in presence of air, moisture, light and in contact with metals up to 130°C. When heated with ozone, it decomposes rapidly into products such as hydrogen chloride, phosgene, carbon monoxide and chlorine peroxide. At 700°C and above, the vapour decomposes to give a mixture of dichloroethylene, tetrachloroethylene, carbon tetrachloride, chloroform and methyl chloride (Hardie, 1964). Upon contact with certain metals, high temperatures, open flame or ultraviolet light, it decomposes almost instantly to phosgene and/or hydrogen chloride, chlorine and dichloroacetyl chloride. In the presence of alkali, trichloroethylene decomposes to highly toxic dichloroacetylene (US Occupational Safety & Health Administration, 1975).
(1) **Reactivity:** The most important reaction of trichloroethylene is its oxidative breakdown of atmospheric oxygen, greatly accelerated by elevation of temperature and exposure to light, especially ultra-violet; not hydrolysed by water under normal conditions; reacts with alkali under pressure at 150°C to produce glycolic acid and with sulphuric acid to give mono-chloroacetic acid (Hardie, 1964)

(m) **Conversion factor:** 1 ppm in air is equivalent to 5.37 mg/m³.

1.4 **Technical products and impurities**

Trichloroethylene is available in the US in high-purity, electronic USP, technical, metal degreasing and extraction grades (Hawley, 1971). Typical analysis of a commercial grade is: boiling-range at 760 mm, 86.6-87.8°C; density, $d_{15}^{20}$ 1.467-1.471; acidity (as HCl), 0.0005% max; alkalinity (as NaOH), 0.001% max; no free halogen; residue on evaporation, 0.005 max; moisture content, not cloudy at -12°C.

Antioxidants, such as amines (0.001-0.01% or more) (Copelin, 1957) or combinations of epoxides such as epichlorohydrin (see also IARC, 1976b) and esters (0.2-2% total) (Starks, 1956), are added to trichloroethylene.

Specifications for trichloroethylene produced in Japan are: specific gravity (15°C/40°C), 1.4680; boiling-range, 86.5-88.2°C; nonvolatile matter, 0.005% max; acid content (as HCl), 0.0002% max.

2. **Production, Use, Occurrence and Analysis**

2.1 **Production and use**

(a) **Production**

Trichloroethylene was prepared by Fischer in 1864 during experiments on the reduction of hexachloroethane with hydrogen (Hardie, 1964). The first commercial method for its preparation was the dehydrochlorination of acetylene-derived 1,1,2,2-tetrachloroethane (see monograph, p. 477) by reaction with calcium hydroxide or by gas-phase pyrolysis. Although this method is still used today, over 90% of the trichloroethylene produced in the US is prepared by the chlorination and dehydrochlorination of 1,2-dichloroethane (see monograph, p. 429). The same process is used in Japan.
Trichloroethylene has been produced commercially in Austria and the UK since 1908, in Germany since 1910, in the US since 1925 (Hardie, 1964) and in Japan since 1935. Production of trichloroethylene in the US in 1977 was 132 million kg (US International Trade Commission, 1977); output has been decreasing since 1970, when a reported 277 million kg were produced by 7 companies (US Tariff Commission, 1972), due primarily to legislation restricting the use and emissions of trichloroethylene and to the closing of 3 acetylene-based and 1 ethylene-based plants.

US exports of trichloroethylene in 1976 were 16 million kg, mostly to the Federal Republic of Germany (3.8 million kg), France (3.4 million kg), Mexico (2.1 million kg) and Brazil (2 million kg) (US Department of Commerce, 1977a). US imports during that year totalled 7 million kg (US Department of Commerce, 1977b).

At least 9 companies in western Europe produce trichloroethylene, with a total production in excess of 200 million kg/year. In at least 3 countries (the Federal Republic of Germany, France and the UK) annual production is estimated to exceed 50 million kg/year. These countries and Italy import and export 10-50 million kg/year trichloroethylene. Annual production of trichloroethylene in eastern Europe is estimated to be more than 100 million kg.

In Japan, 4 companies produced 80 million kg trichloroethylene in 1976, compared with 106 million kg in 1972; in 1976, 11 million kg trichloroethylene were exported.

(b) Use

Of the trichloroethylene produced in the US in 1977, 82% was used for vapour degreasing of fabricated metal parts, 15% was exported and the remainder (3%) was used in a variety of miscellaneous applications.

Trichloroethylene is widely used in vapour degreasing, since all of its physical and chemical properties fall within the limits required in such processes. One disadvantage of trichloroethylene in this use is its high photochemical reactivity, which causes smog and led to restrictions on its use. Since trichloroethylene decomposes rapidly upon exposure to high temperatures, open flame or ultra-violet light [see section 1.3 (k)], a proposed standard was issued by the US Occupational Safety and Health Administration on 20 October, 1975, which requires that operations involving high temperatures, open flames or ultra-violet light take place outside areas in which trichloroethylene vapours are present, unless such operations are appropriately shielded and ventilated (US Occupational Safety & Health Administration, 1975).

Miscellaneous applications of trichloroethylene include its use as a solvent in the textile industry; as a solvent for adhesives and lubricants; and as a low-temperature heat transfer fluid. It has also
been used as a component in several consumer products (e.g., spot removers, cleaning fluids for rugs) (Lloyd et al., 1975).

A pharmaceutical grade of trichloroethylene is used as a general anaesthetic in surgical, dental and obstetrical procedures and as an analgesic in the treatment of trigeminal neuralgia. It has been used as a disinfectant and detergent for skin, minor wounds and surgical instruments. It has also been used on a variety of animals as a volatile anaesthetic.

The use of trichloroethylene as an extraction solvent (e.g., for use in the manufacture of decaffeinated coffee and for the extraction of spice oleoresins) was approved by the US Food and Drug Administration (FDA) for many years. However, on 27 September 1977, the FDA proposed regulations prohibiting the use of trichloroethylene as a food additive, directly or indirectly. Specific examples of practices to be prohibited include use in hop extraction, decaffeination of coffee, the isolation of spice oleoresins, adhesive coatings and components, and in vinyl chloride-hexene-1 copolymers. Food containing any added or detectable level of trichloroethylene will be deemed to be adulterated when the final order has been issued. On the same date, the FDA also proposed a regulation that any human drug containing trichloroethylene will be considered a new drug and will be deemed to be misbranded; under this regulation anaesthetics containing trichloroethylene would be banned. It was also proposed to declare trichloroethylene a deleterious substance, thereby causing any cosmetic product containing it to be deemed adulterated under existing law. The FDA also proposed a regulation prohibiting the use of trichloroethylene as an additive in animal and pet food; such practices as the use of trichloroethylene for the extraction of oil-seed products would be prohibited. The FDA also proposed an order prohibiting the use of trichloroethylene in animal drug products, such as its use as an inhalation anaesthetic, skin disinfectant and in detergents (US Food & Drug Administration, 1977).

No data on its use in Europe were available. In 1977, trichloroethylene was used in Japan in metal cleaning (63%), solvent and other uses (23%) and exports (14%).

It was reported in May 1978 that trichloroethylene has been accepted by the US Environmental Protection Agency as a candidate for issuance of a notice of a rebuttable presumption against renewal of registration (RPAR) (see General Remarks on Substances Considered, p. 31) on the basis of its possible carcinogenicity (Anon., 1978).

The US Occupational Safety and Health Administration's health standards for exposure to air contaminants require that an employee's exposure to trichloroethylene not exceed an 8-hr time-weighted average of 535 mg/m³ (100 ppm) in the working atmosphere in any 8-hr work shift.
of a 40-hr work week (US Occupational Safety & Health Administration, 1975). The corresponding standard in the Federal Republic of Germany is 260 mg/m³, that in the German Democratic Republic and Czechoslovakia, 250 mg/m³ and that in Sweden, 160 mg/m³ (Winell, 1975).

It was proposed on 20 October 1975 that the maximum allowable concentration in the US be reduced from 1070 mg/m³ (200 ppm) to 805 mg/m³ (150 ppm) (US Occupational Safety & Health Administration, 1975). The maximum acceptable ceiling concentration in the USSR is 10 mg/m³ (1.86 ppm) (Winell, 1975).

The US National Institute for Occupational Safety and Health has recently recommended that occupational exposure to halogenated anaesthetic agents, including trichloroethylene, be controlled so that no worker is exposed to concentrations greater than 10.7 mg/m³ (2 ppm) (National Institute for Occupational Safety & Health, 1977b).

2.2 Occurrence

Trichloroethylene is not known to occur as a natural product. Its occurrence in air, water, soil and sediments, food, marine organisms and humans has been reviewed (Battelle Columbus Laboratories, 1977).

(a) Air

The US Environmental Protection Agency has estimated that approximately 60% of the total annual world production of trichloroethylene is released to the environment, with annual emissions of about 540 million kg to the atmosphere and 9.1 million kg to the ocean (Fuller, 1976). The dispersive uses of trichloroethylene (metal cleaning and solvent applications) have been estimated to result in annual emissions of 192 million kg in the US (Fuller, 1976) and 100 million kg in Japan (Ohta et al., 1976).

The background ambient air concentration of trichloroethylene has been reported for several locations: (1) western Eire, levels of 80 ng/m³ (15 ppt); (2) over the North Atlantic, < 27 ng/m³ (5 ppt) (Lovelock, 1974); (3) in a rural area, < 27 ng/m³ (5 ppt) (Grimsrud & Rasmussen, 1975); (4) in the northern hemisphere, about 80 ng/m³ (15 ppt); and (5) in the southern hemisphere, about 8 ng/m³ (1.5 ppt) (Cox et al., 1976).

Trichloroethylene has also been detected in ambient air: (1) in north-eastern US, at typical levels of 1 µg/m³ (0.18 ppb) in urban areas and < 0.1 µg/m³ (0.02 ppb) in rural areas (Lillian et al., 1975); (2) in Michigan, at levels of 150-500 ng/m³ (30-90 ppt) (Russell & Shadoff, 1974).

1 ppt in air is equivalent to 5.37 ng/m³.
2 ppb in air is equivalent to 5.37 µg/m³.
TRICHLORETHYLENE

(1977); (3) at 4 sites in California, at levels of 83-1670 ng/m³
(15.6-310.8 ppt) (Singh, 1976); (4) at 5 US land stations, at levels
ranging from 2-28 ng/m³ (0.4-5.2 ppt); (5) at 11 sea stations, at
levels ranging from 1-22 ng/m³ (0.2-4 ppt) (Murray & Riley, 1973);
(6) in Tokyo, at 26 sites, at average levels of 6.4 μg/m³ (1.2 ppb)
(Ohta et al., 1976); and (7) in Manchester, UK, at levels of 5.35-
343 μg/m³ (1-64 ppb) (Pearson & McConnell, 1975).

(b) Water

Trichloroethylene has been found in 2 raw-water samples, 1 lake-water
sample, 10 finished drinking-water samples, 1 raw sewage sample, 5 rivers
and samples of effluent from 4 chemical plants and 4 sewage treatment
plants in the US (Shackelford & Keith, 1976). It was detected in
samples of surface-water from 88/204 sites near heavily industrialized
areas, at levels > 1 μg/l (Ewing et al., 1977).

It has also been detected in: (1) a river, at a level of 25 μg/l
(Rook et al., 1975); (2) ground-water near waste deposits, at a level
of 100 μg/l (Kotzias et al., 1975); (3) the drinking-water of 5
cities, at levels of 0-0.5 μg/l (Coleman et al., 1976); and (4)
influent and effluent water from a sewage treatment plant, at levels of
8.6-40.4 μg/l (Bellar et al., 1974).

(c) Soil and sediments

Concentrations of trichloroethylene in soil and sediment near
production and user sites in the US ranged from 0- > 100 μg/kg
(Battelle Columbus Laboratories, 1977).

(d) Food and drink

Trichloroethylene has been detected in the following foodstuffs
in the UK: dairy products (0.3-10 μg/kg), meat (12-22), oils and fats
(0-19), beverages (0-60) and fruits and vegetables (McConnell et al.,
1975). Traces of trichloroethylene have also been found in edible
oils after extraction (Gracián & Martel, 1972).

(e) Marine organisms

Trichloroethylene has been detected in 3 species of mollusc at
levels of 0-250 ng/g, and in 5 species of fish at levels of 0-479 ng/g
(dry weight) (Dickson & Riley, 1976).
(f) Humans

Trichloroethylene has been detected in post-mortem human tissue samples, at levels of < 1-32 µg/kg (wet tissue) (McConnell et al., 1975) and in human expired air, at levels of 0-3.9 µg/hr/subject (Conkle et al., 1975).

It has been estimated that about 60,000 people are exposed annually to trichloroethylene as an anaesthetic (Fuller, 1976).

(g) Occupational exposure

Occupational exposure to trichloroethylene has been reviewed (National Institute for Occupational Safety & Health, 1973).

Trichloroethylene has been detected in the atmosphere of dry-cleaning plants (Babenko, 1974). Levels of 1076-43,000 mg/m³ (200-8000 ppm) were found in a small factory (Kleinfeld & Tabershaw, 1954).

Concentrations of trichloroethylene vapour in a dial assembly workshop ranged from < 135 - 538 mg/m³ (25-100 ppm); those in the degreasing room were 800-1350 mg/m³ (150-250 ppm) (Takamatsu, 1962).

The concentration to which surgeons and nurses were exposed in operating-rooms varied from 1.6-554 mg/m³ (0.3-103 ppm) (Corbett, 1973). About 5000 medical, dental and hospital personnel are routinely exposed to trichloroethylene.

A 1974 National Occupational Hazard Survey indicated that workers primarily exposed to trichloroethylene are those in hospitals, in the aircraft manufacturing industry, in blast furnaces and in steel mills (National Institute for Occupational Safety & Health, 1977a).

(h) Other

Trichloroethylene has been detected as a trace impurity in helium (Schehl, 1973).

2.3 Analysis

A review of methods for the analysis of trichloroethylene in wastetreatment plant sludge was made by Camisa (1975). Analytical methods to determine trichloroethylene in air, oleoresins, blood and urine have also been reviewed (Kouer, 1975; Walter et al., 1976).

Methods used for the analysis of trichloroethylene in environmental samples are listed in Table 1.
### Table 1. Methods for the Analysis of Trichloroethylene

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Extraction/Clean-Up</th>
<th>Detection</th>
<th>Limit of Detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough syrups and</td>
<td>Transfer to ethanol, dilute as appropriate, transfer to separator containing 10%</td>
<td>IR</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>encapsulated liquids</td>
<td>sucrose solution and carbon disulphide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Air</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td>Trap on charcoal, extract (carbon disulphide)</td>
<td>GC/FID</td>
<td>Useful range, 519-2176 mg/m³</td>
<td>National Institute for Occupational Safety &amp; Health (1977c)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Trap in Drechsel flask fitted with rubber septum, sample with gas syringe</td>
<td>GC/ECD</td>
<td>1 µg/m³</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Analyse directly</td>
<td>GC/ECD</td>
<td>10 mg/m³</td>
<td>Krynska et al. (1976)</td>
</tr>
<tr>
<td>Rural</td>
<td>Trap on porous polymer, desorb by heating, retrap in line on GC column</td>
<td>GC/ECD; GC/MS</td>
<td>160 ng/m³ (30 ppt)</td>
<td>Russell &amp; Shadoff (1977)</td>
</tr>
<tr>
<td>Atmosphere</td>
<td>Analyse directly</td>
<td>GC/MS</td>
<td>27 ng/ml (5 ppt)</td>
<td>Grimsrud &amp; Rasmussen (1975)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Analyse directly</td>
<td>Carbon dioxide laser</td>
<td>1.8 µg/m³ (0.7 ppb)</td>
<td>Kreuzer et al. (1977)</td>
</tr>
<tr>
<td>Ambient</td>
<td>Analyse directly</td>
<td>Carbon dioxide laser</td>
<td>23 µg/m³ (4.2 ppb)</td>
<td>Schnell &amp; Fischer (1975)</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea- and fresh-water</td>
<td>Extract (pentane), dry</td>
<td>GC/ECD</td>
<td>50 ng/l</td>
<td>Bureau International Technique des Solvants Chlorés (1976)</td>
</tr>
<tr>
<td>Waste-water</td>
<td>Extract (freon)</td>
<td>GC/FID</td>
<td>0.7 ng</td>
<td>Austern et al. (1974)</td>
</tr>
<tr>
<td>River water</td>
<td>Headspace analysis</td>
<td>GC/MS</td>
<td></td>
<td>Rook et al. (1975)</td>
</tr>
<tr>
<td>SAMPLE TYPE</td>
<td>EXTRACTION/CLEAN-UP</td>
<td>DETECTION</td>
<td>LIMIT OF DETECTION</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Drinking-water</td>
<td>Inject directly</td>
<td>GC/ECD</td>
<td>2 ( \mu )g/l</td>
<td>Nicholson et al. (1977)</td>
</tr>
<tr>
<td>Tap-water</td>
<td>Inject directly</td>
<td>GC/MS</td>
<td>0.2 ( \mu )g/l</td>
<td>Fujii (1977)</td>
</tr>
<tr>
<td>Food</td>
<td>Dilute with ethanol, add internal standard</td>
<td>GC/microcoulometry</td>
<td></td>
<td>Horwitz (1975)</td>
</tr>
<tr>
<td>Spice oleoresins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological</td>
<td>Analyse directly, using precolumn on GC and internal standard</td>
<td>GC/FID</td>
<td></td>
<td>Cole et al. (1975a,b)</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Headspace analysis</td>
<td>GC/FID</td>
<td>0.2 ( \mu )g</td>
<td>Drexler &amp; Osterkamp (1977)</td>
</tr>
<tr>
<td>Oils and liquid paraffin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IR - infra-red spectrometry; GC/FID - gas chromatography/flame-ionization detection; ECD - electron capture detection; MS - mass spectrometry
Use of gas chromatography with electron capture detection to detect trichloroethylene residues in grain has been studied collaboratively by 8 European laboratories. The limit of detection ranged from 0.005-0.2 mg/kg (Panel on Fumigant Residues in Grain, 1974). Gas chromatography has also been used by Kuchinskii (1977) and Lillian et al. (1975).

A system to determine trichloroethylene in water is described by Ellison & Wallbank (1974).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

Oral administration

Mouse: Groups of 50 male and 50 female B6C3Fl hybrid mice, 5 weeks old, were administered 99% pure trichloroethylene, containing 0.19% 1,2-epoxybutane and 0.09% epichlorohydrin (see IARC, 1976b) in corn oil by gavage on 5 days a week for 78 weeks. High-dose males received 2000-2400 mg/kg bw/day, and females 1400-1800 mg/kg bw/day; low-dose males and females received 1000-1200 mg/kg bw/day and 700-900 mg/kg bw. All surviving animals were observed until they were 95 weeks of age. Time-weighted average doses were 1169 and 869 in low-dose males and females and 2339 and 1739 mg/kg bw/day in high-dose males and females. Groups of 20 male and 20 female mice served as vehicle-treated matched controls. Survival was reduced in high-dose males and control males. Hepatocellular carcinomas occurred in 1/20 control males and 0/20 control females, in 26/50 low-dose males and 4/50 low-dose females, and in 31/48 high-dose males and 11/47 high-dose females. Metastases of the liver-cell tumours to the lung were found in 7/98 treated males and in 1 control male. The first hepatocellular carcinoma was observed in a mouse treated with the high dose of trichloroethylene which died during week 27. Lung tumours occurred in treated animals of both sexes: 5/50 (5 adenomas) in males and 4/50 (2 adenomas, 2 carcinomas) in females in the low-dose group, and 2/48 (1 adenoma, 1 carcinoma) in males and 7/47 (5 adenomas, 2 carcinomas) in females treated with the high dose of trichloroethylene. Among controls, only one lung adenoma was reported in a

The Working Group was aware of studies in progress to assess the carcinogenicity of trichloroethylene in mice by skin, subcutaneous and oral administration (IARC, 1978a) and of an inhalation study in rats and mice carried out under contract to the Manufacturing Chemist's Association (Toxicology Information Program, 1976). Preliminary results of the inhalation study (Page & Arthur, 1978) indicate findings similar to those of the National Cancer Institute (1976).
female (National Cancer Institute, 1976) [The Working Group noted that the low-dose males and females also received 1 and 0.7 mg/kg bw/day epichlorohydrin, and the high-dose males and females received 2.1 and 1.56 mg/kg bw/day epichlorohydrin].

Rat: Groups of 50 male and 50 female Osborne-Mendel rats, 7 weeks of age, received 99% pure trichloroethylene, containing 0.19% 1,2-epoxybutane and 0.09% epichlorohydrin (see IARC, 1976b) in corn oil by gavage on 5 days a week for 78 weeks. High-dose animals received varying dose schedules of 1000-1500 mg/kg bw/day, and low-dose animals received 500-750 mg/kg bw/day. All surviving animals were killed 110 weeks after the start of treatment. The time-weighted average doses were 549 and 1097 mg/kg bw/day. A group of 20 male and 20 female vehicle-treated rats served as controls. Of the males, 17/20 controls, 42/50 low-dose and 47/50 high-dose animals died before the end of the study; of the females, 12/20 controls, 35/48 low-dose animals and 37/50 high-dose animals died. Median survival times were approximately 60 weeks for high-dose males, 85 weeks for low-dose males and 70 weeks for high- and low-dose females. Of the males, 5/20 controls, 7/50 low-dose and 5/50 high-dose rats developed tumours; of the females, 7/20 controls, 12/48 low- and 12/50 high-dose rats developed tumours. No liver-cell tumours occurred; tumours that occurred in various other organs in treated and vehicle control animals were mainly reticulum-cell sarcomas, lymphosarcomas or malignant lymphomas, fibroadenomas of the mammary gland, haemangiosarcomas at various sites, follicular adenocarcinomas of the thyroid, chromophobe adenomas of the pituitary and renal hamartomas. Toxic nephropathy was observed in rats of both sexes treated with high and low doses of trichloroethylene (National Cancer Institute, 1976) (The Working Group noted the poor survival of treated rats and that the low- and high-dose animals also received 0.5 and 1 mg/kg bw/day epichlorohydrin).

In a preliminary report of a study in progress, groups of 30 male and 30 female Sprague Dawley rats, 13 weeks of age, were given 50 or 250 mg/kg bw trichloroethylene (purity unspecified) in olive oil by gavage 4-5 times per week for 52 weeks, followed by observation for life. A group of 30 male and 30 female controls received olive oil alone. Results were reported 76 weeks after the start of treatment, at which time 46 controls, 39 low-dose and 34 high-dose males and females combined of each group were still alive. Among high-dose rats that died, 1 lymphoid leukaemia and 1 plasmocytoma were observed (minimum latent period, 38 weeks); 2 plasmocytomas occurred in low-dose animals that died (minimum latent period, 70 weeks). No such tumours were found in controls (Maltoni & Maioli, 1977).
3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

Wide variations in impurities and manufacturing processes of trichloroethylene produce inconsistencies in experimental toxicity tests (Defalque, 1961); in addition, pure trichloroethylene decomposes readily into highly toxic products. The extensive literature on the toxicity of trichloroethylene has been reviewed by Aviado et al. (1976), Browning (1965), Defalque (1961), the US Occupational Safety & Health Administration (1975), Lloyd et al. (1975), Von Oettingen (1964), Smith (1966) and Walter et al. (1976).

The oral LD$_{50}$ in rats is 7.2 g/kg bw (Smyth et al., 1969) and in mice, 2.85 g/kg bw (Aviado et al., 1976). The i.p. LD$_{50}$ in mice is 3.2 g/kg bw (Klaassen & Plaa, 1966) or 1.83 g/kg bw (Schumacher & Grandjean, 1960); that in dogs is 2.8 g/kg bw (Klaassen & Plaa, 1967). The lowest lethal i.v. dose for dogs is 150 mg/kg bw; in rabbits, the s.c. lethal dose is 1.8 g/kg bw (Barsoum & Saad, 1934).

The maximum concentrations of vapour that produced no toxic effects after exposure for 7 hrs daily on 5 days a week for 6 months were: rats and rabbits, 1076 mg/m$^3$ (200 ppm); guinea-pigs, 538 mg/m$^3$ (100 ppm); and monkeys, 2150 mg/m$^3$ (400 ppm) (Adams et al., 1951). Thirty exposures for 8 hrs daily on 5 days/week to 3825 mg/m$^3$ (700 ppm), or continuous exposure to 189 mg/m$^3$ (35 ppm) for 90 days caused no visible sign of toxicity in rats, dogs, monkeys, guinea-pigs or rabbits (Pendergast et al., 1967).

In 8 cats exposed to concentrations of 108 mg/m$^3$ of air (20 ppm) for 1-1.5 hrs per day for 4-6 months, centrilobular hepatitis, nephritis, hypertrophy of lymphoid glands and splenomegaly were observed (Mosinger & Fiorentini, 1955). In mice, trichloroethylene caused less damage to the kidneys and liver than did carbon tetrachloride or chloroform (Klaassen & Plaa, 1966).

In a chronic toxicity study, the maximal tolerated oral dose of industrial-grade trichloroethylene in Osborne-Mendel rats was 1100 mg/kg bw for animals of both sexes; that in B6C3F1 hybrid mice was 2340 mg/kg (males) and 1740 mg/kg (females) (National Cancer Institute, 1976).

Embryotoxicity and teratogenicity

Groups of rats and mice were exposed by inhalation for 7 hrs daily on days 6-15 of gestation to 1600 mg/m$^3$ in air (300 ppm) trichloroethylene; no effects were observed on the average number of implantation sites per litter, litter size, incidence of foetal resorptions, foetal sex ratios or
foetal body measurements. No treatment-related increased incidence in skeletal or visceral malformations was observed (Schwetz et al., 1975).

Absorption, distribution, excretion and metabolism

A review is available (Piotrowski, 1977).

Following inhalation of trichloroethylene, none was detected in the blood or organs of rats (Kimmerle & Eben, 1973a).

Dogs exposed to trichloroethylene excreted trichloroacetic acid and the glucuronide of trichloroethanol in the urine (Barrett & Johnston, 1939; Butler, 1949). When $^{36}$Cl-trichloroethylene was given by gavage to rats, 10-20% of the dose was excreted in the urine as 1-5% trichloroacetic acid and 10-15% trichloroethanol; 0-0.5% was excreted as trichloroethylene in the faeces and 72-85% as trichloroethylene in the expired air (Daniel, 1963).

The demonstration of the enzymic conversion of trichloroethylene to chloral by liver microsomes from rabbits, rats and dogs supports the suggestion of Powell (1945) that the trichloroethylene oxide intermediate rearranges into chloral hydrate (Byington & Leibman, 1965; Leibman, 1965). Chloral was also isolated in vitro as an intramolecular rearrangement product of trichloroethylene oxide; chloral is then in part reduced to trichloroethanol or oxidized to trichloroacetic acid (Bonse & Henschler, 1976; Bonse et al., 1975). Spectral evidence for the formation of trichloroethylene oxide (2,2,3-trichloro-oxirane) during incubation of trichloroethylene with metabolizing hepatic microsomes was reported by Uehleke et al. (1977).

$^{14}$C-Trichloroethylene is bound irreversibly to liver endoplasmic protein in vivo and in vitro (Allemand et al., 1978; Bolt et al., 1977; Uehleke & Poplawski-Tabarelli, 1977; Van Duuren & Banerjee, 1976); it is bound to exogenous DNA in vitro (Banerjee & Van Duuren, 1978). Binding is correlated with the activity of hepatic mixed-function oxidases (Uehleke & Poplawski-Tabarelli, 1977); thus, treatment of animals with inducers of hepatic mixed-function oxidases, such as phenobarbital, methylcholanthrene, Aroclor 1254 or hexachlorobenzene, increases the hepatotoxicity of trichloroethylene (Carlson, 1974; Moslen et al., 1977a) and depletes hepatic glutathione (Moslen et al., 1977b).

Mutagenicity and other related short-term tests

Trichloroethylene was mutagenic in Escherichia coli K12 and in Salmonella typhimurium TA100 (Greim et al., 1975; Simon et al., 1977) in the presence of a microsomal activation system. In another assay with Salmonella typhimurium TA100, the pure compound was not mutagenic either in the presence or absence of rat liver microsomes; it was shown additionally that two of the impurities in a technical-grade
sample of trichloroethylene, epichlorohydrin and 1,2-epoxybutane, were mutagenic in the absence of rat liver microsomes (Henschler et al., 1977).

In Saccharomyces cerevisiae strain XV185-14C, trichloroethylene induced reverse mutations in the presence of mouse liver microsomes; the mutation frequencies were concentration-dependent. The authors concluded that trichloroethylene induced base-pair as well as frameshift type mutations (Shahin & Von Borstel, 1977). Positive results have been reported in the same species for the induction of gene mutations and mitotic gene conversion (strain D7) in the presence of mammalian microsomes and for the host(mouse)-mediated assay (strain D4) (Bronzetti et al., 1978).

Mice given single i.p. injections of half-LD50 doses of trichloroethylene in dimethylsulphoxide, or five repeated injections of one-sixth the LD50 at one-day intervals, showed no increase in the frequency of chromosome aberrations in their bone-marrow cells (Černá & Kypěnová, 1977).

In spot tests for somatic mutations, i.p. treatment of pregnant mice with 1 mM trichloroethylene induced coat colour mutations in exposed embryos (Fahrig, 1977).

[To what extent the positive mutagenic results reported with trichloroethylene are due to impurities in the test samples could not be determined by the Working Group].

(b) Humans

Numerous fatalities resulting from anaesthesia with trichloroethylene and from industrial intoxications have been compiled. Sudden death, probably due to ventricular fibrillation, has been reported on exertion shortly after intense exposure (Defalque, 1961).

Chronic inhalation of trichloroethylene affects the central nervous system (Grandjean et al., 1955). Accidental ingestions produced inebriety, vomiting, diarrhoea, collapse and coma, followed either by death (pulmonary oedema and liver and kidney necrosis at autopsy) or recovery with transient neurological sequelae (amnesia, headache, numbness, weakness of extremities, psychosis or hemiparesis) (Defalque, 1961). Toxic effects on the liver (Schüttmann, 1970) and cutaneous reactions (Bauer & Rabens, 1974; Schirren, 1971; Stewart et al., 1974) have been reported.

Psychophysiological function was depressed in volunteers exposed to 592 mg/m³ (110 ppm) trichloroethylene for two 4-hr periods (Salvini et al., 1971). Experimental exposure of 10 volunteers to 1070 mg/m³ (200 ppm) trichloroethylene vapour for periods of 7 hrs over 5 days
produced fatigue and sleepiness (Stewart et al., 1970). Impairment of neurological and psychological functions after acute and longer exposure was also reported by Gamberale et al. (1976) and Triebig et al. (1977). It has been suggested that the toxic action in humans was due mainly to contaminants (Browning, 1965; Defalque, 1961).

There is an indication that the hepatotoxic effect of trichloroethylene is enhanced by concomitant exposure to ethanol or isopropyl alcohol (Traiger & Plaa, 1974).

About 60% of inspired trichloroethylene is taken up by the body; the arterial blood concentration increased linearly with the concentration in the alveolar air (Åstrand & Övrum, 1976).

Humans exposed to trichloroethylene excrete trichloracetic acid and trichloroethanol in the urine (Kimmerle & Eben, 1973b; Nomiyama & Nomiyama, 1971; Powell, 1945), and the concentration of trichloracetic acid in the urine is an indication of trichloroethylene exposure (Axelson et al., 1978; Smith, 1978). Kinetic studies of the formation and excretion of trichloroacetic acid and trichloroethanol have been reported (Fernandez et al., 1977; Monster et al., 1976; Müller et al. 1974). Chloral hydrate was also identified as a trichloroethylene metabolite in the blood (Cole et al., 1975a; Scansetti et al., 1959).

3.3 Case reports and epidemiological studies

An epidemiological study of cancer mortality among 518 males exposed occupationally to relatively low levels of trichloroethylene has been reported. Levels of exposure were estimated by concentrations of trichloroacetic acid in the urine: exposure categories with averages below and above 100 mg/l trichloroacetic acid in the urine were used; 100 mg/l corresponds roughly to an 8-hr time-weighted average exposure of 160 mg/m³ (30 ppm) trichloroethylene in air. When compared with the national population rates, 49 deaths from all causes were observed versus 62 expected. With no consideration given to latency or intensity of exposure, 11 deaths due to cancer at all sites were observed versus 14.5 expected. When analyses were restricted to those with 10 or more years since onset of exposure, no significant excess of cancer was demonstrated, either for those exposed to high or lower levels of trichloroethylene. It was concluded, however, that this study could not rule out a cancer risk to humans, particularly for rare types of malignancies such as liver cancer (Axelson et al., 1978) [The small size of the study group and the relatively short latent period (mainly less than 20 years) underline this conclusion].

The Working Group was aware of 2 studies in progress: a cancer mortality study of workers occupationally exposed to trichloroethylene and a follow-up study of workers exposed to organochloride and alkylchloride compounds, vinyl chloride, trichloroethylene and unsaturated compounds (IARC, 1978b).
4. Summary of Data Reported and Evaluation

4.1 Experimental data

Trichloroethylene was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced hepatocellular carcinomas and lung tumours in both males and females. The experiment in rats was considered to be inadequate. Preliminary results of a study in progress by oral administration to rats could not be evaluated.

Trichloroethylene is mutagenic in bacteria and yeast and in spot tests for somatic mutations in mice.

4.2 Human data

No case reports were available to the Working Group. The only epidemiological study available reported no statistically significant excess of cancer associated with exposure to trichloroethylene. However, because of the small size of the group and the relatively short time since onset of exposure, no assessment of carcinogenicity could be made.

The extensive production of trichloroethylene for over 50 years, together with its use as an industrial solvent and metal cleaning agent, as an inhalational anaesthetic and as an additive in drugs, food and consumer products, indicate that widespread human exposure occurs. This is confirmed by many reports of its occurrence in air, water and foods and in human tissues and expired air.

4.3 Evaluation

There is limited evidence that trichloroethylene is carcinogenic in mice.

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1Subsequent to the meeting of the Working Group, the Secretariat became aware of a study of 330 deceased laundry and dry-cleaning workers who had been exposed to carbon tetrachloride, trichloroethylene and tetrachloroethylene. An excess of lung, cervical and skin cancers and a slight excess of leukaemias and liver cancers were observed (Blair et al., 1979).


Babenko, K.V. (1974) Sanitary hygienic assessment of the working conditions for operators involved in the chemical cleaning of clothes (Russ.). Gig. Sanit., 11, 77-79


Browning, E. (1965) Toxicity and Metabolism of Industrial Solvents, Amsterdam, Elsevier, pp. 189-212

Bureau International Technique des Solvants Chlorés (1976) Standardization of methods for the determination of traces of some volatile chlorinated aliphatic hydrocarbons in air and water by gas chromatography. Anal. chim. acta, 82, 1-17


Fujii, T. (1977) Direct aqueous injection gas chromatography-mass spectrometry for analysis of organohalides in water at concentrations below the parts per billion level. J. Chromatogr., 139, 297-302


IARC (1976b) IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, 11, Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics, Lyon, pp. 131-139


Mercier, M. (1977) Criteria (Exposure/Effect Relationships) for Organo-Solvents, V/F/177-4, Luxembourg, Commission of the European Communities, pp. 123-190


Panel on Fumigant Residues in Grain (1974) Determination of residues of volatile fumigants in grain. Analyst (Lond.), 99, 570-578


Schirren, J.M. (1971) Skin lesions caused by trichloroethylene in a metal working plant (Germ.). *Berufs-Derm.*, 19, 240-254


FLAME RETARDANT
TRIS(2,3-DIBROMOPROPYL) PHOSPHATE

1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 126-72-7

Chem. Abstr. Name: 2,3-Dibromo-1-propanol phosphate (3:1)

Synonyms: 2,3-Dibromo-1-propanol phosphate; (2,3-dibromopropyl) phosphate; tris(2,3-dibromopropyl) phosphoric acid ester; Tris

Trade names: Anfram 3PB; Apex 462-5; Bromkal P 67-6HP; ES 685; Firemaster LV-T 23P; Firemaster T 23P; Flacavon R; Flamex T 23P; Flammex AP; Flamex T 23P; T 23P; Zetofex ZN

1.2 Structural and molecular formulae and molecular weight

\[
\begin{align*}
\text{BrCH}_2-\text{CHBr-CH}_2\text{O} \\
\text{BrCH}_2-\text{CHBr-CH}_2\text{O} \xrightarrow{\text{P=O}} \\
\text{BrCH}_2-\text{CHBr-CH}_2\text{O}
\end{align*}
\]

\[C_9H_{15}Br_6O_4P\]  \hspace{1cm} \text{Mol. wt: 697.7}

1.3 Chemical and physical properties of the pure substance

From Lande et al. (1976), unless otherwise specified

(a) Description: Viscous, pale-yellow liquid (Hawley, 1977)

(b) Freezing-point: 5.5°C

(c) Density: \(d^{25}\) 2.27

(d) Spectroscopy data: Infra-red and nuclear magnetic resonance spectral data have been tabulated (Grasselli & Ritchey, 1975).

(e) Refractive index: \(n^D_20\) 1.5772 (Hawley, 1977)
(f) **Solubility:** Insoluble in water; miscible with carbon tetrachloride, chloroform and methylene chloride (Stauffer Chemical Co., 1972)

(g) **Volutility:** Vapour pressure is 0.00019 mm at 25°C.

(h) **Stability:** Stable to 200-250°C; major decomposition begins at 308°C; stable in sunlight

(i) **Reactivity:** Hydrolysed by acids and bases

1.4 Technical products and impurities

Tris(2,3-dibromopropyl) phosphate is available in the US in at least two grades. The high-purity grade has the following typical properties: a clear, pale-yellow viscous liquid; density at 25°C, 2.20-2.26; refractive index at 25°C, 1.576-1.577; viscosity at 25°C, 3900-4200 centistokes; acid number (mg KOH/g), 0.05 max; volatiles, 1.5%; max; bromine content, 68.7%; and phosphorus content, 4.4%. Typical properties for a lower grade are as follows: density at 25°C, 2.2-2.3; viscosity at 25°C, 1400-1700 centistokes; acid number (mg KOH/g), 0.05 max; and volatiles, 10% max.

Impurities in tris(2,3-dibromopropyl) phosphate include 2,3-dibromopropanol, 1,2,3-tribromopropane and 1,2-dibromo-3-chloropropene (see monograph, p. 83) (Blum & Ames, 1977).

2. Production, Use, Occurrence and Analysis

A review on haloalkyl phosphates has been published (US Environmental Protection Agency, 1976a).

2.1 Production and use

(a) **Production**

The first described preparation of tris(2,3-dibromopropyl) phosphate is believed to have been in 1950, when it was made by the addition of bromine to a solution of triallyl phosphate in benzene. It is prepared commercially in the US by a two-step process in which bromine is added to allyl alcohol and the resultant 2,3-dibromopropanol is reacted with phosphorous oxychloride (Overbeek & Namety, 1962) (possibly in the presence of an aluminium chloride catalyst).

Commercial production of tris(2,3-dibromopropyl) phosphate in the US was first reported in 1959 (US Tariff Commission, 1960). In 1976,
2 US companies reported production of an undisclosed amount (see preamble, p. 16) (US International Trade Commission, 1977). US production in 1975 has been estimated to have been 4.1-5.4 million kg (US Environmental Protection Agency, 1976a).

No data on its production in Europe were available.

Japanese production of tris(2,3-dibromopropyl) phosphate is estimated to have been 100 thousand kg in 1976, the last year in which the single manufacturer made it; it is not imported.

(b) Use

Tris(2,3-dibromopropyl) phosphate is used primarily as a flame retardant additive for synthetic textiles and plastics (US Environmental Protection Agency, 1976a). It has also been recommended for use in phenolic resins, paints, paper coatings and rubber (Agranoff, 1976).

Tris(2,3-dibromopropyl) phosphate is used mainly in polyester and cellulosic acetate fabrics, but it has also been used in acrylic fabrics; twice as much is used in polyester fabrics as in cellulosic acetate fabrics. About 65% of the tris(2,3-dibromopropyl) phosphate used in the US in 1975 was applied to fabrics for children's clothing (US Environmental Protection Agency, 1976b). It may be added to textiles by the producer, although addition by dyers and finishers is believed to be more usual, at a level of 6-10% by weight.

Its addition to polyurethane foams (see IARC, 1979a) is the major use in plastics; relatively small amounts are believed to be used as an additive to polystyrene foam (see IARC, 1979b). It is added to rigid foams and to a lesser extent to flexible polyurethane foams. It has been estimated that fire-retarded polyurethane requires approximately 0.5% phosphorus and 4-7% bromine; this is equivalent to about 10% tris-(2,3-dibromopropyl) phosphate (by weight) in the product (US Environmental Protection Agency, 1976a).

Flexible polyurethane foams are used primarily for cushioning. Cushioning treated with haloalkyl phosphates is found in automotive and aircraft interiors, institutional bedding, cushions and upholstered furniture. Rigid foams containing tris(2,3-dibromopropyl) phosphate are used in insulation, furniture, automobile interior parts and water flotation devices. Less expensive fire retardants are used for rigid foams used in building insulation (US Environmental Protection Agency, 1976a).

As a result of actions taken on 8 April and 1 June 1977, the US Consumer Product Safety Commission banned children's clothing treated with tris(2,3-dibromopropyl) phosphate, the chemical itself when used or intended to be used in children's clothing and fabric, yarn or fibre
containing it when intended for use in such clothing (US Consumer Product Safety Commission, 1977a,b). However, children's clothing containing tris(2,3-dibromopropyl) phosphate is still available because the ban has not yet been fully enforced (Anon., 1978; US Consumer Product Safety Commission, 1978a,b).

In March 1978, the Consumer Product Safety Commission listed 22 products that contain tris(2,3-dibromopropyl) phosphate and are available to US consumers. These included children's clothing, industrial uniforms, draperies, tent fabric, automobile headliners, epoxy resins for the electronics industry, Christmas decorations and polyester thread (Anon., 1978).

No data on its use in Europe were available. Until 1977, it was used in Japan primarily as a fire retardant in polyester fibres and polyurethane plastics.

2.2 Occurrence

Tris(2,3-dibromopropyl) phosphate is not known to occur as a natural product.

Although environmental levels of tris(2,3-dibromopropyl) phosphate have not been measured, it has been estimated that as much as 10% of US production reaches the environment from textile finishing plants and laundries and that most of the rest will reach the environment as solid waste (US Environmental Protection Agency, 1976b). Several experimental studies conducted on polyester and cellulose acetate fabrics treated with tris(2,3-dibromopropyl) phosphate have shown that it can leach into wash and rinse water during laundering (Lande et al., 1976). When sheets treated with tris(2,3-dibromopropyl) phosphate were washed, up to 6 mg/l were found in the combined wash- and rinse-water (Gutenmann & Lisk, 1975).

Approximately 180 µg/day (9 µg/kg bw) tris(2,3-dibromopropyl) phosphate is absorbed through the skin of children wearing polyester pyjamas (Blum et al., 1978).

A 1974 National Occupational Hazard Survey indicated that workers primarily exposed to tris(2,3-dibromopropyl) phosphate are those in the telephone communication industry (National Institute for Occupational Safety & Health, 1977).

2.3 Analysis

Methods used for the analysis of tris(2,3-dibromopropyl) phosphate are listed in Table 1.
TABLE 1. METHODS FOR THE ANALYSIS OF TRIS(2,3-DIBROMOPROPYL) PHOSPHATE

<table>
<thead>
<tr>
<th>SAMPLE TYPE</th>
<th>EXTRACTION/CLEAN-UP</th>
<th>DETECTION</th>
<th>REFERENCE</th>
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</thead>
<tbody>
<tr>
<td>Textile</td>
<td>Pyrolysis</td>
<td>GC/flame photometry</td>
<td>Cope (1973)</td>
</tr>
<tr>
<td>Polyester flannel</td>
<td>Heat in distilled water; evaporate to dryness; hydrolyse by refluxing with hydrobromic acid; complex with molybdenum blue</td>
<td>Spectrophotometry</td>
<td>Gutenmann &amp; Lisk (1975)</td>
</tr>
</tbody>
</table>

Abbreviation: GC - gas chromatography
3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(a) Oral administration

Mouse: Groups of 50 male and 50 female B6C3F1 hybrid mice, 6 weeks of age, were fed various concentrations of technical-grade tris(2,3-dibromo-propyl) phosphate (containing no detectable 1,2-dibromo-3-chloropropane) in the diet for 103 weeks followed by a 1-week observation period. The experimental design of the study is shown in Table 2. Of the males, 43/50 high-dose, 38/50 low-dose and 44/55 matched control mice survived until the end of the study; of the females, 38/50 high-dose, 37/50 low-dose and 44/55 control mice survived. The compound increased the incidence of squamous-cell carcinomas and papillomas of the forestomach and of adenomas and carcinomas of the lungs in both male and female treated animals as compared with controls; there was also an increased incidence of renal tubular-cell adenomas and adenocarcinomas in treated male mice and of liver-cell adenomas and carcinomas in treated female mice. Neoplastic lesions associated with the administration of tris(2,3-dibromopropyl) phosphate are summarized in Table 2. Renal tubular dysplasia was observed in 30/49 high-dose males, 37/50 low-dose males, 12/46 high-dose females and 1/50 low-dose females but in none of the controls (National Cancer Institute, 1978).

Rat: Groups of 55 male and 55 female Fischer 344 rats, 6 weeks old, were fed diets containing various concentrations of technical-grade tris(2,3-dibromopropyl) phosphate for 103 weeks, followed by a 1- or 2-week observation period. The experimental design of the study is shown in Table 2. Of the males, 40/55 high-dose, 35/55 low-dose and 39/55 control rats survived until the end of the study; of the females, 36/55 high-dose, 44/55 low-dose and 36/55 control rats survived. The compound increased the incidence of renal tubular-cell adenomas in rats of both sexes and of tubular-cell adenocarcinomas in high-dose males. Neoplastic lesions associated with the administration of tris(2,3-dibromopropyl) phosphate are summarized in Table 2. Renal tubular dysplasia was observed in 6/54 high-dose males and in 35/54 high-dose females, but not in the control or low-dose groups (National Cancer Institute, 1978).

(b) Skin application

Mouse: Female ICR/Ha Swiss mice, 6-8 weeks old, were treated thrice weekly with tris(2,3-dibromopropyl) phosphate (97% pure) in 0.2 ml acetone applied to the shaved dorsal skin for 474-496 days. Most of the animals survived to the end of the study. The compound increased the incidence of tumours of the skin, lung, forestomach and oral cavity in treated mice.
<table>
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<tr>
<th>SPECIES</th>
<th>SEX</th>
<th>NO. OF ANIMALS TREATED</th>
<th>CONCENTRATION (mg/kg DIET)</th>
<th>DURATION (WEEKS)</th>
<th>NUMBER OF TUMOUR-BEARING ANIMALS/NUMBER OF ANIMALS EXAMINED</th>
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<td>FORESTOMACH (SQUAMOUS-CELL CARCINOMAS OR PAPILLOMAS)</td>
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<td>0</td>
<td>105</td>
<td>0/51(^{a})</td>
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<tr>
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<td>M</td>
<td>50</td>
<td>500</td>
<td>105</td>
<td>10/47(^{b})</td>
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<tr>
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<td>50</td>
<td>1000</td>
<td>105</td>
<td>13/48(^{d})</td>
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<tr>
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<td>F</td>
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<td>0</td>
<td>105</td>
<td>2/53(^{g})</td>
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<tr>
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<td>F</td>
<td>50</td>
<td>500</td>
<td>105</td>
<td>14/48(^{i})</td>
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<tr>
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<td>F</td>
<td>50</td>
<td>1000</td>
<td>103</td>
<td>22/44(^{l})</td>
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<tr>
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<td>55</td>
<td>100</td>
<td>103</td>
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</tr>
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</table>

**Fisher analysis of treated group versus control:**

\(^{a}\) Squamous-cell papillomas; \(P < 0.01\)

\(^{b}\) Squamous-cell carcinomas & papillomas; \(P < 0.01\)

\(^{c}\) Alveolar/bronchiolar adenomas & carcinomas; \(P < 0.05\)

\(^{d}\) Alveolar/bronchiolar adenomas & carcinomas; \(P < 0.01\)

\(^{e}\) Tubular-cell adenomas & adenocarcinomas; \(P < 0.01\)

\(^{f}\) Hepatocellular adenomas & carcinomas; \(P < 0.01\)
as compared with controls. The experimental design and the neoplastic lesions associated with the dermal application of tris(2,3-dibromopropyl) phosphate are summarized in Table 3 (Van Duuren et al., 1978).

### TABLE 3. TUMOUR INCIDENCES IN FEMALE SWISS MICE AFTER DERMAL APPLICATION OF TRIS(2,3-DIBROMOPROPYL) PHOSPHATE

<table>
<thead>
<tr>
<th>NUMBER OF ANIMALS TREATED</th>
<th>DOSE (mg/ANIMALS)</th>
<th>NUMBER OF MICE WITH TUMOURS(NUMBER NECROPSIED)²</th>
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<tr>
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<td>FORESTOMACH</td>
</tr>
<tr>
<td>29</td>
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<tr>
<td>30</td>
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</table>

²Increases in incidences of tumours of forestomach, lung, skin and oral cavity in treated animals were statistically significant when compared with those in controls (P < 0.05).

3.2 Other relevant biological data

(a) Experimental data

**Toxic effects**

Tris(2,3-dibromopropyl) phosphate containing less than 1% volatile impurities has an oral LD₅₀ of 5.24 g/kg bw in rats and a dermal LD₅₀ of > 8 g/kg bw in rabbits.

In rabbits, administration of 0.22 g/animal to the eye or 1.1 g/animal to the skin caused no irritation (Daniher, 1976; Kerst, 1974). No evidence of skin sensitization was seen in guinea-pigs (Morrow et al., 1976).

Application of commercial, high-purity (99.76%) tris(2,3-dibromo-propyl) phosphate weekly for 3 months at a dose of 2.27 g/kg bw to intact and abraded skin of the backs of female and male rabbits produced a 50% decrease in testicular weight in 7/8 males, with spermatogonia in the seminiferous tubules and occasional progression to secondary spermatocytes. In addition, chronic interstitial nephritis was seen in 6/8 males (Osterberg et al., 1977).

No data on the embryotoxicity or teratogenicity of tris(2,3-dibromo-propyl) phosphate were available.
Absorption, distribution, excretion and metabolism

Tris(2,3-dibromopropyl) phosphate was absorbed from the digestive system of male weanling rats fed 100 and 1000 mg/kg of diet for 28 days. Dose-related bromine concentrations were detected by neutron activation analysis in muscle, liver and fat after 28 days' feeding; these concentrations were reduced to control levels 6 weeks after administration of the compound was discontinued (Kerst, 1974). The absorption of tris(2,3-dibromopropyl) phosphate was dose-dependent in rabbits that received daily skin applications of 500, 1000 and 2000 mg/kg of diet, as shown by increased blood bromide levels (Daniher, 1976).

After application of fabric treated with $^{14}$C-tris(2,3-dibromopropyl) phosphate to the clipped skin of rabbits, up to 17% of the radiolabel in the cloth penetrated the skin over a 96-hr period of exposure. Most of the radiolabel appeared in the urine. Even higher absorption of radiolabel occurred when cloth moistened with human urine was applied to the skin (Ulsamer et al., 1978).

When a dose of 100 mg/animal was applied to the shaven skin of a male Lewis rat, a metabolic hydrolysis product, 2,3-dibromopropanol, was detected in free and conjugated form in the urine for several days (St John et al., 1976).

Mutagenicity and other related short-term tests

Tris(2,3-dibromopropyl) phosphate is mutagenic in Salmonella typhimurium TA100 and TA1535, but not in TA1537 and TA1538, indicating that the mutations induced are of the base-pair substitution type (Blum & Ames, 1977; Brusick et al., 1977; Prival et al., 1977). In the study of Prival et al. (1977), although tris(2,3-dibromopropyl) phosphate behaved as a direct-acting mutagen at higher concentrations (> 1 µl/plate), much lower concentrations (0.01 µl/plate) had significant genetic activity only when microsomal preparations were present. On a quantitative basis, no significant difference in mutagenic activity was observed among 9 different commercial samples.

The urine of rats treated orally or dermally with tris(2,3-dibromopropyl) phosphate in doses of 500 and 5000 mg/kg bw also showed mutagenic activity in Salmonella typhimurium TA1535 (Brusick et al., 1977).

Tris(2,3-dibromopropyl) phosphate was mutagenic in Drosophila melanogaster, inducing sex-linked recessive lethals in male germ-cell stages; the spermatids were the most sensitive (Valencia, 1978).

Results of a forward mutation assay with the thymidine kinase system in mouse lymphoma cells (L5178Y) were inconclusive, although a 2-3-fold increase in mutation frequency was obtained consistently with concentrations of 5 µg/ml (Brusick et al., 1977).
Exposure to concentrations of 2 \mu l tris(2,3-dibromopropyl) phosphate per ml of growth medium for 4.5 hrs induced reparable lesions (single-strand breaks) in the DNA of human cells (KB) in culture, as evidenced by a lowering of the sedimentation rate in alkaline sucrose gradients (Gutter & Rosenkranz, 1977).

2,3-Dibromo-1-propanol, a metabolite and also an impurity present in tris(2,3-dibromopropyl) phosphate, was mutagenic in Salmonella typhimurium TA100 and TA1535 but not in TA1538 (Carr & Rosenkranz, 1978).

A significant, dose-dependent increase in sister chromatid exchanges was observed in Chinese hamster V79 cells treated with tris(2,3-dibromopropyl) phosphate; chromosome aberrations were not significantly increased (Furukawa et al., 1978).

(b) Humans

No skin irritation or sensitization was seen among 52 people who received 10 patch-test applications of the compound (Kerst, 1974). In another study with undiluted tris(2,3-dibromopropyl) phosphate, sensitization reactions occurred in 8/24 subjects; with a concentration of 20% in petroleum jelly, 2/25 subjects were sensitized. Seven of 8 treated fabrics elicited a response in the sensitized subjects (Morrow et al., 1976).

Tris(2,3-dibromopropyl) phosphate is absorbed through the skin in humans (Blum & Ames, 1977). Approximately 180 \mu g/day (9 \mu g/kg bw) is absorbed through the skin of children wearing pyjamas treated with tris-(2,3-dibromopropyl) phosphate. Up to 29 ng/ml 2,3-dibromo-1-propanol, a mutagenic metabolite of tris(2,3-dibromopropyl) phosphate, has been found in the urine of children wearing such pyjamas (Blum et al., 1978).

3.3 Case reports and epidemiological studies

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Tris(2,3-dibromopropyl) phosphate was tested in one experiment in mice and in one in rats by oral administration and in one experiment in female mice by skin application. In mice, following oral administration, it produced tumours of the forestomach and lung in animals of both sexes, benign and malignant liver tumours in females and benign and malignant tumours of the kidney in males. In rats, it produced benign and malignant tumours of the kidney in males and benign kidney tumours in females.
After skin application to female mice, it produced tumours of the skin, lung, forestomach and oral cavity.

Tris(2,3-dibromopropyl) phosphate is mutagenic in Salmonella typhimurium and Drosophila melanogaster.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

The extensive production and use of tris(2,3-dibromopropyl) phosphate over the past two decades, primarily as a flame retardant for textiles and plastics, indicate that widespread human exposure occurs. The Working Group knew of no published attempts to determine levels of this compound in the environment; however, estimates of the amounts released from industrial operations and textile leaching suggest that it is widely distributed. Its widespread use in childrens' sleepwear was noted.

4.3 Evaluation

There is sufficient evidence that tris(2,3-dibromopropyl) phosphate is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard tris(2,3-dibromopropyl) phosphate as if it presented a carcinogenic risk to humans.
5. References


TRIS(2,3-DIBROMOPROPYL) PHOSPHATE


IARC (1979b) IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 19, Some Monomers, Plastics and Synthetic Elastomers, and Acrolein, Lyon, pp. 231-274


Stauffer Chemical Company (1972) *Fyroli® HB-32, Product Data Sheet*, Westport, CT, Specialty Chemical Division


US Environmental Protection Agency (1976b) Summary Characterizations of Selected Chemicals of Near-Term Interest, EPA 560/4-76-004, Washington DC, Office of Toxic Substances, p. 53


Corrigenda covering Volumes 1-6 appeared in Volume 7, others appeared in Volumes 8, 10, 11, 12, 13, 15, 16, 17, 18 and 19.

Volume 4

p. 253  1.3(b)  add 'at 1.4 mm' after '112°C'

Volume 18

p. 3  line 15  replace '29' by '37'
### Cumulative Index to IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans

Numbers underlined indicate volume, and numbers in italics indicate page. References to corrigenda are given in parentheses. Compounds marked with an asterisk (*) were considered by the Working Groups, but monographs were not prepared because no adequate data on their carcinogenicity were available.

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Thiourea
Thiram
2,4-Toluene diisocyanate
2,6-Toluene diisocyanate
ortho-Toluidine and its hydrochloride
Toxaphene (polychlorinated camphenes)
1,1,1-Trichloroethane
1,1,2-Trichloroethane
Trichloroethylene
2,4,5- and 2,4,6-Trichlorophenols
Trichlorotriethylamine hydrochloride
Trichlorophon*
Triethylene glycol diglycidyl ether
Tris(aziridinyl)-para-benzoquinone
Tris(1-aziridinyl)phosphine oxide
Tris(1-aziridinyl)phosphine sulphide
2,4,6-Tris(1-aziridinyl)-s-triazine
1,2,3-Tris(chloromethoxy)propane
Tris(2,3-dibromopropyl) phosphate
Tris(2-methyl-1-aziridinyl)phosphine oxide
Trypan blue
CUMULATIVE INDEX

U
Uracil mustard  9,235
Urethane  7,111

V
Vinyl acetate  19,341
Vinyl bromide  19,367
Vinyl chloride  7,291  19,377
Vinyl chloride-vinyl acetate copolymers  7,311  19,412
4-Vinylcyclohexene  11,277
Vinylidene chloride  19,439
Vinylidene chloride-vinyl chloride copolymers  19,448
Vinylidene fluoride*  19,468
N-Vinyl-2-pyrrolidone  19,461

X
2,4-Xyldine and its hydrochloride  16,367
2,5-Xyldine and its hydrochloride  16,377
2,6-Xyldine*  16,377

Y
Yellow AB  8,279
Yellow OB  8,287

Z
Zectran  12,237
Zineb  12,245
Ziram  12,259
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