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Some Antineoplastic and Immunosuppressive Agents

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Last updated: 8 April 1998

AZATHIOPRINE

VOL.: 26 (1981) (p. 47)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Azathioprine was tested by intraperitoneal, subcutaneous and/or intramuscular administration in mice and by oral and intraperitoneal administration in rats. Suggestive evidence was obtained for the induction of lymphomas after intraperitoneal, subcutaneous or intramuscular injection in mice and for ear-duct carcinomas in rats after oral administration. Because of limitations in design and reporting, however, the results were considered to be inconclusive.

Studies in which azathioprine was tested in combination with other agents were inadequate for evaluation.

Azathioprine is embryolethal at doses nontoxic to the mother and can induce a variety of severe teratogenic effects in several animal species. It is mutagenic in bacteria and yeast *in vitro* and in *Drosophila melanogaster* and mice *in vivo*. At high concentrations, the drug is clastogenic to human lymphocytes *in vitro*.

5.2 Human data

Azathioprine has been widely used since the 1970s to prevent rejection following organ transplantation. It is also used to treat a variety of autoimmune diseases.

Use of azathioprine during pregnancy may reduce birth weight significantly. The data were insufficient to evaluate the teratogenic potential of this drug to humans. Azathioprine produces chromosomal abnormalities and increases in sister chromatid exchanges in the peripheral lymphocytes of non-cancer patients. No data were available to evaluate the mutagenic potential of this drug to humans.

There is evidence that azathioprine, often combined with prednisone, is associated with an increased incidence of non-Hodgkin's lymphoma, squamous-cell cancers of the skin, hepato-biliary carcinomas, mesenchymal tumours, and perhaps certain other rare neoplasms. The risk of non-Hodgkin's lymphoma is higher in organ transplant recipients; the presence of the graft may make some contribution to this increased incidence.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of azathioprine in mice and rats. There is *sufficient evidence* that azathioprine is carcinogenic in humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

BISCHLOROETHYL NITROSOUREA (BCNU)

VOL.: 26 (1981) (p. 79)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

BCNU is carcinogenic in rats, producing tumours of the lung after intraperitoneal or intravenous administration, and intra-abdominal tumours after intraperitoneal administration. Tests in mice by intraperitoneal administration and skin application and in rats by oral administration could not be evaluated.

When tested in mice by skin application together with ultra-violet B irradiation, BCNU caused an earlier appearance of skin tumours.

BCNU is embryo- and fetolethal in rats and rabbits at doses nontoxic to the mother and can induce a variety of severe teratogenic effects in rats.

BCNU is mutagenic in bacteria, *Drosophila melanogaster* and mammalian cells. It also produces chromosomal aberrations in mammalian cells both in cell culture and *in vivo*.

5.2 Human data

BCNU has had limited use since the mid-1960s in the treatment of neoplastic diseases.

No data were available to evaluate the teratogenic potential or the mutagenicity or chromosomal effects of BCNU in humans.

BCNU has been associated in case reports with the development of acute nonlymphocytic leukaemia following treatment of primary malignant diseases. In all such cases, BCNU was administered with other anticancer therapies known or suspected of being carcinogenic. No epidemiological study was available.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of BCNU in rats. The data from studies in humans are inadequate to evaluate the carcinogenicity of BCNU in man.

This chemical should be regarded for practical purposes as if it presented a carcinogenic risk to humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

BLEOMYCINS (SULPHATES AND HYDROCHLORIDES)

VOL.: 26 (1981) (p. 97)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

No adequate study on the carcinogenicity of bleomycins in experimental animals was available to the Working Group.

No data were available to evaluate the teratogenic potential of bleomycin in animals. It is mutagenic in yeast and in *Drosophila melanogaster*. It induces chromosomal changes and increases in sister chromatid exchanges in various mammalian cells in culture. The drug also induced neoplastic transformation in a mouse cell line.

5.2 Human data

Bleomycin sulphate or hydrochloride has been used since the early 1970s, mainly in the treatment of Hodgkin's and non-Hodgkin's lymphoma, squamous-cell carcinoma at various sites and testicular malignancies.

No data were available to evaluate the teratogenic potential of bleomycin in humans. Chromosomal changes were seen in bone-marrow cells and peripheral lymphocytes of patients treated with bleomycin alone. No data were available to evaluate its mutagenic potential in humans.

The development of acute nonlymphocytic leukaemia following the administration of bleomycin with multiple other cytotoxic agents has been described in patients with Hodgkin's disease or non-Hodgkin's lymphoma. In a small epidemiological study of short duration, no excess of subsequent neoplasms was observed in patients treated with a regimen consisting of bleomycin, adriamycin, vinblastine and dacarbazine.

5.3 Evaluation

The available data from studies in experimental animals and in humans were inadequate to evaluate the carcinogenicity of bleomycins to man.

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

1-(2-CHLOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA (CCNU)

VOL.: 26 (1981) (p. 137)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

CCNU is carcinogenic in rats following its intraperitoneal or intravenous injection, producing lung carcinomas. It was also tested in mice by intraperitoneal injection; a slight increase in the incidence of lymphomas was observed.

CCNU can induce embryo- and fetolethality in rats and rabbits at doses nontoxic to the mother and a variety of severe teratogenic effects in rats.

It is mutagenic in *Salmonella typhimurium* and in Chinese hamster lung cells.

5.2 Human data

CCNU has had limited use since the early 1970s in the treatment of lymphomas and carcinomas, usually in conjunction with other antineoplastic drugs.

The frequency of sister chromatid exchanges is increased in the lymphocytes of patients who have been treated with CCNU. No data were available to evaluate the teratogenic or mutagenic potential of this drug in humans.

Several case reports describe the development of acute nonlymphocytic leukaemia in cancer patients who received CCNU. With one exception, all such patients had also received other cytotoxic agents and/or irradiation. No epidemiological study of CCNU as a single agent was available to the Working Group.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of CCNU in rats. The data from studies in humans are *inadequate* to evaluate the carcinogenicity of CCNU in man.

This chemical should be regarded for practical purposes as if it presented a carcinogenic risk to humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

CHLORAMBUCIL

VOL.: 26 (1981) (p. 115)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Chlorambucil has been tested in mice and rats by intraperitoneal injection. It produced tumours of the lung in mice and probably produced tumours of the haematopoietic system and ovary in mice and haematopoietic tumours in male rats. It was also tested in a two-stage skin carcinogenesis experiment in mice, in which it had an initiating effect.

Chlorambucil can induce teratogenic effects in several animal species and embryoletality at doses nontoxic to the mother. It has been shown to induce mutations in bacteria and yeast, and chromosomal aberrations in human lymphocytes in culture.

5.2 Human data

Chlorambucil has been used widely since the early 1960s, often for long periods, in the treatment of lymphomas, chronic leukaemias and certain solid tumours. It has also been used, to a lesser extent, in the treatment of rheumatoid arthritis, chronic glomerulonephritis and other nonmalignant diseases.

The available data are not sufficient to evaluate the teratogenic or mutagenic potential or chromosomal effects of chlorambucil in humans.

Although no well-controlled epidemiological study of chlorambucil alone was available to the Working Group, several highly suggestive descriptive studies and numerous case reports point to the increased occurrence of acute nonlymphocytic leukaemia in patients treated with chlorambucil.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of chlorambucil in mice and rats. There is *limited evidence* that it is carcinogenic in humans.

The experimental and clinical evidence taken together indicate that chlorambucil is very likely to be a human carcinogen.

N.B. - Since the meeting of the Working Group, the Secretariat became aware of a new epidemiological study, which documents an excess incidence of acute leukaemia in patients treated with chlorambucil (Berk et al., 1981). In a prospective, randomized clinical trial, 431 previously untreated patients with polycythemia vera were treated by phlebotomy alone, by phlebotomy plus chlorambucil or by phlebotomy plus radioactive phosphorus. The risk of acute leukaemia in patients given chlorambucil was 13 times that in patients treated by phlebotomy alone ($p < 0.002$). This study, in conjunction with the evaluation of the Working Group would provide *sufficient evidence* that chlorambucil is carcinogenic in humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: [Vol. 9 \(1975\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

Last updated: 8 April 1998

CISPLATIN

VOL.: 26 (1981) (p. 151)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Cisplatin was tested by intraperitoneal administration in mice, increasing the incidence of lung tumours. When cisplatin was administered intraperitoneally, alternately with croton oil application to the skin, papillomas and carcinomas of the skin were produced, along with small numbers of internal neoplasms.

In mice, high doses of cisplatin can induce embryoletality. The limited data available do not allow an evaluation of the teratogenic potential of the drug.

Cisplatin is a mutagen in bacterial and cultured mammalian cells. It also induces chromosomal aberrations in various cells in culture and in mice *in vivo*. Additionally, treatment of Syrian hamster embryo cells in culture with the drug resulted in the induction of morphological transformation.

5.2 Human data

Cisplatin has been used since the 1970s primarily in the treatment of testicular and ovarian cancer, often in combination with other antineoplastic drugs.

No data were available to evaluate the teratogenic potential or the mutagenicity or chromosomal effects of cisplatin in humans.

No case report or epidemiological study was available to the Working Group.

5.3 Evaluation

There is *limited evidence* that cisplatin is carcinogenic in mice. No data from studies in humans were available.

The available data were insufficient for the Working Group to evaluate the carcinogenicity of cisplatin to humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

CYCLOPHOSPHAMIDE

VOL.: 26 (1981) (p. 165)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Cyclophosphamide is carcinogenic in rats after its oral or intravenous administration, producing benign and malignant tumours at various sites, including the bladder. It is carcinogenic in mice following its subcutaneous injection, producing benign and malignant tumours at the site of injection and at distant sites. There was some evidence of its oncogenicity in mice and rats following intraperitoneal injection. The combined administration of cyclophosphamide intraperitoneally and of 2-naphthylamine orally to mice resulted in the induction of carcinomas of the bladder at doses of the compounds which, given individually, did not produce bladder cancer.

The teratogenic effects of cyclophosphamide are well established in many animal species. The drug can also be embryolethal at doses nontoxic to the mother.

Cyclophosphamide demonstrated mutagenic activity in several different assays (bacteria, yeast and mammalian cells *in vitro*, and *Drosophila* and mice *in vivo*). The agent also induced chromosomal aberrations in mammalian cells of several species *in vitro* and *in vivo*. Moreover, it induced morphological transformation of mammalian cells *in vitro*.

5.2 Human data

Cyclophosphamide has been widely used since the early 1950s in the treatment of malignant lymphoma, multiple myeloma, and cancers of the breast, ovary and lung. It has also been used in the treatment of certain chronic diseases, such as rheumatoid arthritis and chronic glomerulonephritis and other nonmalignant diseases.

Although two cases of limb reduction defects have been reported among the offspring of women treated with cyclophosphamide during pregnancy, no epidemiological data were available to the Working Group for assessing the embryotoxic risk to man. Increases in chromosomal aberrations and sister chromatid exchanges were seen in peripheral blood lymphocytes of patients treated with cyclophosphamide.

There is epidemiological evidence that cyclophosphamide increases the incidence of bladder cancer, and there is a suggestion that the incidence of other cancers may also be increased. There are also many case reports of cancer, particularly bladder cancer and acute nonlymphocytic leukaemia, following cyclophosphamide therapy.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of cyclophosphamide in mice and rats. There is *sufficient evidence* that cyclophosphamide is carcinogenic in humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: [Vol. 9 \(1987\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

Last updated: 8 April 1998

DACARBAZINE

VOL.: 26 (1981) (p. 203)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Dacarbazine is carcinogenic in mice and rats. Following its oral or intraperitoneal administration to rats, dacarbazine produced tumours at various sites, including breast, thymus, spleen and brain, in as little as 18 weeks after initial exposure. After its intraperitoneal administration to mice, dacarbazine produced tumours at various sites, including lung, haematopoietic tissue and uterus.

Dacarbazine can induce teratogenic effects in several species. It is mutagenic in mammalian cells in culture.

5.2 Human data

Dacarbazine has been used since the early 1970s in the treatment of malignant melanoma and is occasionally used in the therapy of other neoplastic diseases which have become resistant to alternative treatment.

The available data are insufficient to evaluate the teratogenicity, mutagenicity or chromosomal effects of dacarbazine in humans.

A single case of acute leukaemia following treatment with dacarbazine in combination with other cytotoxic agents has been reported. The only epidemiological study was small and of short duration and showed no excess of subsequent neoplasms in patients treated with a regimen consisting of dacarbazine, adriamycin, bleomycin and vinblastine.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of dacarbazine in mice and rats. The data from studies in humans are inadequate to evaluate the carcinogenicity of dacarbazine.

This chemical should be regarded for practical purposes as if it presented a carcinogenic risk to humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

5-FLUOROURACIL

VOL.: 26 (1981) (p. 217)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

5-Fluorouracil was tested by intravenous administration in mice and rats and by oral administration in rats. No evidence of carcinogenicity was found, but the studies suffered from limitations with regard to duration or dose.

5-Fluorouracil can induce embryotoxic and teratogenic effects in several animal species and may be embryo-lethal in monkeys at doses nontoxic to the mother. The available experimental data on the mutagenicity of 5-fluorouracil are inconclusive; the agent did induce transformation in a mouse cell line.

5.2 Human data

5-Fluorouracil has been used since the late 1950s as the main antineoplastic agent in the treatment of gastrointestinal tumours; it is used frequently in combination with other agents for the treatment of a variety of solid tumours.

Data available to the Working Group were insufficient to evaluate the teratogenic potential of this drug in humans. Data on chromosomal aberrations produced by 5-fluorouracil, though limited, suggest that the drug has clastogenic potential.

5-Fluorouracil has been associated in a few case reports with a variety of subsequent neoplasms. In almost all of these cases, the drug was given together with other agents known or suspected of being carcinogens. No epidemiological study was available to the Working Group.

5.3 Evaluation

There was no evidence for the carcinogenicity of 5-fluorouracil in the limited studies in experimental animals. The data from case reports in humans were insufficient to arrive at a conclusion.

On the basis of the available data, no evaluation could be made of the carcinogenic risk of 5-fluorouracil to humans.

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

ISOPHOSPHAMIDE

VOL.: 26 (1981) (p. 237)

CAS No.: 3778-73-2

Chem. Abstr. Name: 2*H*-1,3,2-Oxazaphosphorin-2-amine, *N*,3-bis(2-chloroethyl)-tetrahydro-, 2-oxide

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Isophosphamide was tested in four studies in mice and in one in rats by subcutaneous or intraperitoneal administration. In one study in mice with intraperitoneal injection it produced an increased incidence of lung adenomas. The other four studies, although indicating a carcinogenic effect, could not be evaluated.

Isophosphamide can induce teratogenic effects in mice and embryoletality at doses nontoxic to the mother. Isophosphamide is mutagenic in bacteria and produced chromosomal aberrations in Chinese hamster bone-marrow cells.

5.2 Human data

Isophosphamide has been used to a limited but increasing extent since the early 1970s as an antineoplastic and immunosuppressive drug.

No data were available to evaluate the teratogenic or mutagenic potential or chromosomal effects of isophosphamide in humans.

No case report or epidemiological study on isophosphamide was available to the Working Group.

5.3 Evaluation

There is *limited evidence* for the carcinogenicity of isophosphamide in mice and rats.

In the absence of data on humans, no evaluation can be made of the carcinogenic risk of isophosphamide to man.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: Suppl. 7 (1987) (p. 65: **Group 3**)

Synonyms for Isophosphamide

- A 4942
- Asta Z 4942
- 3-(2-Chloroethyl)-2-[(2-chloroethyl)amino]perhydro-2*H*-1,3,2-oxazaphosphorine 2-oxide
- Holoxan 1000
- Ifosamid
- Ifosamide
- lphosphamid
- lphosphamide
- Isoendoxan

- Isofosfamide
- Isofosfamidum
- NSC 109724
- Z 4942

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6-MERCAPTOPURINE

VOL.: 26 (1981) (p. 249)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

6-Mercaptopurine was tested by intraperitoneal administration and by skin painting (followed by croton oil) in mice and by intraperitoneal, subcutaneous and intravenous routes of administration in rats. Limitations to the data in all the reports precluded evaluation of the possible carcinogenicity of 6-mercaptopurine.

6-Mercaptopurine and 6-mercaptopurine riboside were proven to cause embryoletality at doses nontoxic to the mother and to induce severe teratogenic effects in several animal species. 6-Mercaptopurine is mutagenic in bacteria and in mice. It also produces chromosomal aberrations in various mammalian cells, including human peripheral lymphocytes tested in culture.

5.2 Human data

6-Mercaptopurine has been used commonly since the 1960s in the treatment of acute leukaemias.

It produces chromosomal aberrations in peripheral lymphocytes. No data were available to evaluate the mutagenic potential of the drug in humans. The available data are not sufficient to establish whether 6-mercaptopurine can induce a teratogenic effect.

A small number of case reports document the occurrence of acute nonlymphocytic leukaemia in patients who received 6-mercaptopurine for both non-neoplastic and neoplastic disorders. No epidemiological study was available to the Working Group.

5.3 Evaluation

There was no evidence for the carcinogenicity of 6-mercaptopurine in the limited studies in experimental animals. The data from case reports in humans were insufficient to arrive at a conclusion.

On the basis of the available data, no evaluation could be made of the carcinogenic risk of 6-mercaptopurine to humans.

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

METHOTREXATE

VOL.: 26 (1981) (p. 267)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Methotrexate was tested by oral administration in mice and hamsters, by intraperitoneal injection in mice and rats, and by intravenous injection in rats. One study in mice by oral administration reported a high incidence of lung carcinomas, but it did not include matched controls. All other studies failed to reveal a carcinogenic effect, but the significance of several was limited because of deficiencies in experimental design or reporting of data.

Methotrexate can induce teratogenic effects in several species and embryolethality at doses nontoxic to the mother. In monkeys, only embryolethality was observed.

Methotrexate is mutagenic in mice *in vivo*. In various mammalian cells in culture the drug causes chromosomal aberrations and increases in sister chromatid exchanges. Methotrexate also induces morphological transformation in mouse cells.

5.2 Human data

Methotrexate is an antineoplastic agent that has been commonly used since the early 1950s for the treatment of haematological and solid malignancies and as an immunosuppressive agent in bone-marrow transplantation. It is also used in the treatment of psoriasis.

Methotrexate is a human teratogen which causes a variety of malformations. It causes chromosomal aberrations in bone-marrow cells. No data were available to evaluate the mutagenic potential of this drug.

Methotrexate has been associated in case reports with a variety of subsequent neoplasms. One study of a defined group of patients, in which no expected numbers were presented, produced no suggestion of a cancer excess. The only other epidemiological study showed no excess of cancer in patients treated with methotrexate.

5.3 Evaluation

There was no evidence for the carcinogenicity of methotrexate in rats; its carcinogenicity could not be evaluated in mice and hamsters. The available data from studies in humans were inadequate to evaluate its carcinogenicity.

On the basis of the available data, no evaluation could be made of the carcinogenicity of methotrexate to humans.

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

PREDNISONONE

VOL.: 26 (1981) (p. 293)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Prednisone was tested in mice and rats by intraperitoneal administration. Little or no carcinogenic effect was observed, but the studies suffered from limitations in design and reporting.

Prednisone can induce teratogenic effects (predominantly cleft palate) in rodents. The available data do not indicate that the agent produces mutations or chromosomal damage.

5.2 Human data

Prednisone is a common anti-inflammatory and immunosuppressive agent frequently used in the therapy of a great variety of non-neoplastic and neoplastic conditions.

Use of prednisone during pregnancy may have a significant effect on reducing birth weight. The data are not sufficient to evaluate whether this drug can induce teratogenic effects in humans. There are no data available indicating that prednisone is mutagenic or clastogenic.

In view of its wide use, the many references to previous administration of prednisone in patients with cancer are to be expected by chance alone. There is no epidemiological evidence suggesting an etiological relationship between prednisone and neoplasia.

5.3 Evaluation

The available data from studies in experimental animals and in humans were *inadequate* to evaluate the carcinogenicity of prednisone to humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

PROCARBAZINE HYDROCHLORIDE

VOL.: 26 (1981) (p. 311)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Procarbazine hydrochloride is carcinogenic in mice and rats after its intraperitoneal administration, producing malignant tumours of the nervous system, haematopoietic system and possibly other organs in both species, and tumours of the mammary gland in rats only. Evidence of carcinogenicity was also found in mice and rats following its oral administration, in rats following its intravenous administration, and in one instance following transplacental exposure. Two studies in two species of nonhuman primates suggest that procarbazine hydrochloride may also produce myelogenous leukaemia when administered by multiple routes in the same animal.

Procarbazine hydrochloride can induce teratogenic effects in rats and embryoletality at doses nontoxic to the mother. This compound is mutagenic in bacteria, yeast, cultured mammalian cells and *Drosophila melanogaster*, and in mice and rats *in vivo*.

5.2 Human data

Procarbazine hydrochloride is used primarily in the treatment of Hodgkin's disease, non-Hodgkin's lymphoma and lung cancer, in combination with other drugs.

The available data are insufficient to evaluate the teratogenicity, mutagenicity or chromosomal effects of procarbazine hydrochloride in humans.

Both case reports and epidemiological studies indicate that acute nonlymphocytic leukaemia is produced in patients with Hodgkin's disease treated with combined therapeutic regimens which include vinca alkaloids, alkylating agents and procarbazine hydrochloride, often in conjunction with radiotherapy. No data were available to the Working Group which permit the assessment of the separate effects of procarbazine hydrochloride.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of procarbazine hydrochloride in mice and rats. There is *limited evidence* of its carcinogenicity in monkeys. There is sufficient evidence for the carcinogenicity in humans of intensive chemotherapeutic regimens that include alkylating agents, vinca alkaloids, procarbazine hydrochloride and prednisone. There is inadequate evidence of the carcinogenicity of procarbazine hydrochloride alone in humans.

On the basis of the combined experimental and human evidence, this compound should be considered for practical purposes as if it presented a carcinogenic risk to humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

TREOSULPHAN

VOL.: 26 (1981) (p. 341)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

No data on the carcinogenicity or teratogenicity of treosulphan in experimental animals were available to the Working Group.

The only available studies on chromosomal effects showed that it produces chromosomal aberrations in plants.

5.2 Human data

Treosulphan has had limited use since 1969, almost exclusively in the treatment of ovarian cancer.

The only epidemiological study indicates that use of this drug is followed by an increased risk of acute nonlymphocytic leukaemia.

5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of treosulphan in humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

Last updated: 8 April 1998

VINBLASTINE SULPHATE

VOL.: 26 (1981) (p. 349)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Vinblastine sulphate was tested in three studies, two by intraperitoneal injection in mice and rats, and one by intravenous injection in rats. No evidence of carcinogenicity was found, but vinblastine sulphate has not been adequately tested at high doses.

Vinblastine sulphate can induce teratogenic effects in several animal species and embryoletality at doses nontoxic to the mother. On the basis of the available data, this compound cannot be considered to be mutagenic.

5.2 Human data

Vinblastine sulphate has been widely used since the early 1960s, almost always in combination with other cytotoxic agents, in the treatment of neoplastic diseases, particularly lymphoma.

The available data are insufficient to evaluate its teratogenic effects in humans. No data on the mutagenicity or chromosomal effects of vinblastine sulphate in humans were available.

Vinblastine sulphate, mainly in combination therapy, has been associated in case reports with the subsequent development of leukaemias. The only epidemiological study was small and of short duration and showed no excess of subsequent neoplasms in patients treated with a regimen including vinblastine sulphate, adriamycin, bleomycin and dacarbazine.

5.3 Evaluation

There is no evidence of carcinogenicity in rats or mice on the basis of the available data. The data from studies in man are inadequate to evaluate the carcinogenicity of vinblastine sulphate in humans.

There is no evidence currently available to indicate that vinblastine sulphate is carcinogenic to humans, but the compound has not been extensively investigated.

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

VINCRIStINE SULPHATE

VOL.: 26 (1981) (p. 365)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Vincristine sulphate was tested in mice and rats by intraperitoneal injection. In these limited studies no evidence of carcinogenicity was found.

Vincristine sulphate can induce teratogenic effects in several animal species, and it induced embryoletality at doses nontoxic to the mother. There is no evidence to suggest that this compound is mutagenic.

5.2 Human data

Vincristine sulphate has been used since the early 1960s for treatment of acute leukaemia in children, often in combination with other antineoplastic agents. It is also frequently a part of combination chemotherapeutic regimens for Hodgkin's disease, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and other adult neoplasms.

The available data are insufficient to evaluate the teratogenicity of this drug in humans. No data were available on its mutagenic or chromosomal effects.

Both case reports and epidemiological studies indicate that acute nonlymphocytic leukaemia is produced in patients with Hodgkin's disease treated with combined therapeutic regimens which include vincristine sulphate, alkylating agents and procarbazine hydrochloride, often in conjunction with radiotherapy. No data were available on vincristine sulphate alone.

5.3 Evaluation

The available data in experimental animals were insufficient for evaluation. There is *sufficient evidence* for the carcinogenicity in humans of intensive chemotherapeutic regimens that include alkylating agents, vincristine sulphate, procarbazine hydrochloride and prednisone. There is *inadequate evidence* for the carcinogenicity of vincristine sulphate itself.

On the basis of the available data, no conclusion could be drawn as to the carcinogenicity of vincristine sulphate.

For definition of the italicized terms, see [Preamble Evaluation](#).

Subsequent evaluation: [Suppl. 7 \(1987\)](#)