GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

Introduction

This seventy-seventh volume of the *IARC Monographs* reviews sixteen industrial organic chemicals, seven of which have previously been evaluated one or more times. For these seven substances, the most recent previous evaluations are summarized below. Since these previous evaluations, new data have become available, and these have been incorporated into the monographs and taken into consideration in the present evaluations.

Table 1. Previous evaluations of compounds covered in this volume

	Human	Animal	Overall evaluation	*Monograph* volume (year)
4-Chloro-*ortho*-toluidine	L	S	2A	48 (1990)
Cinnamyl anthranilate	ND	L	3	Suppl. 7 (1987)
Coumarin	ND	L	3	Suppl. 7 (1987)
Di(2-ethylhexyl) adipate	ND	L	3	Suppl. 7 (1987)
Di(2-ethylhexyl) phthalate	ND	S	2B	Suppl. 7 (1987)
N-Nitrosodiethanolamine	ND	S	2B	Suppl. 7 (1987)
ortho-Toluidine	I	S	2B	Suppl. 7 (1987)

L, limited evidence; S, sufficient evidence; ND, no data; I, inadequate evidence; 2A, probably carcinogenic to humans; 2B, possibly carcinogenic to humans; 3, cannot be classified as to its carcinogenicity to humans

Exposures

This volume includes evaluations of the carcinogenicity of several chemical intermediates or additives to which a large number of workers are exposed in various industries. Information on the extent of occupational exposures to many of these compounds in the United States was available from the National Occupational Exposure Survey (NOES) conducted by the United States National Institute for Occupational Safety and Health (NIOSH). NOES was a nationwide observational survey conducted in a sample of 4490 establishments from 1981 to 1983. The target population was defined as employees working in establishments or job sites in the United States of America employing eight or more workers in a defined list of Standard Industrial Classifications.

Generally, these classifications emphasized coverage of construction, manufacturing, transportation, private and business service and hospital industries. The NOES had little or no coverage of agriculture, mining, wholesale/retail trade, finance/real estate, or government operations. NOES addressed recordable potential exposure that had to meet two criteria: (1) a chemical, physical or biological agent or tradename product had to be observed in sufficient proximity to an employee such that one or more physical phases of that agent or product were likely to come into contact with or enter the body of the employee; and (2) the duration of the potential exposure had to meet the minimum duration guidelines, i.e., it must have presented a potential exposure for at least 30 min per week (on an annual average) or be used at least once per week for 90% of the weeks of the work year (NOES, 1999). No exposure measurements were made.

The Toxics Release Inventory (TRI) is a compilation of data reported by chemical manufacturers and processors to the United States Environmental Protection Agency under a regulation promulgated in 1986. TRI, which is updated every year, contains data on the reported annual releases of toxic chemicals from industrial facilities in the United States to the environment—air, water, soil, underground injection; amounts transferred off-site for waste treatment; and source reduction and recycling data. Data reported from selected categories of the TRI database are reported in these monographs. These categories include air emissions (fugitive or non-point emissions plus stack or point emissions), surface water discharges, underground injection and releases to land. Categories typically not included in the monographs are classified as transfers (recycling, energy recovery, treatment, POTWs [Publicly Owned Treatment Works], disposal and movement to other off-site locations). Due to changes in reporting requirements, apparent trends in reported releases do not always indicate an actual increase or decrease in quantities released.

Aromatic amines such as those evaluated in this volume are sometimes used commercially and/or in laboratory studies as their strong acid (e.g., hydrochloride) salts. The carcinogenicity of an amine and that of its strong acid salts are expected to be qualitatively similar, as the salts dissociate readily under physiological conditions.

Although epidemiological studies of some of the industries where exposure to chemicals considered in this volume occurs have been conducted, exposure to many of these chemicals has rarely been specifically assessed for epidemiological purposes. Quantitative estimates of historical exposure are often not available and therefore it is difficult to identify highly exposed subgroups or to estimate individual exposures. Without such data, it is difficult to evaluate exposure–response relationships which might, in some cases, allow cancer excesses to be attributed to specific agents when there is mixed exposure.

The presence of chemicals as intermediates, additives or contaminants in the workplace implies co-exposure to complex, often varying mixtures of potential carcinogens other than the compound of interest. Thus, when epidemiological studies of populations with mixed and complex exposures find positive results, it is often difficult to ascribe causality to a single agent, and for many compounds it may never

be possible to establish sufficient evidence of carcinogenicity in humans using traditional epidemiological data. In these cases, additional evidence from biomarkers of exposure or effect such as haemoglobin or DNA adducts in exposed humans to demonstrate and quantify genotoxic effects or other relevant mechanisms may allow a more definitive classification of potential carcinogenicity to humans. Such data were not available to the Working Group for most of the agents evaluated in this volume.

Metalworking fluids and ethanolamines

Epidemiological studies relevant to the evaluation of di- and triethanolamine and *N*-nitrosodiethanolamine involve occupational cohorts exposed to metalworking fluids. Metalworking fluids can be divided into four broad categories: straight oils, soluble oils, semi-synthetic and synthetic fluids.

Straight oils are generally mineral oils (60–100%) and do not contain ethanolamines as additives. Untreated and mildly treated mineral oils containing polycyclic aromatic hydrocarbons that were used in the past are recognized as human carcinogens (IARC, 1984). Straight oils may contain elemental sulfur, sulfur compounds and chlorinated compounds such as chlorinated paraffins, some of which are carcinogenic (National Toxicology Program, 1986a,b; IARC, 1990). Before the 1940s, metalworking fluids were predominantly straight oils. Refined straight oils continue to be used in lower-production operations and those requiring lubrication.

'Soluble oils' are emulsions of highly refined petrochemicals (30–85%) typically diluted 1:5 to 1:40 with water for use. Oils were not always highly refined before the 1970s. Emulsifiers are petroleum sulfonates and other detergents. Soluble oils may frequently contain ethanolamines and antimicrobial agents of various types. In the past, nitrites were occasionally added to soluble oils. *N*-Nitrosodiethanolamine has been detected in some bulk samples of soluble oils (National Institute for Occupational Safety and Health, 1998). By the 1950s, water-soluble fluids were being increasingly used in high-production operations.

Semi-synthetic fluids contain smaller amounts of oil than soluble oils (3–30%), along with the same mixture of additives mentioned below for synthetic fluids. They are typically diluted 1:10 to 1:40 for use. This category has not been examined separately in epidemiological studies. One study (Sullivan *et al*., 1998) grouped semi-synthetic oil exposure with soluble oil exposures.

Synthetic fluids contain no oil, but rather are primarily water with additives including buffers such as ethanolamines, organic polyglycols, organic esters, phosphates and antimicrobial agents. Mono- and diethanolamine may be present in concentrations of 2–3% and triethanolamine may be present in concentrations of up to 25% of undiluted fluids. They are typically diluted 1:10 to 1:40 for use. Diethanolamine may be converted to *N*-nitrosodiethanolamine in the presence of nitrosating agents. The semi-synthetic and synthetic fluids became more common in the 1960s and 1970s.

In addition to the chemicals evaluated in this volume, some synthetic and soluble fluids may contain chlorinated paraffins, formaldehyde (see IARC, 1995a)-releasing biocides, microbial contaminants and metal and metal alloy contaminants (National Institute for Occupational Safety and Health, 1998).

Genetically modified animal models

For three chemicals reviewed in this volume (diethanolamine, triethanolamine and pyridine), carcinogenicity experiments have been performed using genetically modified mice designed to be particularly susceptible to the induction of tumours at certain organ sites through specific mechanisms. The use of such animals for evaluation of the carcinogenicity of chemicals has been discussed (McGregor *et al*., 1999). The transgenic Tg.AC mice carry the v-Ha-*ras* gene under a zeta-globin promoter and are specifically designed to detect chemical carcinogens and tumour promoters in skin carcinogenesis experiments. Genetically modified mice which lack one copy of an essential tumour-suppressor gene such as *p53* model the situation in which a functioning copy of the suppressor gene has been lost in somatic cells of a normal individual. The transgenic and/or knock-out models, therefore, may also be useful not only for carcinogen identification but also for studies aimed at identifying the mode of action of chemicals and, in particular, to test genetic targets of carcinogenicity. However, because of the limited available database on the responses of any particular genetically modified mice to chemical carcinogens, bioassays using these animals must be interpreted with caution.

Peroxisome proliferation

Three of the compounds evaluated in this volume (di(2-ethylhexyl) phthalate, di(2-ethylhexyl) adipate and cinnamyl anthranilate) are carcinogenic to the liver in mice and/or rats, and have been proposed to act by a mechanism involving peroxisomal proliferation in hepatocytes in those species. The role of peroxisome proliferation in evaluating carcinogenicity in humans has been discussed (IARC, 1995b). When, for any chemical, the relationship between peroxisome proliferation and liver tumours in rats or mice has been established, this should be considered relevant information in the evaluation of the possible risks for cancer in humans, taking into account the following:

(a) whether information is available to exclude mechanisms of carcinogenesis other than those related to peroxisome proliferation;

(b) whether peroxisome proliferation (increases in peroxisome volume density or fatty acid β-oxidation activity) and hepatocellular proliferation have been demonstrated under the conditions of the bioassay;

(c) whether such effects have been looked for and have not been found in adequately designed and conducted investigations of human groups and systems.

Two primary responses have been proposed to account for liver carcinogenesis in rats and mice by peroxisome proliferators. These are (i) induction of peroxisome

proliferation and (ii) increased hepatocellular proliferation (Lake, 1995a; Cattley *et al*., 1998). Such responses, together with the ability of peroxisome proliferators to inhibit apoptosis in rat and mouse hepatocytes and their properties as liver tumour promoters in these rodents, account for peroxisome proliferator-induced liver tumour formation in these species (Popp & Cattley, 1993; Ashby *et al*., 1994; Lake, 1995a,b; Roberts, 1996; Cattley *et al*., 1998). Details are presented in the monograph on di(2-ethylhexyl) phthalate.

References

Ashby, J., Brady, A., Elcombe, C.R., Elliott, B.M., Ishmael, J., Odum, J., Tugwood, J.D., Kettle, S. & Purchase, I.F. (1994) Mechanistically-based human hazard assessment of peroxisome proliferator-induced hepatocarcinogenesis. *Hum. exp. Toxicol*., **13** (Suppl 2), S1–S117

Cattley, R.C., DeLuca, J., Elcombe, C., Fenner, C.P., Lake, B.G., Marsman, D.S., Pastoor, T.A., Popp, J.A., Robinson, D.E., Schwetz, B., Tugwood, J. & Wahli, W. (1998) Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul. Toxicol. Pharmacol*., **27**, 47–60

IARC (1984) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 33, *Polynuclear Aromatic Hydrocarbons, Part 2: Carbon Blacks, Mineral Oils and Some Nitroarenes*, Lyon, IARC*Press*

IARC (1990) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 48, *Some Flame Retardants and Textile Chemicals, and Exposures in the Textile Manufacturing Industry*, Lyon, IARC*Press*, pp. 55–72

IARC (1995a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 62, *Wood Dust and Formaldehyde*, Lyon, IARC*Press*, pp. 217–362

IARC (1995b) *Peroxisome Proliferation and its Role in Carcinogenesis* (IARC Technical Report No. 24), Lyon, IARC*Press*

Lake, B.G. (1995a) Peroxisome proliferation: current mechanisms relating to nongenotoxic carcinogenesis. *Toxicol. Lett*., **82–83**, 673–681

Lake, B.G. (1995b) Mechanisms of hepatocarcinogenicity of peroxisome-proliferating drugs and chemicals. *Ann. Rev. Pharmacol. Toxicol*., **35**, 483–507

McGregor, D.B., Rice, J.M. & Venitt, S., eds (1999) *The Use of Short- and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation* (IARC Scientific Publications No. 146), Lyon, IARC*Press*

National Institute for Occupational Safety and Health (1998) *Criteria for a Recommended Standard: Occupational Exposure to Metalworking Fluids* (DHHS (NIOSH) Publ. No. 98-102), Cincinnati, OH

National Toxicology Program (1986a) *Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{23}, 43% Chlorine) in F344/N Rats and B6C3F$_1$ Mice* (NTP TR 305), Research Triangle Park, NC

National Toxicology Program (1986b) *Toxicology and Carcinogenesis Studies of Chlorinated Paraffins (C_{12}, 60% Chlorine) in F344/N Rats and B6C3F$_1$ Mice* (NTP TR 308), Research Triangle Park, NC

NOES (1999) *National Occupational Exposure Survey 1981–83*. Unpublished data as of July 1999. Cincinnati, OH, Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health

Popp, J.A. & Cattley, R.C. (1993) Peroxisome proliferators as initiators and promoters of rodent hepatocarcinogenesis. In: Gibson, G. & Lake, B., eds, *Peroxisomes: Biology and Importance in Toxicology and Medicine*, London, Taylor and Francis, pp. 653–665

Roberts, R.A. (1996) Non-genotoxic hepatocarcinogenesis: suppression of apoptosis by peroxisome proliferators. *Ann. N.Y. Acad. Sci.*, **804**, 588–611

Sullivan, P.A., Eisen, E.A., Woskie, S.R., Kriebel, D., Wegman, D.H., Hallock, M.F., Hammond, S.K., Tolbert, P.E., Smith, T.J. & Monson, R.R. (1998) Mortality studies of metalworking fluid exposure in the automobile industry: VI. A case–control study of esophageal cancer. *Am. J. ind. Med.*, **34**, 36–48