**WORLD HEALTH ORGANIZATION**
**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER**

# IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
# Overall Evaluations of Carcinogenicity:
# An Updating of *IARC Monographs*
# Volumes 1 to 42

**Supplement 7**

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Dimethylcarbamoyl Chloride
Dimethyl Sulphate
1,4-Dioxane
Epichlorohydrin
Erionite
Ethylene Dibromide
Ethylene Thiourea
Fluorides (Inorganic, Used in Drinking-Water
5-Fluorouracil
Furniture and Cabinet-Making
Griseofulvin
Gyromitrin
Haematite and Ferric Oxide
Hexachlorobenzene
Hexachlorocyclohexanes
Hydralazine
Hydrazine
Iron & Steel Founding
Iron Dextran Complex
Isonicotinic Acid Hydrazide (Isoniazid)
Isopropyl Alcohol Manufacture (strong-acid process), Isopropyl Alcohol and Isopropyl Oils
Lead and Lead Compounds
Leather Goods Manufacture
Leather Tanning & Processing
Lumber and Sawmill Industries
Medroxyprogesterone Acetate
Melphalan
6-Mercaptopurine
Methotrexate
5-Methoxypsoralen
8-Methoxypsoralen (methoxsalen) plus Ultraviolet Radiation
Methyl Bromide
Methyl Chloride
4,4'-Methylene Bis(2-Methylaniline)
*N*-Methyl-*N'*-Nitro-*N*-Nitrosoguanidine (MNNG)
Methyl Parathion
Metronidazole
Mineral Oils
MOPP and Other Combined Chemotherapy Including Alkylating Agents
Mustard Gas (Sulphur Mustard)

1-Naphthylamine
2-Naphthylamine
1-Naphthylthiourea (ANTU)
Nitrogen Mustard
Oestrogens, Nonsteroidal
Oestrogen-Progestin Replacement Therapy
Oestrogen Replacement Therapy
Oestrogens, Steroidal
Oral Contraceptives, Combined
Oral Contraceptives, Sequential
Phenacetin and Analgesic Mixtures Containing Phenacetin
Phenazopyridine Hydrochloride
Phenelzine Sulphate
Phenobarbital
Phenylbutazone
*N*-Phenyl-2-Naphthylamine
Polybrominated Biphenyls
Polychlorinated Biphenyls
Prednisone
Procarbazine Hydrochloride
Progestins
Propylthiouracil
Pulp and Paper Manufacture
Reserpine
Rubber Industry
Saccharin
Shale Oils
Sodium-*o*-Phenylphenate
Soots
Spironolactone
Sulfafurazole (Sulphisoxazole)
Sulfamethoxazole
Talc
1,1,2,2-Tetrachloroethane
Tobacco Products, Smokeless
Tobacco Smoke
*ortho*-Toluidine
Treosulphan
4,5',8-Trimethylpsoralen
Triaziquone
Tris(2,3-dibromopropyl) phosphate
Uracil Mustard
Vinblastine Sulphate
Vincristine Sulphate
Vinyl Chloride
Vinylidine Chloride

# ACETAMIDE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 389)

**CAS No.**: 60-35-5

**Evidence for carcinogenicity to animals** (*sufficient*)

Acetamide produced benign and malignant liver tumours in rats following its oral administration [ref: 1-3]. In male mice, an increased incidence of malignant lymphomas was also observed [ref: 3].

**Overall evaluation**

Acetamide is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 71 (1999)

**Also see previous evaluation**: Vol. 7 (1974)

**References**

1. IARC Monographs, 7, 197-202, 1974

2. Flaks, B., Trevan, M.T. & Flaks, A. (1983) An electron microscope study of hepatocellular changes in the rat during chronic treatment with acetamide. Parenchyma, foci and neoplasms. Carcinogenesis, 4, 1117-1125

3. Fleischman, R.W., Baker, J.R., Hagopian, M., Wade, G.G., Hayden, D.W., Smith, E.R., Weisburger, J.H. & Weisburger, E.K. (1980) Carcinogenesis bioassay of acetamide, hexanamide, adipamide, urea and p-tolylurea in mice and rats. J. environ. Pathol. Toxicol., 3, 149-170

**Synonyms**

- Acetic acid amide
- Ethanamide
- Methane carboxamide

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Last updated: 13 April 1999

# ACTINOMYCIN D
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 80)

**CAS No.**: 50-76-0

**A. Evidence for carcinogenicity to humans** (*inadequate*)

A comparison was made in the USA between survivors of childhood cancer who developed second malignant neoplasms and controls, also survivors, matched on hospital, primary diagnosis, length of follow-up, site and dose of radiotherapy, and chronological period. Subjects who had received no radiotherapy, or who were believed to have some 'predisposing genetic syndrome', and whose second tumour had been diagnosed within six months of the first diagnosis, or with tumours that lay outside the field previously treated with radiation were excluded. Unexpectedly, cases had been treated much less often with actinomycin D than controls (relative risk, 0.13; upper 95% confidence limit, 0.47), and those who had been treated had received fewer courses of treatment (median, 2, compared to 6.5). For each type of primary childhood malignancy, except for bone tumours, the majority of cases had not been treated with actinomycin D. Second malignancies included soft-tissue sarcomas, haematological malignancies and various solid tumours. A relationship is plausible in view of the radiomimetic properties of actinomycin D, the simultaneous exposure of the treated patients to radiation, and the modal shape of radiation dose-effect curves in some laboratory systems [ref: 1].

A single attempt to confirm this finding covered only eight second malignancies (meeting criteria comparable to those in the first study) occurring among 412 patients who had been treated with radiation for Wilms' tumour of whom 222 had also received actinomycin D. No similar reduction in risk was observed. This study differed from the original in the small sample size, the uniformity with respect to primary diagnosis and that the comparison was made with historical controls [ref: 2].

**B. Evidence for carcinogenicity to animals** (*limited*)

Actinomycin D was tested for carcinogenicity in rats by intraperitoneal injection and by intragastric administration and in mice by repeated subcutaneous injections. It produced peritoneal sarcomas in rats following intraperitoneal injections [ref: 3,4] and a low incidence of subcutaneous sarcomas occurred in mice following repeated subcutaneous injections [ref: 3]. No tumour was observed in rats after intragastric administration of actinomycin D, but the duration of the experiment was short [ref: 5].

**C. Other relevant data**

Actinomycin D did not induce sister chromatid exchanges in peripheral blood lymphocytes of treated patients in one study [ref: 6].

Actinomycin D induced chromosomal aberrations and DNA strand breaks in human cells *in vitro*. It transformed mouse C3H 10T1/2 cells and induced chromosomal aberrations, sister chromatid exchanges, mutation, DNA strand breaks and unscheduled DNA synthesis, but not aneuploidy, in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations in *Drosophila*. Actinomycin D did not cause chromosomal aberrations in plants. It was mutagenic to *Neurospora crassa* but not to *Saccharomyces cerevisiae*, and conflicting results were obtained for gene conversion and mitotic recombination. It did not induce DNA damage in *Schizosaccharomyces pombe*. It was not mutagenic to bacteria and did not induce prophage [ref: 6].

**Overall evaluation**

Actinomycin D is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 10 (1976)

**References**


1. D'Angio, G.J., Meadows, A., Miké, V., Harris, C., Evans, A., Jaffe, N., Newton, W., Schweisguth, O., Sutow, W. & Morris-Jones, P. (1976) Decreased risk of radiation-associated second malignant neoplasms in actinomycin-D-treated patients. Cancer, 37, 1177-1185

2. Li, F.P., Yan, J.C., Sallan, S., Cassady, J.R., Jr, Danahy, J., Fine, W., Gelber, R.D. & Green, D.M. (1983) Second neoplasms after Wilms' tumor in childhood. J. natl Cancer Inst., 71, 1205-1209

3. IARC Monographs, 10, 29-41, 1976

4. Weisburger, J.H., Griswold, D.P., Prejean, J.D., Casey, A.E., Wood, H.B. & Weisburger, E.K. (1975) The carcinogenic properties of some of the principal drugs used in clinical cancer chemotherapy. Recent Results Cancer Res., 52, 1-17

5. Philips, F.S. & Sternberg, S.S. (1975) Tests for tumor induction by antitumor agents. Recent Results Cancer Res., 52, 29-35

6. IARC Monographs, Suppl. 6, 32-34, 1987


**Synonyms**

- Actinomycin A IV
- Actinomycin C1
- Actinomycin D deriv. of 1*H*-pyrrolo(2,1-1)(1,4,7,10,13)oxatetra-azacyclohexadecine
- Actinomycin D deriv. of 3H-phenoxaocardazine
- Actinomycin I
- Actinomycin IV
- Actinomycin X1
- Actinomycin-(threo-val-pro-sar-meval)
- 10,10'-[(2-Amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-Diyl)bis(carbonylimino)]bis-[dodecahydro-6,13-diisopropyl-2,5,9-trimethyl-1*H*-Pyrrolo-(2,1-1)(1,4,7,10,13)oxatetra-azacyclohexadecine]-1,4,7,11,14-pentone
- 1*H*-Pyrrolo(2,1-1)-(1,4,7,10,13)oxatetraazacyclohexadecine
- 2-Amino-*N*,*N*'-bis-[hexadecahydro-2,5,9-trimethyl-6,13-bis(1-methylethyl)-1,4,7,11,14-pentaoxo-1*H*-pyrrolo(2,1-1)(1,4,7,10,13)oxatetraazacyclohexadecin-10-yl]-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-dicarboxamide
- 2-Amino-*N*,*N*'-bis[hexadecahydro-6,13-diisopropyl-2,5,9-trimethyl-1,4,7,11,14-pentaoxo-1*H*-pyrrolo(2,1-1)(1,4,10,13)oxatetraazacyclohexadecin-10-yl]-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-dicarboxamide
- Bis(XI-lactone)*N*,*N*'-[(2-amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-diyl)bis-[carbonylimino(3-hydroxy-1-oxobutylidene)imino(3-methyl-1-oxobutylidene)(tetrahydro-1*H*-pyrrole-1,2-diyl)carbonyl(methylimino)-(1-oxo-1,2-ethanediyl)]bis(*N*-methyl)L-valine
- Cosmegen
- Dactinomycin
- Dactinomycin D
- Dilactone actinomycin D acid
- Dilactone actinomycindioic D acid
- HBF 386 meractinomycin
- *N*,*N*'-[(2-Amino-4,6-dimethyl-3-oxo-3*H*-phenoxazine-1,9-diyl)bis(carbonylimino[3-hydroxy-1-oxo-butylidene(tetrahydro-1*H*-pyrrole-1,2-diyl)carbonyl(methylimino)(1-oxo-1,2-

ethanediyl)-])
bis(*N*-methyl-L-valine)bis-(ζ-lactone)](stereoisomer)
- Oncostatin K

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Last updated: 9 March 1998

# ADRIAMYCIN
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 81)

**CAS No.:** 23214-92-8
**Chem. Abstr. Name**: (85-*cis*)-10-[(3-Amino-2,3,6-trideoxy-α-L-lyxohexapyranosyl)oxy]-7,8,9,10-tetrahydro- 6,8,11-trihydroxy-8-(hydroxyacetyl)-l-methoxy-5,12-naphthacenedione

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of adriamycin as a single agent was available to the Working Group. Occasional case reports, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis.

In a large systematic follow-up of patients with Hodgkin's disease treated with an intensive chemotherapeutic combination including adriamycin (plus vinblastine, bleomycin and dacarbazine) but no alkylating agent, preliminary evidence suggested no excess of acute nonlymphocytic leukaemia in the first decade after therapy [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Adriamycin was tested for carcinogenicity in rats by a single intravenous injection, producing mammary tumours [ref: 2-5], and by single or repeated subcutaneous injections, producing local sarcomas and mammary tumours [ref: 6,7]. Intravesicular instillation of adriamycin in rats resulted in a low incidence of bladder papillomas and enhanced the incidence of bladder tumours induced by *N*-nitroso-*N*-(4-hydroxybutyl)-*N*-butylamine [ref: 8].

**C. Other relevant data**

Adriamycin induced chromosomal aberrations in treated patients in one of two studies and sister chromatid exchanges in both studies. In another study, cisplatin-adriamycin combination chemotherapy induced sister chromatid exchanges in peripheral blood lymphocytes of treated patients. DNA strand breaks were induced in the cells of treated patients in one study [ref: 9].

Adriamycin has been tested extensively for genetic effects in a wide variety of tests *in vivo* and *in vitro*, giving consistently positive results. It induced chromosomal aberrations, micronuclei, sister chromatid exchanges and DNA damage in rodents *in vivo* and chromosomal aberrations, micronuclei, sister chromatid exchanges and DNA damage in human cells *in vitro*. It transformed virus-infected Fischer rat embryo cells and induced chromosomal aberrations, sister chromatid exchanges, mutation and DNA damage in cultured rodent cells. Adriamycin induced sex-linked recessive lethal mutations in *Drosophila*, chromosomal aberrations in plants and mutation in fungi. It was mutagenic to bacteria and induced DNA damage [ref: 9].

**Overall evaluation**

Adriamycin is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 10 (1976)

## References


1. Valagussa, P., Santoro, A., Kenda, R., Fossati Bellani, F., Franchi, F., Banfi, A., Rilke, F. & Bonadonna, G. (1980) Second malignancies in Hodgkin's disease: a complication of certain forms of treatment. Br. med. J., i, 216-219

2. IARC Monographs, 10, 43-49, 1976

3. Marquardt, H., Philips, F.S. & Sternberg, S.S. (1976) Tumorigenicity *in vivo* and induction of malignant transformation and mutagenesis in cell cultures by adriamycin and daunomycin. Cancer Res., 36, 2065-2069

4. Solcia, E., Ballerini, L., Bellini, O., Sala, L. & Bertazolli, C. (1978) Mammary tumors induced in rats by adriamycin and daunomycin. Cancer Res., 38, 1444-1446

5. Bucciarelli, E. (1981) Mammary tumor induction in male and female Sprague-Dawley rats by adriamycin and daunomycin. J. natl Cancer Inst., 66, 81-84

6. Maltoni, C. & Chieco, P. (1975) Adriamycin: a new potent carcinogen (Ital.). Osp. Vita, 2, 107-109

7. Casazza, A.M., Bellini, O., Formelli, F., Giuliani, F., Lenaz, L. & Magrini, U. (1977) Tumors and dental abnormalities after treatment of infant rats with adriamycin. Tumori, 63, 331-338

8. Ohtani, M., Fukushima, S., Okamura, T., Sakata, T., Ito, N., Koiso, K. & Niijima, T. (1984) Effects of intravesical instillation of antitumor chemotherapeutic agents on bladder carcinogenesis in rats treated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. Cancer, 54, 1525-1529

9. IARC Monographs, Suppl. 6, 35-39, 1987


## Synonyms

- 10-[(3-Amino-kg,6-trideoxy-D-lyxohexopyranosyl)oxy]-8-glycolcyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione
- Doxorubicin
- F.I. 106
- 1,2,3,4,6,11-Hexahydro-4β,5,12-trihydroxy-4-(hydroxyacetyl)-10- methoxy-6,11-dioxonaphthacen-1β-yl-3-amino-2,3,6-trideoxy-α-L-lyxohexopyranoside
- 14-Hydroxydaunomycin
- 14'-Hydroxydaunomycin
- NSC 123127

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# ALDRIN
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 88)

**CAS No.**: 309-00-2

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Specific mention of aldrin in analytical epidemiological studies is limited to reports of follow-up of two cohorts of men employed in its manufacture in plants where dieldrin and endrin (and, in one, telodrin) were also manufactured [ref: 1-4]. In the most recent report of the first of these cohorts [ref: 3], 232 of 233 exposed workers were successfully followed from four to 29 (mean, 24) years, with duration of exposure to pesticides varying between four and 27 (mean, 11) years. There were nine deaths from cancer with 12 expected (standardized mortality ratio [SMR], 75; 95% confidence interval, 25-125). In the second cohort [ref: 4], 90% of 1155 men were followed for 13 years or more. Mortality from all cancers was not increased (SMR, 82; 56-116), although there were apparent increases in mortality from cancers of the oesophagus, rectum and liver, based on very small numbers.

**B. Evidence for carcinogenicity to animals** (*limited*)

Aldrin was tested for carcinogenicity by the oral route in mice and rats. In mice, it produced malignant liver neoplasms [ref: 1,5]. In rats, the incidence of thyroid tumours was increased in exposed animals in one study ref: 5], but this could not be clearly associated with treatment; three other studies in rats gave negative results [ref: 1,6] and one was inadequate [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of aldrin in humans. It did not induce dominant lethal mutations in mice. In single studies, it induced chromosomal aberrations in bone-marrow cells of rats and mice, but no micronuclei in bone-marrow cells of mice treated *in vivo*. It induced chromosomal aberrations in cultured human lymphocytes; studies of DNA damage in human and rodent cells *in vitro* were inconclusive. Aldrin inhibited intercellular communication in both human and rodent cell systems. It did not induce sex-linked recessive lethal mutations in *Drosophila* but was mutagenic to yeast. It was not mutagenic to bacteria and did not induce breakage of plasmid DNA [ref: 7].

**Overall evaluation**

Aldrin is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 5 (1974)

**References**

1. IARC Monographs, 5, 25-38, 1974

2. Van Raalte, H.G.S. (1977) Human experience with dieldrin in perspective. Ecotoxicol. environ. Saf., 1, 203-210

3. Ribbens, P.H. (1985) Mortality study of industrial workers exposed to aldrin, dieldrin and endrin. Int. Arch. occup. environ. Health, 56, 75-79

4. Ditraglia, D., Brown, D.P., Namekata, T. & Iverson, N. (1981) Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand. J. Work Environ. Health, 7 (Suppl. 4), 140-146

5. National Cancer Institute (1978) Bioassays of Aldrin and Dieldrin for Possible Carcinogenicity (Tech. Rep. Ser. No. 21; DHEW Publ. No. (NIH) 78-821), Bethesda, MD, US Department of Health, Education and Welfare

6. Deichmann, W.B., Macdonald, W.E. & Lu, F.C. (1979) Effects of chronic aldrin feeding in two strains of female rats and a discussion on the risks of carcinogens in man. In: Deichmann, W.B., ed., Toxicology and Occupational Medicine, New York, Elsevier/North-Holland, pp. 407-413

7. IARC Monographs, Suppl. 6, 57-59, 1987

**Synonyms**

- 1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-1,4-endo-exo-5,8-dimethano-naphthalene
- 1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-endo-1,4,-exo-5,8-dimethanonaphthalene
- 1,2,3,4,10,10-Hexachloro-1,4,4a,5,8,8a-hexahydro-exo-1,4-endo-5,8,-dimethanonaphthalene
- 1,2,3,4,10,10-Hexachloro-1,4,4a,8,8a-hexahydro-endo,exo-1,4:5,8-dimethanonaphthalene
- Compound 118
- ENT 15,949
- Hexachlorohexahydro-endo-exo-dimethanonaphthalene
- HHDN

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# ALUMINIUM PRODUCTION
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 89)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

The lung has been the most common site identified for which there is an excess cancer risk in populations of aluminium production workers. Overall, early studies showed a borderline excess in relative risk, with some studies showing a doubling of risk and some showing no excess. Smoking histories were not given in any of these studies. In one study in which populations in the industry were compared on the basis of their exposures to pitch volatiles, there was a relationship between incidence of lung cancer and length of exposure, and there was a significant excess of cancer among workers who had worked for 21 years or more [ref: 1].

In three studies in the same aluminium-producing area, an increased risk of bladder cancer was associated with work in aluminium production in plants where primarily the Söderberg process was used. In one study in which smoking was controlled for, while there was a borderline excess in risk for nonsmokers, the risk for smokers was markedly increased [ref: 1].

Excess mortality from lymphosarcoma/reticulosarcoma was noted in two cohort studies, which covered partially the same population [ref: 1].

Statistically significant excess risks for pancreatic cancer and for leukaemia were noted as isolated findings in two studies and in one study, respectively [ref: 1].

Some of these studies have been updated. In Canada, the mortality of a large group of men employed in aluminium production using the Söderberg process was examined between 1950 and 1977, and compared with the pertinent rates for the Province of Quebec. Workers 'ever' exposed to condensed pitch volatiles ('tar') exhibited significantly increased mortality from all cancers (304 observed, 246.6 expected), and from oesophageal and stomach cancer (50 observed, 32.8 expected), lung cancer (101 observed, 70.7 expected) and other malignancies (60 observed, 45.3 expected). Analysis of lung cancer mortality by increasing years of exposure, tar-years of exposure and years since first exposure to tar revealed a steady, statistically significant, increasing trend. No similar clear-cut pattern was noted for cancers of the oesophagus or stomach. Deaths from cancer of the urinary organs (20 observed, 13.7 expected) and bladder (12 observed, 7.5 expected) were more numerous than expected, but not significantly so. Nonetheless, when mortality from cancer at each of these sites was analysed according to tar-years of exposure, significantly increasing trends were noted. Among workers 'never' exposed to tar, mortality was not elevated above expectancy for any cancer site [ref: 2].

The risk for bladder cancer was further investigated in a case-control study based on 488 bladder cancer cases occurring in 1970-1979 in regions of the Province of Quebec where five aluminium plants were operating using the Söderberg production process. A statistically significant odds ratio of 2.7, based on 45 exposed cases, was found for employment in Söderberg reactor rooms. The risk increased steadily with time worked in this department, with odds ratios ranging from 1.9 for those who had worked for one to nine years, up to 4.5 for those who had worked in the department for over 30 years. This trend was statistically significant. The risk also increased steadily with increasing estimated exposure to 'tar' and polycyclic aromatic hydrocarbons and remained almost unchanged after adjusting for cigarette smoking, length of employment and age [ref: 3]. This set of data was later reanalysed in an attempt to quantify the noted exposure-response relationship. More refined quantitative estimates of historical workplace exposure and more complete information on smoking habits were used. Estimates of bladder cancer risk were highly statistically significantly related to three exposure indices: years spent in the Söderberg potroom; cumulative exposure to benzene-soluble material, an indicator of overall exposure to tar volatiles; and cumulative exposure to benzo[*a*]pyrene, an indicator of exposure to polycyclic aromatic hydrocarbons. It was estimated that an aluminium smelter worker exposed to 0.2 mg/m$^3$ benzene-soluble material for 40 years has a

likelihood of contracting bladder cancer approximately 2.5-fold that of a nonexposed person. Workers exposed to 5 µg/m$^3$ benzo[*a*]pyrene for 40 years had a likelihood of contracting bladder cancer approximately five-fold that of an unexposed person. Smoking did not confound the relationship [ref: 4].

There is sufficient evidence that certain exposures occurring during aluminium production cause cancer. Pitch volatiles have fairly consistently been suggested in epidemiological studies as being possible causative agents. Dose-response relationships have been clarified, and confounding by smoking controlled for.

**B. Other relevant data**

No effect on the incidence of sister chromatid exchanges in peripheral blood lymphocytes of workers in the aluminium industry was observed in one study. No increase in the incidence of structural chromosomal aberrations was observed in the lymphocytes of workers in an aluminium reduction plant exposed to coal-tar pitch volatiles (anode production area); analyses of the semen showed no effect on sperm morphology, sperm count or double-Y bodies, when compared to matched controls from the same area, but there was an excess of mutagenic urine samples among these workers as compared to controls. Urine samples from workers in an anode manufacturing plant were not mutagenic to *Salmonella typhimurium* in the presence of a metabolic system. Methanol extracts of sputum and bronchial expectorates, pooled separately for smoking and for nonsmoking workers in a Söderberg process potroom, were tested for mutagenicity to *S. typhimurium* in the presence of an exogenous metabolic system. Expectorates from smokers were mutagenic, while those from nonsmokers yielded inconclusive results; samples from pooled controls were inactive [ref: 5].

**Overall evaluation**

Aluminium production is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 34 (1984)

**References**

1. *IARC Monographs, 34*, 37-64, 1984

2. Gibbs, G.W. (1985) Mortality of aluminum reduction plant workers, 1950 through 1977. *J. occup. Med., 27*, 761-770

3. Thériault, G., Tremblay, C., Cordier, S. & Gingras, S. (1984) Bladder cancer in the aluminium industry. *Lancet, i*, 947-950

4. Armstrong, B.G., Tremblay, C.G., Cyr, D. & Thériault, G.P. (1986) Estimating the relationship between exposure to tar volatiles and the incidence of bladder cancer in aluminum smelter workers. *Scand. J. Work Environ. Health, 12*, 486-493

5. *IARC Monographs, Suppl. 6*, 57-59, 1987

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Last updated: 6 February 1998

# *para*-AMINOAZOBENZENE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 390)

**CAS No.**: 60-09-3
**Chem. Abstr. Name**: 4-(Phenylazo)benzenamine

**Evidence for carcinogenicity to animals** (*sufficient*)

*para*-Aminoazobenzene produced liver tumours in rats following its oral administration and produced epidermal tumours in rats after application to the skin [ref: 1]. In mice, hepatomas were found in 50-100% of males after one or four intraperitoneal injections of *para*-aminoazobenzene, compared to 3% in controls and in females. In two other strains of mice, 93% and 46% of males had hepatomas at 11 months of age after a single intraperitoneal injection of the compound [ref: 2]. When pregnant and newborn male and female mice were administered high doses of *para*-aminoazobenzene by subcutaneous injection, there was a borderline increase in the incidences of tumours of the liver and of the haematopoietic and lymphoid tissues in mice treated transplacentally and a statistically significant increase in the incidence of these tumours in neonates [ref: 3].

**Overall evaluation**

*para*-Aminoazobenzene is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 8 (1975)

**References**

1. IARC Monographs, 8, 53-60, 1975

2. Delclos, K.B., Tarpley, W.G., Miller, E.C. & Miller, J.A. (1984) 4-Aminoazobenzene and *N*,*N*-dimethyl-4-aminoazobenzene as equipotent hepatic carcinogens in male C57BL/6xC3H/He$F_1$ mice and characterization of *N*-(deoxyguanosin-8-yl)-4-aminoazobenzene as the major persistent hepatic DNA-bound dye in these mice. Cancer Res., 44, 2540-2550

3. Fujii, K. (1983) Induction of tumors in transplacental or neonatal mice administered 3'-methyl-4-dimethylaminoazobenzene or 4-aminoazobenzene. Cancer Lett., 17, 321-325

**Synonyms**

- AAB
- Aminoazobenzene
- 4-Aminoazobenzene
- 4-Amino-1,1'-azobenzene
- Aminoazobenzene [indicator]
- 4-Aminoazobenzol
- *para*-Aminoazobenzol
- *para*-Aminoazotoluene
- *para*-Aminodiphenylimide
- Aniline Yellow
- 4-Benzeneazoaniline

- Brasilazina oil Yellow G
- Ceres Yellow R
- Fast spirit Yellow
- Fast spirit Yellow AAB
- Fat Yellow AAB
- Induline R
- Oil-sol. aniline Yellow
- Oil Yellow AAB
- Oil Yellow AN
- Oil Yellow B
- Oil Yellow 2G
- Oil Yellow R
- Organol Yellow
- Organol Yellow 2A
- Paraphenolazo aniline
- *para*-(Phenylazo)aniline
- 4-(Phenylazo)benzenamine
- *para*-Phenylazophenylamine
- Solvent Yellow 1
- Somalia Yellow 2G
- Stearix brown 4R
- Sudan Yellow R
- Sudan Yellow RA

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Last updated: 27 February 1998

# 4-AMINOBIPHENYL
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 91)

**CAS No.**: 92-67-1
**Chem. Abstr. Name**: 4-Biphenylamine

**A. Evidence for carcinogenicity to humans** (*sufficient*)

The extent of bladder cancer risk associated with exposure to 4-aminobiphenyl was first documented by a descriptive study in the mid 1950s: of 171 men exposed to 4-aminobiphenyl between 1935 and 1955, 19 developed bladder tumours [ref: 1]. This observation appears to have been sufficient to prompt discontinuation of production and to prevent widespread use of the chemical. In 1955, a surveillance programme was initiated on workers reported to have been exposed to the chemical: during the following 14 years, 541 men were kept under surveillance by clinical and laboratory examinations; 86 had positive or suspicious cytology of the urinary sediment some time during the observation period, and 43 developed histologically confirmed carcinoma of the urinary bladder [ref: 2].

The hypothesis that another potential carcinogen, 4-nitrobiphenyl, was actually associated with the increased bladder cancer risk among these workers was raised but was dismissed by careful reconsideration of the processes involved and the possible exposures of the workers under surveillance [ref: 3].

In a survey of cancer mortality among workers at a chemical plant producing a variety of chemicals, a ten-fold increase in mortality from bladder cancer was reported. All of the nine cases on which the excess was based had started work in the plant before 1949, and 4-aminobiphenyl was known to have been used from 1941 until 1952 [ref: 4].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

4-Aminobiphenyl was tested for carcinogenicity by oral administration in rabbits, dogs and mice and by subcutaneous administration in rats. Following its oral administration, it induced bladder papillomas and carcinomas in rabbits [ref: 1] and dogs [ref: 1,5], and neoplasms at various sites in mice, including dose-related increases in the incidences of angiosarcomas [ref: 6], hepatocellular tumours [ref: 1,6] and bladder carcinomas [ref: 1,6]. Following its subcutaneous administration to rats, it induced tumours of the mammary gland and intestine [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of 4-aminobiphenyl in humans. It formed DNA adducts in the bladder epithelium of dogs and protein adducts in serum albumin of rats treated *in vivo*. It induced mutation in human fibroblasts and mutation, DNA strand breaks and unscheduled DNA synthesis in cultured rodent cells. 4-Aminobiphenyl was mutagenic to bacteria and induced prophage [ref: 7].

**Overall evaluation**

4-Aminobiphenyl is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 1 (1972)

## References


1. *IARC Monographs*, *1*, 74-79, 1972

2. Melamed, M.R. (1972) Diagnostic cytology of urinary tract carcinoma. A review of experience with spontaneous and carcinogen induced tumors in man. *Eur. J. Cancer*, *8*, 287-292

3. Melick, W.F. (1972) Bladder carcinoma and xenylamine. *New Engl. J. Med.*, *287*, 1103

4. Zack, J.A. & Gaffey, W.R. (1983) A mortality study of workers employed at the Monsanto Company plant in Nitro, West Virginia. *Environ. Sci. Res.*, *26*, 575-591

5. Block, N.L., Sigel, M.M., Lynne, C.M., Ng, A.B. & Grosberg, R.A. (1978) The initiation, progress, and diagnosis of dog bladder cancer induced by 4-aminobiphenyl. *Invest. Urol.*, *16*, 50-54

6. Schieferstein, G.J., Littlefield, N.A., Gaylor, D.W., Sheldon, W.G. & Burger, G.T. (1985) Carcinogenesis of 4-aminobiphenyl in BALB/cStCr1fC3HfNctr mice. *Eur. J. Cancer clin. Oncol.*, *21*, 865-873

7. *IARC Monographs, Suppl. 6*, 60-63, 1987


## Synonyms

- *para*-Aminobiphenyl
- *para*-Aminodiphenyl
- 4-Aminodiphenyl
- *para*-Biphenylamine
- *para*-Phenylaniline
- Xenylamine

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# AMITROLE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 92)

**CAS No.**: 61-82-5
**Chem. Abstr. Name**: 1*H*-1,2,4-Triazol-3-amine

**A. Evidence for carcinogenicity to humans** (*inadequate*)

In a small cohort study of 348 Swedish railroad workers exposed for 45 days or more to amitrole, 2,4-D or 2,4,5-T and to other organic (e.g., monuron and diuron) and inorganic chemicals (e.g., potassium chlorate), there was an excess of deaths from malignant neoplasms (17 observed, 11.9 expected). There was a statistically significant excess of all cancers among those exposed to amitrole and chlorophenoxy herbicides: six deaths from cancer with 2.9 expected, of which all six - with 1.8 expected ($p < 0.005$) - occurred in those first exposed ten years or more before death. No significant excess was seen among those exposed mainly to amitrole: five deaths from cancer with 3.3 expected; three deaths with two expected occurring in those first exposed ten years or more before death [ref: 1]. The role of amitrole exposure is therefore not possible to evaluate.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Amitrole was tested for carcinogenicity in mice by oral administration, skin application and transplacental exposure, in rats by oral and subcutaneous administration and in hamsters by oral administration. After oral administration, it produced thyroid tumours and benign and malignant liver tumours in mice of each sex, benign and malignant thyroid tumours in male and female rats and benign pituitary tumours in female rats [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of amitrole in humans.

Amitrole did not induce micronuclei in bone-marrow cells of mice or unscheduled DNA synthesis in hepatocytes of rats treated *in vivo*. It induced transformation of Syrian hamster embryo cells and increased the incidence of sister chromatid exchanges in Chinese hamster ovary cells; both positive and negative results were reported for mutation in cultured rodent cells. Amitrole did not induce sex-linked recessive lethal mutations or aneuploidy in *Drosophila*; it induced chromosomal aberrations in plants. Both positive and negative results were obtained in assays for gene conversion and mutation in fungi, but amitrole induced aneuploidy. It was not mutagenic to bacteria and did not induce DNA damage [ref: 2].

**Overall evaluation**

Amitrole is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001)

**Also see previous evaluations**: Vol. 7 (1974); Vol. 41 (1986)

**References**

1. IARC Monographs, 41, 293-317, 1986

2. IARC Monographs, Suppl. 6, 64-67, 1987

**Synonyms**

- 3-Amino-s-triazole
- 3-Amino-1,2,4-triazol
- Aminotriazole
- 2-Aminotriazole
- 3-Aminotriazole
- 3-Amino-1,2,4-triazole
- 3-Amino-1*H*-1,2,4-triazole
- 2-Amino-1,3,4-triazole
- 5-Amino-1*H*-1,2,4-triazole
- 5-Amino-1,2,4-triazole
- Amitrol
- Amitrol 90
- Amizol
- AT
- 3,A-T
- ATA
- Azaplant
- Cytrol
- Cytrole
- ENT 25445
- Herbidal total
- 1,2,4-Triazole-3-amine

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# ANAESTHETICS, VOLATILE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 93)

**A. Evidence for carcinogenicity to humans** (*inadequate* for volatile anaesthetics)

Data from postal surveys of cancer incidence among working populations showed a higher rate of cancer among female operating-room personnel than among controls [ref: 1-4], partly reflecting an excess of leukaemia and lymphoma [ref: 2]. In one of the studies [ref: 4], a higher rate of cancer was reported among dental assistants with relatively heavy exposure to anaesthetics, reflecting a higher prevalence of cervical and uterine cancer in women with heavier exposure to anaesthetics than in those with a lighter exposure (significant only for cancer of the cervix). All of these postal surveys had major shortcomings [ref: 5], with response rates varying from 40-82%. Five mortality studies were carried out on anaesthetists [ref: 6-10]. A deficiency of deaths from cancer was seen in four [ref: 6,8-10]; however, in one study [ref: 6], there was an excess of deaths from lymphoma and myeloma (17 observed, 8.9 expected, with a ratio of 1.91 [95% confidence interval, 1.2-2.6) and, in another, a possible excess of cancer of the pancreas [ref: 7]. Cancer incidence was also studied in 28 235 registered nurses. Minor excesses of breast cancer, lymphoma and acute myelogenous leukaemia were balanced by deficits in cancers at other sites. No significant difference was found for active operation and anaesthetic nurses as compared to the female Norwegian population [ref: 11]. In a study of the incidence of cancer among offspring born to nurse anaesthetists, three neoplasms occurred in two of 434 children born to anaesthetists who had worked during pregnancy (a neuroblastoma and a carcinoma of the thyroid in one, and a carcinoma of the parotid in the other) and one leukaemia among the 261 children born to anaesthetists who had not worked during pregnancy [ref: 12].

It is not possible to consider exposure to different volatile anaesthetics separately, although the study of US anaesthesiologists working during 1930-1946 [ref: 10] concerned the period before fluorinated anaesthetic agents were introduced in the 1950s.

**B. Evidence for carcinogenicity to animals** (*inadequate* for enflurane, halothane, isoflurane, methoxyflurane and nitrous oxide)

Enflurane was tested for carcinogenicity by inhalation in one strain of mice at the maximum tolerated dose [ref: 13] and at several dose levels in a limited study in which treatment started *in utero* [ref: 14]. No treatment-related neoplasm was observed.

Halothane was tested for carcinogenicity by inhalation in mice and rats. When mice were exposed *in utero* and then three times weekly for 78 weeks at the maximum tolerated dose [ref: 15] or 24 times at several dose levels [ref: 14], no treatment-related neoplasm was observed. No carcinogenic effect was seen in rats exposed to a low level of halothane alone or in combination with nitrous oxide [ref: 16].

Isoflurane was tested for carcinogenicity by inhalation in one strain of mice. It induced liver tumours in one experiment [ref: 1] but no treatment-related neoplasm in another [ref: 14]. Both experiments had limitations.

Methoxyflurane was tested for carcinogenicity in mice by inhalation *in utero* in one limited study. No treatment-related neoplasm was observed [ref: 14].

Nitrous oxide was tested for carcinogencity by inhalation in mice and rats. In one limited study in mice in which exposure started *in utero*, no treatment-related neoplasm was observed [ref: 14]. No carcinogenic effect was seen in rats exposed chronically to a low dose of nitrous oxide alone or in combination with halothane [ref: 16].

**C. Other relevant data**

Studies in hospital personnel exposed to inhalation anaesthetics showed an increased frequency of chromosomal aberrations but not of sister chromatid exchanges in peripheral blood lymphocytes [ref: 17,18].

Neither enflurance nor halothane induced dominant lethal mutations in rodents *in vivo*, and halothane did not induce chromosomal aberrations, micronuclei or sister chromatid exchanges in rodents treated *in vivo* [ref: 19].

Divinyl ether and fluroxene induced sister chromatid exchanges in cultured Chinese hamster ovary cells and mutation in bacteria. Negative results were obtained in these tests with halothane, enflurane, diethyl ether, isoflurane, methoxyflurane and nitrous oxide. Halothane caused gene conversion and mutation in yeast under conditions that enhanced endogenous levels of cytochrome P450. Diethyl ether was not mutagenic to fungi. Cyclopropane was not mutagenic to bacteria [ref: 19].

**Overall evaluation**

Anaesthetics, volatile are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see General considerations on volatile anaesthetics**: Vol. 11 (1976) (p. 285)

**References**

1. IARC Monographs, 11, 285-293, 1976

2. American Society of Anesthesiologists Ad Hoc Committee on the Effect of Trace Anesthetics on the Health of Operating Room Personnel (1974) Occupational disease among operating room personnel: a national study. Anesthesiology, 41, 321-340

3. Spence, A.A., Cohen, E.N., Brown, B.W., Jr, Knill-Jones, R.P. & Himmelberger, D.U. (1977) Occupational hazards for operating room-based physicians. Analysis of data from the United States and the United Kingdom. J. Am. med. Assoc., 238, 955-959

4. Cohen, E.N., Brown, B.W., Wu, M.L., Whitcher, C.E., Brodsky, J.B., Gift, H.C., Greenfield, W., Jones, T.W. & Driscoll, E.J. (1980) Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J. Am. dent. Assoc., 101, 21-31

5. Vessey, M.P. (1978) Epidemiological studies of the occupational hazards of anaesthesia - a review. Anaesthesia, 33, 430-438

6. Bruce, D.L., Eide, K.A., Linde, H.W. & Eckenhoff, J.E. (1968) Causes of death among anesthesiologists: a 20-year survey. Anesthesiology, 29, 565-569

7. Doll, R. & Peto, R. (1977) Mortality among doctors in different occupations. Br. med. J., i, 1433-1436

8. Bruce, D.L., Eide, K.A., Smith, N.J., Seltzer, F. & Dykes, M.H.M. (1976) A prospective survey of anesthesiologist mortality, 1967-1971. Anesthesiology, 41, 71-74

9. Lew, E.A. (1979) Mortality experience among anesthesiologists, 1954-1976. Anesthesiology, 51, 195-199

10. Linde, H.W., Mesnick, P.S. & Smith, N.J. (1981) Causes of death among anesthesiologists: 1930-1946. Anesth. Analg., 60, 1-7

11. Lund, E. (1985) Cancer among nurses especially in relation to exposure to anaesthetic gases (Norv.). Tidsskr. Laeg., 105, 572-575

12. Corbett, T.H., Cornell, R.G., Endres, J.L. & Lieding, K. (1974) Birth defects among children of nurse-anesthetists. Anesthesiology, 41, 341-344

13. Baden, J.M., Egbert, B. & Mazze, R.I. (1982) Carcinogen bioassay of enflurane in mice. Anaesthesiology, 56, 9-13

14. Eger, E.I., White, A.E., Brown, C.L., Biava, C.G., Corbett, T.H. & Stevens, W.C. (1978) A test of the carcinogenicity of enflurane, isoflurane, halothane, methoxyflurane, and nitrous oxide in mice. Anesth. Analg., 57, 678-694

15. Baden, J.M., Mazze, R.I., Wharton, R.S., Rice, S.A. & Kosek, J.C. (1979) Carcinogenicity of halothane in Swiss/ICR mice. Anesthesiology, 51, 20-26

16. Coate, W.B., Ulland, B.M. & Lewis, T.R. (1979) Chronic exposure to low concentrations of halothane-nitrous oxide: lack of carcinogenic effect in the rat. Anesthesiology, 50, 306-309

17. Bigatti, P., Lamberti, L., Ardito, G., Armellino, F. & Malanetto, C. (1985) Chromosome aberrations and sister chromatid exchanges in occupationally exposed workers. Med. Lav., 76, 334-339

18. Husum, B. & Wulf, H.C. (1980) Sister chromatid exchanges in peripheral lymphocytes in operating room personnel. Acta anaesth. scand., 24, 22-24

19. IARC Monographs, Suppl. 6, 68, 206-207, 248-249, 282-285, 319-320, 325-327, 345-346, 375-376, 425-426, 1987

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Last updated: 9 March 1998

# ANDROGENIC (ANABOLIC) STEROIDS
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 96)

**Oxymetholone**
**CAS No.:** 437-07-1
**Chem. Abstr. Name:** 17-Hydroxy-2-(hydroxymethylene)-17-methyl-5α, 17 β-androstan-3-one

**Testosterone**
**CAS No.:** 58-22-0
**Chem. Abstr. Name**: (17β)-17-Hydroxyandrost-4-en-3-one

**Testosterone oenanthate**
**CAS No.**: 315-37-7
**Chem. Abstr. Name**: (17β)-17-[(1-Oxoheptyl)oxy]-androst-4-en-3-one

**Testosterone propionate**
**CAS No.**: 57-85-2
**Chem. Abstr. Name**: (17β)-17-(1-Oxopropoxy)-androst-4-en-3-one

**A. Evidence for carcinogenicity to humans** (*limited*)

Cases of benign hepatoma, peliosis hepatis, primary hepatocellular carcinoma and hepatic cholangiocarcinoma have all been linked to the use of androgenic steroids, mostly oxymetholone [ref: 1-13]. At least 25 cases of liver-cell tumour have been reported in patients with Fanconi's anaemia [ref: 1-6,11,12], aplastic anaemia [ref: 1,4,7,8], paroxysmal nocturnal haemoglobinuria [ref: 1,12,13], panmyelopathy [ref: 9] or megaloblastic anaemia [ref: 10] treated with oxymetholone alone or in combination with other androgenic steroid drugs. Usually, treatment was given for years, but cancer has occurred within as little as two months of therapy [ref: 6], and there have been well-documented instances of remission following the withdrawal of oxymetholone treatment [ref: 8,9,11]. Hepatocellular carcinomas were also reported after extended treatment with oxymetholone of one patient with nephrolithiasis [ref: 14] and of another with chronic renal failure [ref: 15]; and hepatocellular carcinomas [ref: 1,16], cholangiocarcinomas [ref: 15] and adenomas [ref: 16] were reported after extended treatment of patients with methyltestosterone, testosterone enanthate and nandrolone decanoate for hypogonadism [ref: 16], hypopituitarism [ref: 13], chronic renal failure [ref: 15] and generalized weakness [ref: 15].

The fact that castration palliates prostatic cancers suggests that testosterone may be involved in the genesis of these tumours [ref: 17], and a number of epidemiological observations suggest that increased testosterone levels may increase the risk for prostatic cancer. In addition, patients with cirrhosis, who have depressed testosterone levels [ref: 18], have low rates of prostatic cancer [ref: 19], and prostatic cancer is seemingly unknown among castrates [ref: 20]. There have also been a number of case reports [ref: 21-23] of prostatic cancer developing after androgen therapy; there was only one, unusual case, however, in which the cancer developed in a 'body-builder' at the age of 40 who had taken anabolic steroids for 18 years [ref: 23].

Blacks in the USA have the highest prostatic cancer rates in the world. Their two-fold increased risk, compared to US whites, is evident at the earliest age at which prostatic cancer occurs. Ross *et al.* [ref: 24] showed that young US blacks have a 15% higher mean testosterone serum level than young US whites, and argued that this difference could readily explain the two-fold difference in rates.

In one study [ref: 25], prostatic cancer cases were found to have higher mean levels of serum testosterone than healthy controls of the same age. Prostatic cancer cases in this study had a clear excess of high testosterone values. Another study [ref: 26] showed significantly higher levels of

serum testosterone in prostatic cancer cases than in age-matched controls among US blacks, but not among African blacks. A number of case-control studies, however, showed no significant difference between cases and controls [ref: 7-29]. At present, there are insufficient data to permit firm conclusions to be drawn.

The development of myeloid leukaemia as a complication of Fanconi's anaemia has been reported in association with the use of oxymetholone [ref: 11,30,31], and there has been one case report of paroxysmal nocturnal haemoglobinuria in which a myeloproliferative disorder developed after oxymetholone therapy [ref: 32].

The evidence that anabolic steroids can cause both benign and malignant liver tumours is quite strong. However, because no analytical epidemiological study has been done, the Working Group felt constrained to classify the evidence for carcinogenicity to humans as no more than 'limited'.

**B. Evidence for carcinogenicity to animals** (*sufficient* for testosterone)

Testosterone propionate was tested for carcinogenicity in mice and rats by subcutaneous implantation, producing cervical-uterine tumours in female mice and prostatic adenocarcinomas in male rats. Neonatal treatment of female mice by subcutaneous injection of testosterone induced hyperplastic epithelial lesions of the genital tract and increased the incidence of mammary tumours. 5β-Dihydrotestosterone, which is considered hormonally inactive in adults, also increased the incidence of mammary tumours in mice when given neonatally by subcutaneous injection [ref: 33]. Depots of testosterone propionate implanted in rats resulted in an increased incidence of prostatic adenocarcinomas [ref: 34]. Subcutaneous administration of testosterone propionate following intravenous treatment with *N*-methyl-*N*-nitrosourea produced a high incidence of prostatic adenocarcinoma not seen with the individual compounds alone [ref: 35].

No data were available to the Working Group on oxymetholone.

**C. Other relevant data**

No data were available on the genetic and related effects of testosterone in humans.

Testosterone did not induce sperm abnormalities or micronuclei in mice treated *in vivo* and was not mutagenic to bacteria [ref: 36].

**Overall evaluation**

Androgenic (anabolic) steroids are *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 6 (1974); Vol. 13 (1977); Vol. 21 (1979)

**References**

1. IARC Monographs, 13, 131-139, 1977

2. Port, R.B., Petasnick, J.P. & Ranniger, K. (1971) Angiographic demonstration of hepatome in association with Fanconi's anemia. Am. J. Roentgenol., 113, 82-83

3. Kew, M.C., Van Coller, B., Prowse, C.M., Skikne, B., Wolfsdorf, J.I., Isdale, J., Krawitz, S., Altman, H., Levin, S.E. & Bothwell, T.H. (1976) Occurrence of primary hepatocellular cancer and peliosis hepatis after treatment with androgenic steroids. S.A. med. J., 50, 1233-1237

4. Sweeney, E.C. & Evans, D.J. (1976) Hepatic lesions in patients treated with synthetic anabolic steroids. J. clin. Pathol., 29, 626-633

5. Shapiro, P., Ikede, R.M., Ruebner, B.H., Connors, M.H., Halsted, C.C. & Abildgaard, C.F. (1977) Multiple hepatic tumors and peliosis hepatis in Fanconi's anemia treated with androgens. Am. J. Dis. Child., 131, 1104-1106

6. Mokrohisky, S.T., Ambruso, D.R. & Hathaway, W.E. (1977) Fulminant hepatic neoplasia after androgen therapy. New Engl. J. Med., 296, 1411-1412

7. Sale, G.E. & Lerner, K.G. (1977) Multiple tumors after androgen therapy. Arch. Pathol. Lab. Med., 101, 600-603

8. Montgomery, R.R., Ducore, J.M., Githens, J.H., August, C.S. & Johnson, M.L. (1980) Regression of oxymetholone-induced hepatic tumors after bone marrow transplantation in aplastic anemia. Transplantation, 30, 90-96

9. Treuner, J., Niethammer, D., Flach, A., Fischbach, H. & Schenck, W. (1980) Hepatocellular carcinoma following oxymetholone treatment (Ger.). Med. Welt., 31, 952-955

10. Stromeyer, F.W., Smith, D.H. & Ishak, K.G. (1979) Anabolic steroid therapy and intrahepatic cholangiocarcinoma. Cancer, 43, 440-443

11. Obeid, D.A., Hill, F.G.H., Harnden, D., Mann, J.R. & Wood, B.S.B. (1980) Fanconi anemia. Oxymetholone hepatic tumors, and chromosome aberrations associated with leukemic transition. Cancer, 46, 1401-1404

12. Cap, J., Ondrus, B. & Danihel, L. (1983) Focal nodular hyperplasia of the liver and hepatocellular carcinoma in children with Fanconi's anaemia after long-term treatment with androgen (Czech.). Bratisl. lek. Listy., 79, 73-81

13. McCaughan, G.W., Bilous, M.J. & Gallagher, N.D. (1985) Long-term survival with tumor regression in androgen-induced liver tumors. Cancer, 56, 2622-2626

14. Zevin, D., Turani, H., Cohen, A. & Levi, J. (1981) Androgen-associated hepatoma in a hemodialysis patient. Nephron, 29, 274-276

15. Turani, H., Levi, J., Zevin, D. & Kessler, E. (1983) Hepatic lesions in patients on anabolic androgenic therapy. Isr. J. med. Sci., 19, 322-337

16. Westaby, D., Portmann, B. & Williams, R. (1983) Androgen related primary hepatic tumors in non-Fanconi patients. Cancer, 51, 1947-1952

17. Huggins, C. & Hodges, C.V. (1941) Studies on prostatic cancer. I. The effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res., 1, 293-297

18. Gordon, G.G., Altman, K., Southren, A.L., Rubin, E. & Lieber, C.S. (1976) Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. New Engl. J. Med., 295, 793-797

19. Glantz, G.M. (1964) Cirrhosis and carcinoma of the prostate gland. J. Urol., 91, 291-293

20. Hovenanian, M.S. & Deming, C.L. (1948) The heterologous growth of cancer of the human prostate. Surg. Gynecol. Obstet., 86, 29-35

21. Sanderman, T.F. (1975) The possible dangers of androgens used for male climacteric. Med. J. Aust., i, 634-635

22. Guinan, P.D., Sadoughi, W., Alsheik, H., Ablin, R.J., Alrenga, D. & Bush, I.M. (1976) Impotence therapy and cancer of the prostate. Am. J. Surg., 131, 599-600

23. Roberts, J.T. & Essenhigh, D.M. (1986) Adenocarcinoma of prostate in a 40-year-old body-builder. Lancet, ii, 742

24. Ross, R., Bernstein, L., Judd, H., Hanisch, R., Pike, M. & Henderson, B. (1986) Serum testosterone levels in healthy young black and white men. J. natl Cancer Inst., 76, 45-48

25. Ghanadian, R., Puah, C.M. & O'Donoghue, E.P.N. (1979) Serum testosterone and dihydrotestosterone in carcinoma of the prostate. Br. J. Cancer, 39, 696-699

26. Ahluwalia, B., Jackson, M.A., Jones, G.W., Williams, A.O., Rao, M.S. & Rajguru, S. (1981) Blood hormone profiles in prostate cancer patients in high-risk and low-risk populations. Cancer, 48, 2267-2273

27. Hammond, G.L., Kontturi, M., Vihko, P. & Vihko, R. (1978) Serum steroids in normal males and patients with prostatic diseases. Clin. Endocrinol., 9, 113-121

28. Bartsch, W., Steins, P. & Becker, H. (1977) Hormone blood levels in patients with prostatic carcinoma and their relationship to the type of carcinoma growth differentiation. Eur. Urol., 3, 47-52

29. Harper, M.E., Peeling, W.B., Cowley, T., Brownsey, B.G., Phillips, M.E.A., Groom, G., Fahmy, D.R. & Griffiths, K. (1976) Plasma steroid and protein hormone concentrations in patients with prostatic carcinoma, before and during oestrogen therapy. Acta endocrinol., 81, 409-426

30. Sarna, G., Tomasulo, P., Lotz, M.J., Bubinak, J.F. & Shulman, N.R. (1975) Multiple neoplasms in two siblings with a variant form of Fanconi's anemia. Cancer, 36, 1029-1033

31. Bourgeois, C.A. & Hill, F.G.H. (1977) Fanconi's anemia leading to acute myelomonocytic leukemia. Cytogenic studies. Cancer, 39, 1163-1167

32. Boyd, A.W., Parkin, J.D. & Castaldi, P.A. (1979) A case of paroxysmal nocturnal haemoglobinuria terminating in a myeloproliferative syndrome. Aust. N.Z. J. Med., 9, 181-183

33. IARC Monographs, 21, 519-547, 1979

34. Pollard, M. & Luckert, P.H. (1986) Promotional effects of testosterone and high fat diet on the development of autochthonous prostate cancer in rats. Cancer Lett., 32, 223-227

35. Pollard, M. & Luckert, P.H. (1986) Production of autochthonous prostate cancer in Lobund-Wistar rats by treatment with *N*-nitroso-*N*-methylurea and testosterone. J. natl Cancer Inst., 77, 583-587

36. IARC Monographs, Suppl. 6, 506-507, 1987

**Synonyms for Oxymetholone:**

- Adroidin
- Adroyd
- Anadrol
- Anadroyd

- Anapolon
- Anasteron
- Anasteronal
- Anasterone
- Becorel
- CI-406
- 4,5-Dihydro-2-hydroxymethylene-17α-methyltestosterone
- Dynasten
- HMD
- 17β-Hydroxy-2-hydroxymethylene-17α-methyl-3-androstanone
- 17β-Hydroxy-2-(hydroxymethylene)-17α-methyl-5α-androstan-3- one
- 17β-Hydroxy-2-(hydroxymethylene)-17-methyl-5α-androstan-3-one
- 2-Hydroxymethylene-17α-methyl-5α-androstan-17β-ol-3-one
- 2-Hydroxymethylene-17α-methyldihydrotestosterone
- 2-(Hydroxynethylene)-17-methyldihydrotestosterone
- 2-(Hydroxymethylene)-17α-methyldihydrotestosterone
- 2-Hydroxymethylene-17α-methyl-17β-hydroxy-3-androstanone
- Nastenon
- Methabol
- 17α-Methyl-2-hydroxymethylene-17-hydroxy-5α-androstan-3-one
- NSC-26 198
- Oximetholonum
- Oximetolona
- Oxymethenolone
- Oxitosona-50
- Pavisoid
- Plenastril
- Protanabol
- Roboral
- Synasteron
- Zenalosyn

**Synonyms for Testosterone**

- δ4-Androsten-17β-ol-3-one; [Ablacton]
- Andrestraq
- Android-T
- Androlan
- Androlin
- Andronaq
- Andrusol
- Cormone
- Cristerona T
- Depotest
- Di-Met
- Dura-Testrone
- Geno-cristaux Gremy
- Histerone
- Homogene S
- Homosteron
- Homosterone
- Hydrotest
- Malestrone
- Mal-O-Fem
- Malogen
- Mertestate
- Nendron
- Neo-Hombreol
- Neo-Hombreol-F
- Neotestis
- Oreton
- Oreton-F
- Orquisteron
- Perandren

- Percutacrine Androgenique
- Primotest
- Primoteston
- Rektandron
- Sterotate
- Sustanon
- Sustanone
- Synandrol F
- Tesamone
- Teslen
- Tesone
- Test 100
- Testa denos
- Testagen
- Testalong
- Testandrone
- Testaqua
- Test-Estrin
- Testiculosterone
- Testobase
- Testodrin
- Testoject-50
- Testolent
- Testolin
- Testopropon
- Testoral
- Testosteroid
- Testosteron
- Testoviron
- Testoviron Schering
- Testoviron T
- Testro-Med
- Testrone
- Testryl
- Virormone
- Virosterone

**Synonyms for Testosterone oenanthate**

- Androtardyl
- Delatestryl
- Orquisteron-E
- Reposo-TMD
- Testoenant
- Testosterone enanthate
- Testosterone heptanoate
- Testosterone heptylate

**Synonyms for Testosterone proprionate**

- Agovirin
- Androlon
- Androsan
- $\Delta^4$-Androstene-17β-propionate-3-one
- Androtest P
- Androteston
- Anertan
- Aguaviron
- Bio-Testiculina
- Enarmon
- Enarmon-oil
- Homandren
- Hormoteston

- Malogen
- Masenate
- Nasdol
- Neo-Hombreol
- NSC 9166
- Okasa-Mascul
- Orchiol
- Orchisteron P
- Orchisterone P
- Orchistin
- Oreton
- Oreton Propionate
- Pantestin
- Paretest
- Perandren
- Propiokan
- Recthormone Testosterone
- Solvotest
- Sterandryl
- Synerone
- Telipex
- Testaform
- Testex
- Testine
- Testodet
- Testodrin
- Testogen
- Testolets
- Testonique
- Testormol
- Testosid
- Testosterone-17β-propionate
- Testosterone-17-propionate
- Testosteron propionate
- Testoviron
- Testoxyl
- Testrex
- Tostrin
- TP
- Uniteston

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# ANILINE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 99)

**CAS No.**: 62-53-3
**Chem. Abstr. Name**: Benzenamine

**A. Evidence for carcinogenicity to humans** (*inadequate*)

The excess of bladder cancer deaths observed in clusters of cases of workers in the aniline-dye industry has been attributed to exposure to chemicals other than aniline. Epidemiological studies of workers exposed to aniline but not to other known bladder carcinogens have shown little evidence of increased risk. These studies are generally methodologically inadequate due to incomplete follow-up of workers who left the industry and to absence of estimates of expected numbers of bladder cancers. In the most methodologically vigorous study, one death from bladder cancer was reported among 1223 men who had produced or used aniline, with 0.83 deaths expected from population rates [ref: 1]. A recent mortality study of 342 men employed in the manufacture of organic dyes, in which two of the three processes involved aniline as a raw material, showed no death from bladder cancer [ref: 2].

**B. Evidence for carcinogenicity to animals** (*limited*)

Aniline hydrochloride was tested for carcinogenicity in single experiments in mice and rats by oral administration. No increase in tumour incidence was observed in mice. In rats, it produced fibrosarcomas, sarcomas and haemangiosarcomas of the spleen and peritoneal cavity [ref: 1]. In several limited studies, largely negative results were obtained following oral administration to rats [ref: 1], subcutaneous injection of mice [ref: 1] and hamsters [ref: 3], and after single intraperitoneal injection of mice [ref: 4].

**C. Other relevant data**

No data were available on the genetic and related effects of aniline in humans.

Aniline induced sister chromatid exchanges, but not micronuclei in bone-marrow cells of mice treated *in vivo*, and DNA strand breakage was induced in liver and kidney of rats *in vivo*. Sister chromatid exchange assays in human cells in vitro gave negative results. Syrian hamster embryo cells and virus-infected Fischer rat embryo cells were not transformed by aniline, but BALB/c 3T3 cells were. It induced sister chromatid exchanges and chromosomal aberrations but not DNA strand breaks or unscheduled DNA synthesis in mammalian cells *in vitro*. Aniline did not induce sex-linked recessive lethal mutations in *Drosophila* and did not induce mutation or mitotic recombination in fungi. It was not mutagenic to bacteria and did not cause DNA damage. Urine from rats treated with aniline was reported to be mutagenic to bacteria [ref: 5].

**Overall evaluation** Aniline is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 4 (1974); Vol. 27 (1982)

References

1. IARC Monographs, 27, 39-61, 1982

2. Ott, M.G. & Langner, R.R. (1983) A mortality survey of men engaged in the manufacture of organic dyes. J. occup. med., 25, 763-768

3. Hecht, S.S., El-Bayoumy, K., Rivenson, A. & Fiala, E.S. (1983) Bioassay for carcinogenicity of 3,2'-dimethyl-4-nitrosobiphenyl, o-nitrosotoluene, nitrosobenzene and the corresponding amines in Syrian golden hamsters. Cancer Lett., 20, 349-354

4. Delclos, K.B., Tarpley, W.G., Miller, E.C. & Miller, J.A. (1983) 4-Aminoazobenzene and N,N-dimethyl-4-aminoazobenzene as equipotent hepatic carcinogens in male C57BL x C3H/He $F_1$ mice and characterization of N-(deoxyguanosin-8-yl)-4-aminoazobenzene as the major persistent hepatic DNA-bound dye in these mice. Cancer Res., 44, 2540-2550

5. IARC Monographs, Suppl. 6, 68-70, 1987

**Synonyms**

- Aminobenzene
- Aminophen
- Aniline oil
- Anyvim
- Blue Oil
- Phenylamine

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# ARSENIC AND ARSENIC COMPOUNDS
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 100)

**CAS No.**: 7440-38-2
**Chem. Abstr. Name**: Arsenic

**Arsanilic acid**:
**CAS No.**: 98-50-0
**Chem. Abstr. Name**: Arsonic acid, (4-aminophenyl)-

**Arsenic pentoxide**:
**CAS No.**: 1303-28-2
**Chem. Abstr. Name**: Arsenic oxide [$As_2O_5$]

**Arsenic sulfide**:
**CAS No.**: 1303-33-9
**Chem. Abstr. Name**: Arsenic sulfide [$As_2S_3$]

**Arsenic trioxide**:
**CAS No.**: 1327-53-3
**Chem. Abstr. Name**: Arsenic oxide [$As_2O_3$]

**Arsine**:
**CAS No.**: 7784-42-1

**Calcium arsenate**:
**CAS No.**: 7778-44-1
**Chem. Abstr. Name**: Arsenic acid [$H_3AsO_4$], calcium salt (2:3)

**Dimethylarsinic acid**:
**CAS No.**: 75-60-5
**Chem. Abstr. Name**: Arsinic acid, dimethyl-

**Lead arsenate**:
**CAS No.**: 7784-40-9
**Chem. Abstr. Name**: Arsenic acid [$H_3AsO_4$], lead (2+) salt (1:1)

**Methanearsonic acid, disodium salt**:
**CAS No.**: 144-21-8
**Chem. Abstr. Name**: Arsonic acid, methyl-, disodium salt

**Methanearsonic acid, monosodium salt**:
**CAS No.**: 2163-80-6
**Chem. Abstr. Name**: Arsonic acid, methyl-, monosodium salt

**Potassium arsenate**:
**CAS No.**: 7784-41-0
**Chem. Abstr. Name**: Arsenic acid [$H_3AsO_4$], monopotassium salt

**Potassium arsenite**:
**CAS No.**: 13464-35-2

**Chem. Abstr. Name**: Arsenenous acid, potassium salt

**Sodium arsenate**:
**CAS No.**: 7631-89-2
**Chem. Abstr. Name**: Arsenic acid, [$H_3AsO_4$], sodium salt

**Sodium arsenite**:
**CAS No.**: 7784-46-5
**Chem. Abstr. Name**: Arsenenous acid, sodium salt

**Sodium cacodylate**:
**CAS No.**: 124-65-2
**Chem. Abstr. Name**: Arsinic acid, dimethyl-, sodium salt

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Many cases of skin cancer have been reported among people exposed to arsenic through medical treatment with inorganic trivalent arsenic compounds, particularly Fowler's solution [ref: 1], and further reports have confirmed these findings [ref: 2-9]. In some instances, skin cancers have occurred in combination with other cancers, such as liver angiosarcoma (after six months' treatment with Fowler's solution giving a total intake of 0.24 g arsenic) [ref: 6], intestinal and bladder cancers [ref: 7] and meningioma [ref: 9]. Liver angiosarcomas have also been associated with medicinal exposure to arsenic [ref: 1,6,10].

Epidemiological studies of cancer following medical treatment with arsenic have shown an excess of skin cancers, but no clear association with other cancers has been obtained [ref: 1], as confirmed by a recent cohort study on individuals treated with Fowler's solution [ref: 11]. No relation was found between prostatic cancer and treatment of syphilis with arsenicals [ref: 12].

An association between environmental exposure to arsenic through drinking-water and skin cancer has been observed [ref: 1] and confirmed [ref: 13,14]; two cases of bladder cancer were also described, with latent periods of eight to 20 years [ref: 15]. The latent periods for two cases of skin cancer related to arsenic in drinking-water were 20 and 23 years, and the concentrations or uptake of arsenic were reported to be 1.2 and 1 mg per day, respectively, with an estimated total ingested dose of about 8 g in one study [ref: 14].

Epidemiological studies in areas with different frequencies of black-foot disease and where drinking-water contained 0.35-1.14 mg/l arsenic revealed elevated risks for cancers of the bladder, kidney, skin, lung, liver and colon in both men and women [ref: 16,17].

A case of liver angiosarcoma was reported in the 20-month-old child of an exposed worker living in the vicinity of a copper mine and smelter [ref: 18]. Four rather inconsistent studies describing the effect of air pollutants containing arsenic [ref.: 1,19,20] were followed by further reports that indicated an effect on lung cancer incidence of arsenic in polluted air from smelters and pesticide production, with risk ratios of 2.0-2.5 near smelters [ref: 21,22]. Two further studies near smelters showed no clear effect [ref: 23,24].

Occupational exposure to inorganic arsenic, especially in mining and copper smelting, has quite consistently been associated with an increased risk of cancer [ref: 1]. A number of studies of smelter workers relate to populations that have been reported previously [ref: 1] and represent both partial [ref: 25-27] and total [ref: 28,29] updates. An almost ten-fold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic, and relatively clear dose-response relationships have been obtained with regard to cumulative exposure [ref: 29] and especially with 30-day ceiling levels [ref: 27]. Sulphur dioxide in the smelter environment appeared to play a minor role, if any, in the development of lung cancer [ref: 27]. Other forms of cancer were considered, but their incidences were not found to be consistently increased [ref: 28]. Other US smelter worker populations have been shown to have consistent increases in lung cancer incidence, as well as increases of about 20% in the incidence of gastrointestinal cancer and of 30% for renal cancer and haematolymphatic malignancies [ref: 30,31]. The observation in an earlier study of an

increase in lung cancer risk among a population of Swedish smelter workers [ref: 1] has been confirmed, with a risk of six to eight fold among roasters [ref: 32].

A decrease in lung cancer risk after cessation of exposure to arsenic has been observed in some studies [ref: 30,33], possibly indicating a late-stage effect of arsenic [ref: 34,35].

With regard to histological type of lung cancer, a significant, relative excess of adenocarcinomas and a slight excess of oat-cell cancers were seen among smelter workers [ref: 36].

A multiplicative effect of arsenic exposure and smoking was observed among Swedish smelter workers [ref: 37]. A slightly increased risk was also indicated for exposure to sulphur dioxide in this study. Other studies have shown a lesser influence of smoking [ref: 25,33].

Relatively high concentrations of arsenic, as well as of antimony, cadmium, lead and lanthanum, were found in lung tissue of lung cancer cases, whereas the concentrations of selenium were low [ref: 38,39].

An approximately two-fold risk for lung and stomach cancers has been observed among (fine) glass workers with some exposure to arsenic but who were also exposed to other potentially carcinogenic metals and to asbestos. Stomach cancer was especially frequent among glass blowers, suggesting an association with oral contact with contaminated pipes [ref: 40].

Some excess of lung cancer was seen among female hat makers exposed to arsenic, but also to mercury [ref: 41].

Additional reports have suggested an increased risk of skin and lung cancers in vineyard workers [ref: 42,43] and have also suggested that ingestion of arsenic in wine byproducts may have contributed to this increase [ref: 42]. One case of lung cancer was reported in an individual involved in the production of lead arsenate and calcium arsenate [ref: 44]; multiple skin keratoses and chronic lymphatic leukaemia were reported in one person involved in the production of copper acetoarsenate [ref: 45].

Three studies of two populations of workers in pesticide production showed an increased risk ratio for lung cancer - up to about 3 - and some excess of malignant neoplasms of the lymphatic and haematopoietic tissues [ref: 1,46]. In a study of liver angiosarcomas, two of 26 cases had been in contact with arsenical pesticides occupationally [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

Various arsenic compounds have been tested for carcinogenicity by perinatal treatment of mice, by intratracheal instillation in hamsters and rats and by implantation into the stomach of rats. Arsenic trioxide produced lung adenomas in mice after perinatal treatment [ref: 47], and induced low incidences of carcinomas, adenomas, papillomas and adenomatoid lesions of the respiratory tract in hamsters after its intratracheal instillation [ref: 48,49]. It induced a low incidence of adenocarcinomas at the site of its implantation into the stomach of rats [ref: 50]. A high incidence of lung carcinomas was induced in rats following a single intratracheal instillation of a pesticide mixture containing calcium arsenate [ref: 1]. Intratracheal instillations of calcium arsenate into hamsters resulted in a borderline increase in the incidence of lung adenomas, while no such effect was observed with arsenic trisulphide [ref: 51]. Sodium arsenite enhanced the incidence of renal tumours induced in rats by intraperitoneal injection of *N*-nitrosodiethylamine [ref: 52].

No adequate data on the carcinogenicity of organic arsenicals were available to the Working Group.

**C. Other relevant data**

In one study of people exposed to trivalent arsenic in drinking-water, no increase in the incidence of sister chromatid exchanges or chromosomal aberrations was observed. A number of other studies published on people occupationally exposed to arsenic or patients treated with arsenic have shown

increased levels of chromosomal aberrations or sister chromatid exchanges. The interpretation of these results remains uncertain because of methodological problems [ref: 53].

Trivalent arsenic did not induce dominant lethal mutations in mice, but it produced a small increase in the incidence of chromosomal aberrations and micronuclei in bone-marrow cells of mice treated *in vivo*. It induced chromosomal aberrations and sister chromatid exchanges in human and rodent cells *in vitro*, and transformation of Syrian hamster embryo cells; it did not induce mutation in rodent cells *in vitro*. It induced gene conversion in yeast but did not cause mutation or induce prophage in bacteria [ref: 53].

Pentavalent arsenic induced chromosomal aberrations in human and rodent cells *in vitro*; equivocal results were obtained in assays for the induction of sister chromatid exchanges. It induced transformation in Syrian hamster embryo cells but did not induce mutation or DNA strand breaks in rodent cells *in vitro*. It induced gene conversion in yeast but did not induce mutation in bacteria [ref: 53].

**Overall evaluation**

Arsenic and arsenic compounds are *carcinogenic to humans (Group 1)*.

N.B. - This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 1 (1972); Vol. 2 (1973); Vol. 23 (1980)

**References**


1. *IARC Monographs*, *23*, 39-141, 1980

2. Heddle, R. & Bryant, G.D. (1983) Small cell lung carcinoma and Bowen's disease 40 years after arsenic ingestion. *Chest*, *84*, 776-777

3. Cowlishaw, J.L., Pollard, E.J., Cowen, A.E. & Powell, L.W. (1979) Liver disease associated with chronic arsenic ingestion. *Aust. N.Z. J. Med.*, *9*, 310-313

4. Kastl, J. & Horácek, J. (1980) Arning's carcinoids in a psoriatic receiving long-term arsenic treatment (Czech.). *Cs. Dermatol.*, *55*, 89-93

5. Kastl, J. & Horácek, J. (1985) Multiple basal cell carcinomas after long-term intake of arsenic (Ger.). *Dermatol. Monatsschr.*, *171*, 158-161

6. Roat, J.W., Wald, A., Mendelow, H. & Pataki, K.I. (1982) Hepatic angiosarcoma associated with short-term arsenic ingestion. *Am. J. Med.*, *73*, 933-936

7. von Roemeling, R., Hartwich, G. & König, H. (1979) Occurrence of tumours at different locations after arsenic therapy (Ger.). *Med. Welt.*, *30*, 1928-1929

8. Southwick, G.J. & Schwartz, R.A. (1979) Arsenically associated cutaneous squamous cell carcinoma with hypercalcemia. *J. surg. Oncol.*, *12*, 115-118

9. Weiss, J. & Jänner, M. (1980) Multiple basal cell carcinomas and meningioma after long-term arsenic therapy (Ger.). *Hautarzt*, *31*, 654-656

10. Falk, H., Caldwell, G.G., Ishak, K.G., Thomas, L.B. & Popper, H. (1981) Arsenic-related hepatic angiosarcoma. *Am. J. ind. Med., 2,* 43-50

11. Cuzick, J., Evans, S., Gillman, M. & Price Evans, D.A. (1982) Medicinal arsenic and internal malignancies. *Br. J. Cancer, 45,* 904-911

12. Lees, R.E.M., Steele, R. & Wardle, D. (1985) Arsenic, syphilis, and cancer of the prostate. *J. Epidemiol. Commun. Health, 39,* 227-230

13. Armando, V.L. & Angel, A.O. (1979) Chronical arsenicism (Span.). *Bol. med. Hosp. Infant., 36,* 849-861

14. Zaldivar, R., Prunés, L. & Ghai, G.L. (1981) Arsenic dose in patients with cutaneous carcinomata and hepatic haemangio-endothelioma after environmental and occupational exposure. *Arch. Toxicol., 47,* 145-154

15. Nagy, G., Németh, A., Bodor, F. & Ficsór, E. (1980) Urinary bladder cancer induced by chronic arsenic poisoning (Hung.). *Orv. Hetil., 121,* 1009-1011

16. Chen, C.-J., Chuang, Y.-C., Lin, T.-M. & Wu, H.-Y. (1985) Malignant neoplasmas among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res., 45,* 5895-5899

17. Chen, C.-J., Chuang, Y.-C., You, S.-L., Lin, T.-M. & Wu, H.-Y. (1986) A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. *Br. J. Cancer, 53,* 399-405

18. Falk, H., Herbert, J.T., Edmonds, L., Heath, C.W., Jr, Thomas, L.B. & Popper, H. (1981) Review of four cases of childhood hepatic angiosarcoma - elevated environmental arsenic exposure in one case. *Cancer, 47,* 382-391

19. Brown, L.M., Pottern, L.M. & Blot, W.J. (1984) Lung cancer in relation to environmental pollutants emitted from industrial sources. *Environ. Res., 34,* 250-261

20. Pershagen, G. (1985) Lung cancer mortality among men living near an arsenic-emitting smelter. *Am. J. Epidemiol., 122,* 684-694

21. Matanoski, G.M., Landau, E., Tonascia, J., Lazar, C., Elliott, E.A., McEnroe, W. & King, K. (1981) Cancer mortality in an industrial area of Baltimore. *Environ. Res., 25,* 8-28

22. Matanoski, G.M., Landau, E., Tonascia, J. & Elliott, E.A. (1983) Epidemiologic approach to arsenic pollution. *J. Univ. occup. environ. Health, 5 (Suppl.),* 117-124

23. Greaves, W.W., Rom, W.N., Lyon, J.L., Varley, G., Wright, D.D. & Chiu, G. (1981) Relationship between lung cancer and distance of residence from nonferrous smelter stack effluent. *Am. J. ind. Med., 2,* 15-23

24. Rom, W.N., Varley, G., Lyon, J.L. & Shopkow, S. (1982) Lung cancer mortality among residents living near the El Paso smelter. *Br. J. ind. Med., 39,* 269-272

25. Higgins, I., Welch, K., Oh, M., Bond, G. & Hurwitz, P. (1981) Influence of arsenic exposure and smoking on lung cancer among smelter workers: a pilot study. *Am. J. ind. Med., 2,* 33-41

26. Lubin, J.H., Pottern, L.M., Blot, W.J., Tokudome, S., Stone, B.J. & Fraumeni, J.R., Jr (1981) Respiratory cancer among copper smelter workers: recent mortality statistics. *J. occup. Med., 23,*

779-784

27. Welch, K., Higgins, I., Oh, M. & Burchfiel, C. (1982) Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. *Arch. environ. Health, 37,* 325-335

28. Lee-Feldstein, A. (1983) Arsenic and respiratory cancer in humans: follow-up of copper smelter employees in Montana. *J. natl Cancer Inst., 70,* 601-609

29. Lee-Feldstein, A. (1986) Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. *J. occup. Med., 28,* 296-302

30. Enterline, P.E. & Marsh, G.M. (1980) Mortality studies of smelter workers. Am. *J. ind. Med., 1,* 251-259

31. Enterline, P.E. & Marsh, G.M. (1982) Cancer among workers exposed to arsenic and other substances in a copper smelter. *Am. J. Epidemiol., 116,* 895-911

32. Wall, S. (1980) Survival and mortality pattern among Swedish smelter workers. *Int. J. Epidemiol., 9,* 73-87

33. Pinto, S.S., Henderson, V. & Enterline, P.E. (1978) Mortality experience of arsenic-exposed workers. *Arch. environ. Health, 33,* 325-331

34. Brown, C.C. & Chu, K.C. (1983) Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. *J. natl Cancer Inst., 70,* 455-463

35. Brown, C.C. & Chu, K.C. (1983) A new method for the analysis of cohort studies: implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. *Environ. Health Perspect., 50,* 293-308

36. Wicks, M.J., Archer, V.E., Auerbach, O. & Kuschner, M. (1981) Arsenic exposure in a copper smelter as related to histological type of lung cancer. *Am. J. ind. Med., 2,* 25-31

37. Pershagen, G., Wall, S., Taube, A. & Linnman, L. (1981) On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. *Scand. J. Work Environ. Health, 7,* 302-309

38. Wester, P.O., Brune, D. & Nordberg, G. (1981) Arsenic and selenium in lung, liver, and kidney tissue from dead smelter workers. *Br. J. ind. Med., 38,* 179-184

39. Gerhardsson, L., Brune, D., Nordberg, I.G.F. & Wester, P.O. (1985) Protective effect of selenium on lung cancer in smelter workers. *Br. J. ind. Med., 42,* 617-626

40. Wingren, G. & Axelson, O. (1985) Mortality pattern in a glass producing area in SE Sweden. *Br. J. ind. Med., 42,* 411-414

41. Buiatti, E., Kriebel, D., Geddes, M., Santucci, M. & Pucci, N. (1985) A case control study of lung cancer in Florence, Italy. I. Occupational risk factors. *J. Epidemiol. Commun. Health, 39,* 244-250

42. Lüchtrath, H. (1983) The consequences of chronic arsenic poisoning among Moselle wine growers. Pathoanatomical investigations of post-mortem examinations between 1960 and 1977. *J. Cancer Res. clin. Oncol., 105,* 173-182

43. Thiers, H., Colomb, D., Moulin, G. & Colin, L. (1967) Arsenical skin cancer in vineyards in the Beaujolais (Fr.). *Ann. Dermatol., 94,* 133-158

44. Horiguchi, S. (1979) A case of lung cancer due to exposure to arsenical compounds in an insecticides factory. (Studies on lead arsenate poisoning. Part 4). *Osaka City med. J.*, *25*, 45-51

45. Leyh, F. & Rothlaender, J.P. (1985) Multiple bowenoid keratoses due to arsenic (Ger.). *Dermatosen*, *33*, 99-101

46. Mabuchi, K., Lilienfeld, A.M. & Snell, L.M. (1980) Cancer and occupational exposure to arsenic: a study of pesticide workers. *Prev. Med.*, *9*, 51-77

47. Rudnay, P. & Börzsönyi, M. (1981) The tumorigenic effect of treatment with arsenic trioxide (Hung.). *Magyar Onkol.*, *25*, 73-77

48. Ishinishi, N., Yamamoto, A., Hisanaga, A. & Inamasu, T. (1983) Tumorigenicity of arsenic trioxide to the lung in Syrian golden hamsters by intermittent instillations. *Cancer Lett.*, *21*, 141-147

49. Pershagen, G., Nordberg, G. & Björklund, N.-E. (1984) Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo[*a*]pyrene by the pulmonary route. *Environ. Res.*, *34*, 227-241

50. Katsnelson, B.A., Neizvestnova, Y.M. & Blokhin, V.A. (1986) Stomach carcinogenesis induction by chronic treatment with arsenic (Russ.). *Vopr. Onkol.*, *32*, 68-73

51. Pershagen, G. & Björklund, N.-E. (1985) On the pulmonary tumorigenicity of arsenic trisulfide and calcium arsenate in hamsters. *Cancer Lett.*, *27*, 99-104

52. Shirachi, D.Y., Johansen, M.G., McGowan, J.P. & Tu, S.-H. (1983) Tumorigenic effect of sodium arsenite in rat kidney. *Proc. West. pharmacol. Soc.*, *26*, 413-415

53. *IARC Monographs, Suppl. 6*, 71-76, 1987

**Synonyms for Arsenic**

- Arsen
- Arsenic black
- Grey arsenic
- Metallic arsenic

**Synonyms for Arsanilic acid**

- 4-Aminobenzenearsonic acid
- *para*-Aminophenylarsenic acid
- Aminophenylarsine acid
- *para*-Aminophenylarsine acid
- *para*-Aminophenylarsinic acid
- 4-Aminophenylarsonic acid
- *para*-Anilinearsonic acid
- Arsanilic acid-100
- *para*-Arsanilic acid
- 4-Arsanilic acid
- Atoxylic acid
- Premix
- Pro gen
- Pro-gen 227
- Progen 90

**Synonyms for Arsenic pentoxide**

- Arsenic acid
- Arsenic acid anhydride
- Arsenic anhydride
- Arsenic oxide
- Arsenic [V] oxide
- Diarsenic pentoxide

**Synonyms for Arsenic sulfide**

- Arsenic sesquisulphide
- Arsenic sulphide
- Arsenic tersulphide
- Arsenic trisulphide
- Arsenic Yellow
- Arsenious sulphide
- Arsenous sulphide
- Auripigment
- Diarsenic trisulphide
- Orpiment
- Pigment Yellow 39

**Synonyms for Arsenic trioxide**

- Arsenic [III] oxide
- Arsenic sesquioxide
- Arsenicum album
- Arsenious acid
- Arsenious oxide
- Arsenious trioxide
- Arsenite
- Arsenolite
- Arsenous acid
- Arsenous acid anhydride
- Arsenous anhydride
- Arsenous oxide
- Arsenous oxide anhydride
- Arsodent
- Claudelite
- Crude arsenic
- Diarsenic trioxide
- White arsenic

**Synonyms for Arsine**

- Arsenic hydrid [$AsH_3$]
- Arsenic hydride
- Arsenic trihydride
- Arseniuretted hydrogen
- Arsenous hydride
- Hydrogen arsenide

**Synonyms for Calcium arsenate**

- Calcium ortho-arsenate
- Spra-cal
- Tricalcium arsenate
- Chip-cal
- Pencal

**Synonyms for Dimethylarsinic acid**

- Agent Blue
- Ansar 138
- Arsan
- Arsine oxide, hydroxydimethyl-
- Cacodylic acid
- Hydroxydimethylarsine oxide
- Dilic
- Phytar 138
- Phytar 560
- Rad-E-Cate 25
- Silvisar 510

**Synonyms for Lead arsenate**

- Acid lead arsenate
- Acid lead *ortho*-arsenate
- Arsenate of lead
- Arsinette
- Gypsine
- Lead acid arsenate
- Plumbous arsenate
- Schultenite
- Standard lead arsenate
- Soprabel
- Talbot

**Synonyms for Methanearsonic acid, disodium salt**

- Arrhenal
- Ansar 184
- Ansar 8100
- Ansar DSMA liquid
- Arsinyl
- Arsynal
- Cacodyl new
- Chipco crab kleen
- Cralo-E-Rad
- Dal-E-Rad 100
- Diarsen
- Disodium methanearsenate
- Disodium methanearsonate
- Disodium methylarsonate
- Disomear
- Di-Tac
- DMA
- DMA 100
- DSMA
- DSMA liquid
- Methar
- Metharsan
- Metharsinat
- Namate
- Neo-asycodile
- Sodar
- Somar
- Stenosine
- Tonarsen
- Tonarsin
- Weed broom

- Weed-E-Rad
- Weed-E-Rad DMA powder
- Weed-E-Rad 360
- Weed-Hoe

**Synonyms for Methanearsonic acid, monosodium salt**

- Ansar 170 H.C.
- Ansar 170 L
- Ansar 529 H.C.
- Arsonate liquid
- Bueno 6
- Daconate 6
- Dal-E-Rad
- Herb-All
- Merge 823
- Mesamate
- Mesamate H.C.
- Mesamate concentrate
- Mesamate 400
- Mesamate 600
- Monosodium acid methanearsonate
- Monosodium acid metharsonate
- Monosodium methanearsonate
- Monosodium methylarsonate
- Monosodium methyl arsonate
- MSMA
- Sodium acid methanearsonate
- Phyban H.C.
- Silvisar 550
- Target MSMA
- Trans-vert
- Weed 108
- Weed-E-Rad
- Weed-hoe

**Synonyms for Potassium arsenate**

- Arsenic acid, monopotassium salt
- Macquer's salt
- Monopotassium arsenate
- Monopotassium dihydrogen arsenate
- Potassium acid arsenate
- Potassium arsenate, monobasic
- Potassium dihydrogen arsenate
- Potassium hydrogen arsenate

**Synonyms for Potassium arsenite**

- Arsenious acid, potassium salt
- Arsenious acid [$H_3AsO_3$], potassium salt
- Arsonic acid, potassium salt
- Fowler's solution
- Potassium metaarsenite

**Synonyms for Sodium arsenate**

- Arsenic acid, sodium salt
- Sodium *ortho*-arsenate

**Synonyms for Sodium arsenite**

- Arsenious acid, sodium salt
- Atlas 'A'
- Chem pels C
- Chem-sen 56
- Kill-all
- Penite
- Prodalumnol
- Sodium *meta*-arsenite
- Sodium *meta*arsenite

**Synonyms for Sodium cacodylate**

- Alkarsodyl
- Arsecodile
- Arsicodile
- Arsine oxide, hydroxydimethyl-, sodium salt
- Arsycodile
- Boll's eye
- Cacodylic acid, sodium salt
- [(Dimethylarsino)oxy]sodium-As-oxide
- Hydroxydi-methylarsine oxide, sodium salt
- Phytar 560
- Rad-E-Cate 25
- Silvisar
- Sodium dimethylarsinate
- Sodium dimethylarsonate

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Last updated: 6 February 1998

# ASBESTOS
# (Actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite)
# (Group 1)

For definition of Groups, see Preamble Evaluation.

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**Asbestos fibre**
**CAS No.:** 1332-21-4

**Actinolite**
**CAS No.:** 13768-00-8

**Amosite**
**CAS No.:** 12172-73-5

**Anthophyllite**
**CAS No.:** 17068-78-9

**Chrysotile**
**CAS No.:** 12001-29-5

**Crocidolite**
**CAS No.:** 12001-28-4

**Tremolite**
**CAS No.:** 14567-73-8

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Numerous reports from several countries have described cases or series of pleural and peritoneal mesotheliomas in relation to occupational exposure to various types and mixtures of asbestos (including talc containing asbestos), although occupational exposures have not been identified in all cases [ref: 1-21]. Mesotheliomas of the tunica vaginalis testis and of the pericardium have been reported in persons occupationally exposed to asbestos [ref: 22-24].

Environmental exposure either in the houses of asbestos workers or in the neighbourhood of asbestos mines or factories has been noted in some of the cases [ref: 1,2,4-6,9,11,25,26]. It has been estimated that a third of the mesotheliomas occurring in the USA may be due to nonoccupational exposure [ref: 27]. In a study from Israel, the incidence of mesothelioma was found to be higher among those born in the USA or in Europe relative to those born in Israel [ref: 9].

In some of these case reports and in other studies, asbestos fibres have been identified in the lung [ref: 5,6,11,28-32]. Amphibole fibres have usually predominated, but in a few cases mainly or only chrysotile fibres were found [ref: 6,28].

The long latency required for mesothelioma to develop after asbestos exposure has been documented in a number of publications [ref: 11,13,26,28,33-37]. An increasing proportion of cases has been seen with increasing duration of exposure [ref: 36].

A number of epidemiological studies of respiratory cancer and mesothelioma have been reported in relation to exposure to unspecified or complex mixtures of asbestos in shipyard work [ref: 38-45]. The risk ratio for lung cancer has usually been moderately increased, both in these studies and in

studies on various other occupational groups with similarly job-related but unspecified or complex asbestos exposures [ref: 35,46-54]. Risk ratios of about 2-5 have been reported in some studies, but the ratio was considerably higher in one rather small study [ref: 55] and did not exceed unity in another [ref: 42]. In one study, individuals suffering from asbestosis had a considerably greater risk for lung cancer, with a risk ratio of 9.0 [ref: 56]. In some of the studies referred to, a number of mesotheliomas were also observed [ref: 41,42,44,47,51,53,55]. Abdominal mesotheliomas have sometimes been mistaken for pancreatic cancer [ref: 57]. Mesothelioma cases have been observed to have a relatively lower fibre content in the lungs than lung cancer cases [ref: 32].

Laryngeal cancer has been considered in two case-control studies, resulting in risk ratios of 2.4 and 2.3 that relate to shipyard work and unspecified exposure, respectively [ref: 40,58] A cohort study of insulation workers showed a relative risk of 1.9, based on nine cases [ref: 57]. A case series indicated a high frequency of exposure to asbestos, especially in low-grade smokers [ref: 59]. A risk ratio of 3.2 for laryngeal cancer was reported among chrysotile miners in an area with generally high incidence [ref: 60], but no increased risk was seen in a cohort of workers with exposure to crocidolite [ref: 61]. Two correlation studies have also indicated a relationship between laryngeal cancer and exposure to asbestos [ref: 39,62].

Mesotheliomas related to shipyard work and other exposures, including household contact with asbestos workers, have also been subject to epidemiological studies [ref: 36,63-67], resulting in risk ratios of about 3-15 in comparison with background rates not clearly referable to asbestos exposure.

Some studies have specifically considered environmental exposures with reference to mesotheliomas [ref: 66,67]. Three correlation studies and one case-control study considering exposure to piped drinking-water [ref: 68-71] did not show consistently increased risks for any type of cancer, whereas another study [ref: 72] considering chrysotile contamination mainly from natural sources gave some indication of an increase in the incidence of peritoneal and stomach cancers in persons of each sex, although no other cancer site was consistent in this respect.

Exposure to crocidolite has been studied with regard to risk of lung cancer [ref: 61,73-76], and risk ratios of about 2-3 have been reported. Three lung cancers and two mesotheliomas occurred in 20 individuals after one year of high exposure to crocidolite; at least 17 of the cases had asbestos-induced lung changes on X-ray films [ref: 77].

One study [ref: 78] of histological types of lung cancers showed that among persons exposed to crocidolite 45.7% of cases were squamous-cell carcinomas, as compared to 35.2% among unexposed persons. In the context of unspecified and complex exposures, small-cell carcinoma was found to be relatively more prevalent than other forms [ref: 50].

Exposure to chrysotile was found in some studies to result in virtually no increase in risk ratio [ref: 60,79-81], or a slightly elevated relative risk of lung cancer [ref: 82-86]. Somewhat higher risk ratios, up to 2.5, 3.5 and 2, respectively, were obtained in one study of chrysotile miners [ref: 87] and in two independent studies from one asbestos [chrysotile] textile plant [ref: 88,89], the latter being the more comprehensive. With regard to mesotheliomas, one study suggested a particularly high risk of combined exposure to chrysotile and amphiboles (risk ratio, 61), thus almost multiplying the risk ratios (6 and 12, respectively) of exposures to chrysotile and amphiboles alone [ref: 90]. Another study showed no mesothelioma among a large worker population with exposure to chrysotile only [ref: 91].

A slight excess of lung cancer and some mesotheliomas appeared in some groups with mixed exposures involving amosite, chrysotile and crocidolite [ref: 92-94]. Exposure predominantly to amosite, but also to chrysotile, was reported to be the probable cause of at least four of five mesotheliomas (one peritoneal) observed in a UK insulation-board factory [ref: 95]. One cohort with exposure to cummingtonite-grunerite, which is closely related to amosite, had no clear excess of lung cancer, although one case of mesothelioma was observed [ref: 96].

Exposure to tremolite and actinolite has been the subject of a few studies in investigations of vermiculite mining and milling [ref: 97,98] and environmental exposure [ref: 99]. The studies of miners indicated a risk ratio for lung cancer of up to approximately six fold. Deaths from mesothelioma were found in the occupational studies, whereas the study of environmental exposure

showed no increased risk, although pleural plaques were reported. Publication of one case report of a mesothelioma after environmental exposure suggests that tremolite was of etiological importance [ref: 31].

Cancers other than of the lung or mesothelioma have been considered in many studies [ref : 1, 17, 35, 39, 41-44, 48, 51, 55, 60-62, 68-70, 72-74, 76, 83, 87, 89, 92, 93, 96, 97, 99-108]. Some indicated an approximately two-fold risk with regard to gastrointestinal cancer in connection with shipyard work [ref: 41,43], and some increased risk was also seen in association with exposure to both chrysotile and crocidolite [ref: 103], to crocidolite [ref: 61,74] or to chrysotile [ref: 87]. Cancer of the colon and rectum was associated with asbestos exposure during chrysotile production, with an approximately two-fold risk [ref: 87]; a similar excess was found for unspecified asbestos exposure [ref: 104]. Some excess of ovary cancer has been reported in two studies [ref: 73,76] but not in another [ref: 92]; exposure to crocidolite was probably more predominant in the studies that showed excesses. Bile-duct cancer appeared in excess in one study based on record-linking [ref: 105], and large-cell lymphomas of the gastrointestinal tract and oral cavity appeared to be strongly related to asbestos exposure in one small study covering 28 cases and 28 controls, giving a risk ratio of 8; however, ten cases and one control also had a history of malaria [ref: 106]. An excess of lymphopoietic and haematopoietic malignancies has been reported in plumbers, pipe-fitters, sheet-metal workers and others with asbestos exposure [ref: 17,54,107,108].

The relationship between asbestos exposure and smoking indicates a synergistic effect of smoking with regard to lung cancer [ref: 1]. Further evaluations indicate that this synergistic effect is close to a multiplicative model [ref: 52,109]. As noted previously [ref: 1], the risk of mesothelioma appears to be independent of smoking [ref: 47,66], and a significantly decreasing trend in risk was observed with the amount smoked in one study [ref: 65].

The studies of the carcinogenic effect of asbestos exposure, including evidence reviewed earlier [ref: 1], show that occupational exposure to chrysotile, amosite and anthophyllite asbestos and to mixtures containing crocidolite results in an increased risk of lung cancer, as does exposure to minerals containing tremolite and actinolite and to tremolitic material mixed with anthophyllite and small amounts of chrysotile. Mesotheliomas have been observed after occupational exposure to crocidolite, amosite, tremolitic material and chrysotile asbestos. Gastrointestinal cancers occurred at an increased incidence in groups occupationally exposed to crocidolite, amosite, chrysotile or mixed fibres containing crocidolite, although not all studies are consistent in this respect. An excess of laryngeal cancer has also been observed in some groups of exposed workers. No clear excess of cancer has been associated with the presence of asbestos fibres in drinking-water. Mesotheliomas have occurred in individuals living in the neighbourhood of asbestos factories and mines and in people living with asbestos workers.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Asbestos has been tested for carcinogenicity by inhalation in rats, by intrapleural administration in rats and hamsters, by intraperitoneal injection in mice, rats and hamsters and by oral administration in rats and hamsters. Chrysotile, crocidolite, amosite, anthophyllite and tremolite produced mesotheliomas and lung carcinomas in rats after inhalation exposure [ref: 1,110,111] and mesotheliomas following intrapleural administration [ref: 1,112]. Chrysotile, crocidolite, amosite and anthophyllite induced mesotheliomas in hamsters following intrapleural administration [ref: 1]. Intraperitoneal administration of chrysotile, crocidolite and amosite induced peritoneal tumours, including mesotheliomas, in mice [ref: 1,113] and rats [ref: 1,111,114]. Given by the same route, crocidolite produced abdominal tumours in hamsters [ref: 115], and tremolite and actinolite produced abdominal tumours in rats [ref: 110,116-118]. A statistically significant increase in the incidence of malignant tumours was observed in rats given filter material containing chrysotile orally [ref: 1]. In more recent studies, tumour incidence was not increased by oral administration of amosite or tremolite in rats [ref: 119], of amosite in hamsters [ref: 120,121] or of chrysotile in hamsters [ref: 121]. In two studies in rats, oral administration of chrysotile produced a low incidence of benign adenomatous polyps of the large intestine in males (9/250 *versus* 3/524 pooled controls) [ref: 122] and of mesenteric haemangiomas (4/22 *versus* 0/47 controls) [ref: 123]. Synergistic effects were observed following intratracheal administration of chrysotile and benzo[*a*]pyrene to rats and hamsters [ref: 1] and of intratracheal administration of chrysotile and subcutaneous or oral administration of *N*-nitrosodiethylamine to hamsters [ref: 124].

**C. Other relevant data**

Insulation workers exposed to asbestos 'displayed a marginal increase' in the incidence of sister chromatid exchanges in lymphocytes in one study [ref: 125].

Chrysotile did not induce micronuclei in bone-marrow cells of mice or chromosomal aberrations in bone-marrow cells of rhesus monkeys treated *in vivo*. In cultured human cells, conflicting results were reported for the induction of chromosomal aberrations and negative results for the induction of sister chromatid exchanges by chrysotile and crocidolite; amosite and crocidolite did not induce DNA strand breaks, and crocidolite was not mutagenic. Amosite, anthophyllite, chrysotile and crocidolite induced transformation of Syrian hamster embryo cells, chrysotile and crocidolite transformed BALB/c3T3 mouse cells, and chrysotile transformed rat mesothelial cells. Neither amosite nor crocidolite transformed CH3 10T1/2 cells. In cultured rodent cells, amosite, anthophyllite, chrysotile and crocidolite induced chromosomal aberrations, and amosite, chrysotile and crocidolite induced sister chromatid exchanges; chrysotile and crocidolite induced aneuploidy and micronuclei. Chrysotile did not induce unscheduled DNA synthesis in rat hepatocytes. Amosite, chrysotile and crocidolite were inactive or weakly active in inducing mutation in rodent cells *in vitro*; none were mutagenic to bacteria [ref: 125].

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 2 (1973); Vol. 14 (1977)

**References**


1. IARC Monographs, 14, 1977

2. Armstrong, B.K., Musk, A.W., Baker, J.E., Hunt, J.M., Newall, C.C., Henzell, H.R., Blunsdon, B.S., Clarke-Hundley, M.D., Woodward, S.D. & Hobbs, M.S.T. (1984) Epidemiology of malignant mesothelioma in Western Australia. Med. J. Aust., 141, 86-88

3. Beck, B. & Irmscher, G. (1979) Extrathoracic mesotheliomas after inhalation of asbestos dust (Ger.). Z. Erkrank. Atm.-Org., 152, 282-293

4. Biava, P.M., Fiorito, A., Canciani, L. & Bovenzi, M. (1983) Epidemiology of mesothelioma of the pleura in the province of Trieste: role of occupational exposure to asbestos (Ital.). Med. Lav., 74, 260-265

5. Edge, J.R. & Choudhury, S.L. (1978) Malignant mesothelioma of the pleura in Barrow-in-Furness. Thorax, 33, 26-30

6. Emonot, A., Marquet, M., Baril, A., Berardj & Braillon (1979) Epidemiology of asbestos mesotheliomas in the region of St Etienne (Fr.). Ann. Med. intern., 130, 71-74

7. Griffiths, M.H., Riddell, R.J. & Xipell, J.M. (1980) Malignant mesothelioma: a review of 35 cases with diagnosis and prognosis. Pathology, 12, 591-603

8. Kovarik, J.L. (1976) Primary pleural mesothelioma. Cancer, 38, 1816-1825

9. Lemesch, C., Steinitz, R. & Wassermann, M. (1976) Epidemiology of mesothelioma in Israel. Environ. Res., 12, 255-261

10. McDonald, A.D. (1980) Malignant mesothelioma in Quebec. In: Wagner, J.C., ed., Biological Effects of Mineral Fibres (IARC Scientific Publications No. 30), Lyon, International Agency for Research on Cancer, pp. 673-680

11. Mowe, G. & Gylseth, B. (1986) Occupational exposure and regional variation of malignant mesothelioma in Norway, 1970-79. Am. J. ind. Med., 9, 323-332

12. Paur, R., Woitowitz, H.-J., Rödelsperger, K. & Jahn, H. (1985) Pleural mesothelioma after asbestos exposure in brake repair work in automobile repair workshop: case observations (Ger.). Prax. klin. Pneumol., 39, 362-366

13. Sheers, G. & Coles, R.M. (1980) Mesothelioma risks in a naval dockyard. Arch. environ. Health, 35, 276-282

14. Vande Weyer, R., Groetenbriel, C., Lauwers, D. & Yernault, J.C. (1982) Evolution of deaths by bronchial carcinoma and pleural mesothelioma among two groups of Belgian workers who died between 1973 and 1981: the role of asbestosis and coalworkers' pneumoconiosis (Abstract No. 5). Eur. J. respir. Dis., 63 (Suppl. 125), 10

15. Xu, Z., Armstrong, B.K., Blundson, B.J., Rogers, J.M., Musk, A.W. & Shilkin, K.B. (1985) Trends in mortality from malignant mesothelioma of the pleura, and production and use of asbestos in Australia. Med. J. Aust., 143, 185-187

16. Ben-Dror, G., Suprun, H. & Shkolnik, T. (1985) Peritoneal mesotheliomas and exposure to asbestos (Arabic). Harefuah, 108, 435-437

17. Cantor, K.P., Sontag, J.M. & Heid, M.F. (1986) Patterns of mortality among plumbers and pipefitters. Am. J. ind. Med., 10, 73-89

18. Gardner, M.J., Jones, R.D., Pippard, E.C. & Saitoh, N. (1985) Mesothelioma of the peritoneum during 1967-82 in England and Wales. Br. J. Cancer, 51, 121-126

19. Mancuso, T.F. (1983) Mesothelioma among machinists in railroad and other industries. Am. J. ind. Med., 4, 501-513

20. Newhouse, M.L., Oakes, D. & Woolley, A.J. (1985) Mortality of welders and other craftsmen at a shipyard in NE England. Br. J. ind. Med., 42, 406-410

21. Sera, Y. & Kang, K.-Y. (1981) Asbestos and cancer in the Sennan district of Osaka. Tohoku J. exp. Med., 133, 313-320

22. Fligiel, Z. & Kaneko, M. (1976) Malignant mesothelioma of the tunica vaginalis propria testis in a patient with asbestos exposure. Cancer, 37, 1478-1484

23. Beck, B., Konetzke, G., Ludwig, V., Röthig, W. & Sturm, W. (1982) Malignant pericardial mesotheliomas and asbestos exposure: a case report. Am. J. ind. Med., 3, 149-159

24. Kahn, E.I., Rohl, A., Barrett, E.W. & Suzuki, Y. (1980) Primary pericardial mesothelioma following exposure to asbestos. Environ. Res., 23, 270-281

25. Arul, K.J. & Holt, P.F. (1977) Mesothelioma possibly due to environmental exposure to asbestos in childhood. Int. Arch. occup. environ. Health, 40, 141-143

26. Bignon, J., Sebastien, P., di Menza, L., Nebut, M. & Payan, H. (1979) French registry of mesotheliomas 1965-1978 (Fr.). Rev. fr. Mal. respir., 7, 223-242

27. Enterline, P.E. (1983) Cancer produced by nonoccupational asbestos exposure in the United States. J. Air Pollut. Control Assoc., 33, 318-322

28. Greenberg, M. & Davies, T.A.L. (1974) Mesothelioma register 1967-68. Br. J. ind. Med., 31, 91-104

29. Chen, W.-J. & Mottet, N.K. (1978) Malignant mesothelioma with minimal asbestos exposure. Hum. Pathol., 9, 253-258

30. Gylseth, B., Mowé, G. & Wannag, A. (1983) Fibre type and concentration in the lungs of workers in an asbestos cement factory. Br. J. ind. Med., 40, 375-379

31. Magee, F., Wright, J.L., Chan, N., Lawson, L. & Churg, A. (1986) Malignant mesothelioma caused by childhood exposure to long-fiber low aspect ratio tremolite. Am. J. ind. Med., 9, 529-533

32. Wagner, J.C., Moncrieff, C.B., Coles, R., Griffiths, D.M. & Munday, D.E. (1986) Correlation between fibre content of the lungs and disease in naval dockyard workers. Br. J. ind. Med., 43, 391-395

33. Browne, K. (1983) Asbestos-related mesothelioma: epidemiological evidence for asbestos as a promoter. Arch. environ. Health, 38, 261-266

34. Churg, A., Warnock, M.L. & Bensch, K.G. (1978) Malignant mesothelioma arising after direct application of asbestos and fiber glass to the pericardium. Am. Rev. respir. Dis., 118, 419-424

35. Beck, E.G. & Schmidt, P. (1985) Epidemiological investigations of deceased employees of the asbestos cement industry in the Federal Republic of Germany. Zbl. Bakt. Hyg., I. Abt. Orig. B, 181, 207-215

36. Hughes, J.M., Hammad, Y.Y. & Weill, H. (1986) Mesothelioma risk in relation to duration and type of asbestos fiber exposure (Abstract). Am. Rev. respir. Dis., 133 (Suppl. 4), A33

37. Selikoff, I.J., Hammond, E.C. & Seidman, H. (1980) Latency of asbestos disease among insulation workers in the United States and Canada. Cancer, 46, 2736-2740

38. Blot, W.J., Harrington, J.M., Toledo, A., Hoover, R., Heath, C.W., Jr & Fraumeni, J.F., Jr (1978) Lung cancer after employment in shipyards during World War II. New Engl. J. Med., 299, 620-624

39. Blot, W.J., Stone, B.J., Fraumeni, J.F., Jr & Morris, L.E. (1979) Cancer mortality in US counties with shipyard industries during World War II. Environ. Res., 18, 281-290

40. Blot, W.J., Morris, L.E., Stroube, R., Tagnon, I. & Fraumeni, J.F., Jr (1980) Lung and laryngeal cancers in relation to shipyard employment in coastal Virginia. J. natl Cancer Inst., 65, 571-575

41. Kolonel, L.N., Yoshizawa, C.N., Hirohata, T. & Myers, B.C. (1985) Cancer occurrence in shipyard workers exposed to asbestos in Hawaii. Cancer Res., 45, 3924-3928

42. Rossiter, C.E. & Coles, R.M. (1980) HM Dockyard, Devonport: 1947 mortality study. In: Wagner, J.C., ed., Biological Effects of Mineral Fibres (IARC Scientific Publications No. 30), Lyon, International Agency for Research on Cancer, pp. 713-721

43. Sandén, A., Näslund, P.-E. & Järvholm, B. (1985) Mortality in lung and gastrointestinal cancer among shipyard workers. Int. Arch. occup. environ. Health, 55, 277-283

44. Lumley, K.P.S. (1976) A proportional study of cancer registrations of dockyard workers. Br. J. ind. Med., 33, 108-114

45. Nicholson, W.J., Lilis, R., Frank, A.L. & Selikoff, I.J. (1980) Lung cancer prevalence among

shipyard workers. Am. J. ind. Med., 1, 191-203

46. Alies-Patin, A.M. & Valleron, A.J. (1985) Mortality of workers in a French asbestos cement factory 1940-82. Br. J. ind. Med., 42, 219-225

47. Berry, G., Newhouse, M.L. & Antonis, P. (1985) Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br. J. ind. Med., 42, 12-18

48. Hodgson, J.T. & Jones, R.D. (1986) Mortality of asbestos workers in England and Wales. Br. J. ind. Med., 43, 158-164

49. Coggon, D., Pannett, B. & Acheson, E.D. (1984) Use of job-exposure matrix in an occupational analysis of lung and bladder cancers on the basis of death certificates. J. natl Cancer Inst., 72, 61-65

50. Kjuus, H., Skjaerven, R., Langard, S., Lien, J.T. & Aamodt, T. (1986) A case-referent study of lung cancer, occupational exposures and smoking. II. Role of asbestos exposure. Scand. J. Work Environ. Health, 12, 203-209

51. Newhouse, M.L., Berry, G. & Wagner, J.C. (1985) Mortality of factory workers in East London 1933-80. Br. J. ind. Med., 42, 4-11

52. Hilt, B., Langard, S., Andersen, A. & Rosenberg, J. (1985) Asbestos exposure, smoking habits, and cancer incidence among production and maintenance workers in an electrochemical plant. Am. J. ind. Med., 8, 565-577

53. Woitowitz, H.-J., Lange, H.-J., Beierl, L., Rathgeb, M., Schmidt, K., Ulm, K., Giesen, T., Woitowitz, R.H., Pache, L. & Rödelsperger, K. (1986) Mortality rates in the Federal Republic of Germany following previous occupational exposure to asbestos dust. Int. Arch. occup. environ. Health, 57, 161-171

54. Zoloth, S. & Michaels, D. (1985) Asbestos disease in sheet metal workers: the results of a proportional mortality analysis. Am. J. ind. Med., 7, 315-321

55. Elmes, P.C. & Simpson, M.J.C. (1977) Insulation workers in Belfast. A further study of mortality due to asbestos exposure (1940-75). Br. J. ind. Med., 34, 174-180

56. Huuskonen, M.S. (1980) Asbestos and cancer in Finland. J. Toxicol. environ. Health, 6, 1261-1265

57. Selikoff, I.J. & Seidman, H. (1981) Cancer of the pancreas among asbestos insulation workers. Cancer, 47 (Suppl.), 1469-1473

58. Burch, J.D., Howe, G.R., Miller, A.B. & Semenciw, R. (1981) Tobacco, alcohol, asbestos, and nickel in the etiology of cancer of the larynx: a case-control study. J. natl Cancer Inst., 67, 1219-1224

59. von Bittersohl, G. (1977) On the problem of asbestos-induced carcinoma of the larynx (Ger.). Z. ges. Hyg., 23, 27-30

60. Rubino, G.F., Piolatto, G., Newhouse, M.L., Scansetti, G., Aresini, G.A. & Murray, R. (1979) Mortality of chrysotile asbestos workers at the Balangero mine, Northern Italy. Br. J. ind. Med., 36, 187-194

61. Musk, A.W., de Klerk, N., Hobbs, M.S.T. & Armstrong, B.K. (1986) Mortality in crocidolite miners and millers from Wittenoom, Western Australia (Abstract). Am. Rev. respir. Dis., 133 (Suppl. 4),

62. Graham, S., Blanchet, M. & Rohrer, T. (1977) Cancer in asbestos-mining and other areas of Quebec. J. natl Cancer Inst., 59, 1139-1145

63. Chiappino, G., Riboldi, L., Todaro, A. & Schulz, L. (1985) Survey of mesotheliomas in Lombardy in the period 1978-1982 (Ital.). Med. Lav., 76, 454-465

64. Mowé, G., Gylseth, G., Hartveit, F. & Skaug, V. (1984) Occupational asbestos exposure, lung-fiber concentration and latency time in malignant mesothelioma. Scand. J. Work Environ. Health, 10, 293-298

65. Tagnon, I., Blot, W.J., Stroube, R.B., Day, N.E., Morris, L.E., Peace, B.B. & Fraumeni, J.F., Jr (1980) Mesothelioma associated with the shipbuilding industry in coastal Virginia. Cancer Res., 40, 3875-3879

66. Thériault, G.P. & Grand-Bois, L. (1978) Mesothelioma and asbestos in the province of Québec, 1969-1972. Arch. environ. Health, 33, 15-19

67. Vianna, N.J. & Polan, A.K. (1978) Non-occupational exposure to asbestos and malignant mesothelioma in females. Lancet, i, 1061-1063

68. Meigs, J.W., Walter, S.D., Heston, J.F., Millette, J.R., Craun, G.F., Woodhull, R.S. & Flannery, J.T. (1980) Asbestos cement pipe and cancer in Connecticut 1955-1974. J. environ. Health, 42, 187-191

69. Wigle, D.T. (1977) Cancer mortality in relation to asbestos in municipal water supplies. Arch. environ. Health, 32, 185-190

70. Harrington, J.M., Craun, G.F., Meigs, J.W., Landrigan, P.J., Flannery, J.T. & Woodhull, R.S. (1978) An investigation of the use of asbestos cement pipe for public water supply and the incidence of gastrointestinal cancer in Connecticut, 1935-1973. Am. J. Epidemiol., 107, 96-103

71. Polissar, L., Severson, R.K. & Boatman, E.S. (1984) A case-control study of asbestos in drinking water and cancer risk. Am. J. Epidemiol., 119, 456-471

72. Kanarek, M.S., Conforti, P.M., Jackson, L.A., Copper, R.C. & Murchio, J.C. (1980) Asbestos in drinking water and cancer incidence in the San Francisco Bay area. Am. J. Epidemiol., 112, 54-72

73. Acheson, E.D., Gardner, M.J., Pippard, E.C. & Grime, L.P. (1982) Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br. J. ind. Med., 39, 344-348

74. Botha, J.L., Irwig, L.M. & Strebel, P.M. (1986) Excess mortality from stomach cancer, lung cancer, and asbestosis and/or mesothelioma in crocidolite mining districts in South Africa. Am. J. Epidemiol., 123, 30-40

75. Hobbs, M.S.T., Woodward, S.D., Murphy, B., Musk, A.W. & Elder, J.E. (1980) The incidence of pneumoconiosis, mesothelioma and other respiratory cancer in men engaged in mining and milling crocidolite in Western Australia. In: Wagner, J.C., ed., Biological Effects of Mineral Fibres (IARC Scientific Publications No. 30), Lyon, International Agency for Research on Cancer, pp. 615-625

76. Wignall, B.K. & Fos, A.J. (1982) Mortality of female gas mask assemblers. Br. J. ind. Med., 39, 34-38

77. Hilt, B., Rosenberg, J. & Langard, S. (1981) Occurrence of cancer in a small cohort of asbestos-

exposed workers. Scand. J. Work Environ. Health, 7, 185-189

78. Baker, J.E., Reutens, D.C., Graham, D.F., Sterrett, G.F., Musk, A.W., Hobbs, M.S.T., Armstrong, B.K. & de Klerk, N.H. (1986) Morphology of bronchogenic carcinoma in workers formerly exposed to crocidolite at Wittenoom Gorge in Western Australia. Int. J. Cancer, 37, 547-550

79. Berry, G. & Newhouse, M.L. (1983) Mortality of workers manufacturing friction materials using asbestos. Br. J. ind. Med., 40, 1-7

80. Gardner, M.J., Winter, P.D., Pannett, B. & Powell, C.A. (1986) Follow up study of workers manufacturing chrysotile asbestos cement products. Br. J. ind. Med., 43, 726-732

81. Weiss, W. (1977) Mortality of a cohort exposed to chrysotile asbestos. J. occup. Med., 19, 737-740

82. Haider, M. & Neuberger, M. (1980) Comparison of lung cancer risks for dust workers, asbestos-cement workers and control groups. In: Wagner, J.C., ed., Biological Effects of Mineral Fibres (IARC Scientific Publications No. 30), Lyon, International Agency for Research on Cancer, pp. 973-977

83. McDonald, A.D., Fry, J.S., Woolley, A.J. & McDonald, J.C. (1984) Dust exposure and mortality in an American chrysotile asbestos friction products plant. Br. J. ind. Med., 41, 151-157

84. Peto, J. (1980) Lung cancer mortality in relation to measured dust levels in an asbestos textile factory. In: Wagner, J.C., ed., Biological Effects of Mineral Fibres (IARC Scientific Publications No. 30), Lyon, International Agency for Research on Cancer, pp. 829-836

85. Peto, J., Doll, R., Howard, S.V., Kinlen, L.J. & Lewinsohn, H.C. (1977) A mortality study among workers in an English asbestos factory. Br. J. ind. Med., 34, 169-173

86. Peto, J., Doll, R., Hermon, C., Binns, W., Clayton, R. & Goffe, T. (1985) Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann. occup. Hyg., 29, 305-355

87. Liddell, F.D.K., Thomas, D.C., Gibbs, G.W. & McDonald, J.C. (1984) Fibre exposure and mortality from pneumoconiosis, respiratory and abdominal malignancies in chrysotile production in Quebec, 1926-75. Ann. Acad. Med., 13, 340-344

88. Dement, J.M., Harris, R.L., Jr, Symons, M.J. & Shy, C. (1982) Estimates of dose-response for respiratory cancer among chrysotile asbestos textile workers. Ann. occup. Hyg., 26, 869-887

89. McDonald, A.D., Fry, J.S., Woolley, A.J. & McDonald, J. (1983) Dust exposure and mortality in an American chrysotile textile plant. Br. J. ind. Med., 40, 361-367

90. Acheson, E.D. & Gardner, M.J. (1979) Mesothelioma and exposure to mixtures of chrysotile and amphibole asbestos. Arch. environ. Health, 34, 240-242

91. Browne, K. & Smither, W.J. (1983) Asbestos-related mesothelioma: factors discriminating between pleural and peritoneal sites. Br. J. ind. Med., 40, 145-152

92. Newhouse, M.L., Berry, G. & Skidmore, J.W. (1982) A mortality study of workers manufacturing friction materials with chrysotile asbestos. Ann. occup. Hyg., 26, 899-909

93. Ohlson, C.-G., Klaesson, B. & Hogstedt, C. (1984) Mortality among asbestos-exposed workers in a railroad workshop. Scand. J. Work Environ. Health, 10, 283-291

94. McDonald, A.D. & Fry, J.S. (1982) Mesothelioma and fiber type in three American asbestos factories - preliminary report. Scand. J. Work Environ. Health, 8 (Suppl. 1), 53-58

95. Acheson, E.D., Gardner, M.J., Bennett, C. & Winter, P.D. (1981) Mesothelioma in a factory using amosite and chrysotile asbestos. Lancet, ii, 1403-1405

96. McDonald, J.C., Gibbs, G.W., Liddell, F.D.K. & McDonald, A.D. (1978) Mortality after long exposure to cummingtonite-grunerite. Am. Rev. respir. Dis., 118, 271-277

97. McDonald, J.C., McDonald, A.D., Armstrong, B. & Sébastien, P. (1986) Cohort study of mortality in vermiculite miners exposed to tremolite. Br. J. ind. Med., 43, 436-444

98. Amandus, H.E. & Wheeler, R. (1987) The morbidity and mortality of vermiculite miners and millers exposed to tremolite-actinolite: Part II. Mortality. Am. J. ind. Med., 11, 15-26

99. Neuberger, M., Kundi, M. & Friedl, H.P. (1984) Environmental asbestos exposure and cancer mortality. Arch. environ. Health, 39, 261-265

100. Ohlson, C.-G. & Hogstedt, C. (1985) Lung cancer among asbestos cement workers. A Swedish cohort study and a review. Br. J. ind. Med., 42, 397-402

101. Thomas, H.F., Benjamin, I.T., Elwood, P.C. & Sweetnam, P.M. (1982) Further follow-up study of workers from an asbestos cement factory. Br. J. ind. Med., 39, 273-276

102. Weill, H., Hughes, J. & Waggenspack, C. (1979) Influence of dose and fiber type on respiratory malignancy risk in asbestos cement manufacturing. Am. Rev. respir. Dis., 120, 345-354

103. Finkelstein, M.M. (1984) Mortality among employees of an Ontario asbestos-cement factory. Am. Rev. respir. Dis., 129, 754-761

104. Hardell, L. (1981) Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. Scand. J. Work Environ. Health, 7, 119-130

105. Malker, H.S.R., McLaughlin, J.K., Malker, B.K., Stone, B.J., Weiner, J.A., Ericsson, J.L.E. & Blot, W.J. (1986) Biliary tract cancer and occupation in Sweden. Br. J. ind. Med., 43, 257-262

106. Ross, R., Nichols, P., Wright, W., Lukes, R., Dworsky, R., Paganini-Hill, A., Koss, M. & Henderson, B. (1982) Asbestos exposure and lymphomas of the gastrointestinal tract and oral cavity. Lancet, ii, 1118-1120

107. Waxweiler, R.J. & Robinson, C. (1983) Asbestos and non-Hodgkin's lymphoma. Lancet, i, 189-190

108. Spanedda, R., Barbieri, D. & La Corte, R. (1983) Asbestos and non-Hodgkin's lymphoma. Lancet, i, 190

109. Saracci, R. (1977) Asbestos and lung cancer: an analysis of the epidemiological evidence on the asbestos-smoking interaction. Int. J. Cancer, 20, 323-331

110. Davis, J.M.G., Addison, J., Bolton, R.E., Donaldson, K., Jones, A.D. & Miller, B.G. (1985) Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis, 6, 667-674

111. Davis, J.M.G., Addison, J., Bolton, R.E., Donaldson, K. & Jones, A.D. (1986) Inhalation and injection studies in rats using dust samples from chrysotile asbestos prepared by a wet dispersion process. Br. J. exp. Pathol., 67, 113-129

112. Stanton, M.F., Layard, M., Tegeris, A., Miller, E., May, M., Morgan, E. & Smith, A. (1981) Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J. natl Cancer Inst., 67, 965-975

113. Suzuki, Y, & Kohyama, N. (1984) Malignant mesothelioma induced by asbestos and zeolite in the mouse peritoneal cavity. Environ. Res., 35, 277-292

114. Bolton, R.E., Davis, J.M.G., Donaldson, K. & Wright, A. (1982) Variations in the carcinogenicity of mineral fibres. Ann. occup. Hyg., 26, 569-582

115. Pott, F., Huth, F. & Spurny, K. (1980) Tumour induction after intraperitoneal injection of fibrous dusts. In: Wagner, J.C., ed., Biological Effects of Mineral Fibres (IARC Scientific Publications No. 30), Lyon, International Agency for Research on Cancer, pp. 337-342

116. Spurny, K., Pott, F., Huth, F., Weiss, G. & Opiela, H. (1979) Identification and carcinogenic action of fibrous actinolite from a diabase rock (Ger.). Staub-Reinhalt. Luft, 39, 386-389

117. Pott, F., Schlipköter, H.W., Ziem, U., Spurny, K. & Huth, F. (1982) New results from implantation experiments with mineral fibres. In: Biological Effects of Man-made Fibres, Vol. 2, Copenhagen, WHO Regional Office for Europe, pp. 286-302

118. Pott, F., Matscheck, A., Ziem, U., Muhle, H. & Huth, F. (1987) Animal experiments with chemically treated fibres. Ann. occup. Hyg. (in press)

119. McConnell, E.E., Rutter, H.A., Ulland, B.M. & Moore, J.A. (1983) Chronic effects of dietary exposure to amosite asbestos and tremolite in F344 rats. Environ. Health Perspect., 53, 27-44

120. National Toxicology Program (1983) Lifetime Carcinogenesis Studies of Amosite Asbestos (CAS No. 121-72-73-5) in Syrian Golden Hamsters (Feed Studies) (NIH Publ. No. 84-2505; NTP TR 249), Research Triangle Park, NC

121. McConnell, E.E., Shefner, A.M., Rust, J.H. & Moore, J.A. (1983) Chronic effects of dietary exposure to amosite and chrysotile asbestos in Syrian golden hamsters. Environ. Health Perspect., 53, 11-25

122. National Toxicology Program (1985) Toxicology and Carcinogenesis Studies of Chrysotile Asbestos (CAS No. 12001-29-5) in F344/N Rats (Feed Studies) (NIH Publ. No. 86-2551; NTP TR 295), Research Triangle Park, NC

123. Bolton, R.E., Davis, J.M.G. & Lamb, D. (1982) The pathological effects of prolonged asbestos ingestion in rats. Environ. Res., 29, 134-150

124. Küng-Vösamäe, A. & Vinkmann, F. (1980) Combined carcinogenic action of chrysotile asbestos dust and N-nitrosodiethylamine on the respiratory tract of Syrian golden hamsters. In: Wagner, J.C., ed., Biological Effects of Mineral Fibres (IARC Scientific Publications No. 30), Lyon, International Agency for Research on Cancer, pp. 305-310

125. IARC Monographs, Suppl. 6, 77-80, 1987

**Overall evaluation**

Asbestos is *carcinogenic to humans (Group 1)*.

**Synonym for Asbestos fibre:**

- Asbestos

**Synonyms for Anthophyllite:**

- Azbolen asbestos
- Ferroanthophyllite

**Synonym for Amosite:**

- Brown asbestos
- Mysorite

**Synonyms for Chrysotile:**

- Avibest C
- Cassiar AK
- Calidria RG 144
- Calidria RG 600
- Serpentine
- White asbestos

**Synonym for Crocidolite:**

- Blue asbestos

**Synonyms for Tremolite:**

- Magnesium salt (8:4)
- Silicic acid, calcium

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# AURAMINE (TECHNICAL-GRADE) (Group 2B)
# and MANUFACTURE OF AURAMINE (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 118)

**CAS No.:** 492-80-8
**Chem. Abstr. Name:** C.I. Solvent yellow 34

**A. Evidence for carcinogenicity to humans** (*inadequate* for auramine, technical-grade; *sufficient* for the manufacture of auramine)

The manufacture of auramine (which also involves exposure to other chemicals) was judged to be causally associated with an increased incidence of bladder cancer on the basis of one study dealing with experiences in the first half of the century in the UK [ref: 1]. Data reported later, in two studies dealing with one group of workers in the Federal Republic of Germany involved in the manufacture of auramine, were judged to show increased risks of both bladder cancer and prostatic cancer; however, these workers had also been exposed to other chemicals, including 2-naphthylamine (see p. 261) [ref: 2,3].

In a study of mortality and cancer incidence among hairdressers, the hypothesis was raised that the observed excess risk of bladder cancer was associated with exposure to colouring agents present in brilliantines used on men's hair. Auramine was reported to be one of the most commonly used dyes in brilliantines, at least in the 1930s; however, the occurrence of impurities, such as 2-naphthylamine could not be ruled out [ref: 4]. Data on exposure to auramine alone were considered to be inadequate for evaluation.

**B. Evidence for carcinogenicity to animals** (*sufficient* for auramine, technical-grade)

Auramine (technical-grade) was tested for carcinogenicity by oral administration in mice and rats and by subcutaneous injection in rats. Following its oral administration, it induced liver neoplasms in animals of each species [ref: 1,2]. After subcutaneous injection in one study in rats, it induced local sarcomas [ref: 1]. Studies in rabbits and dogs were inadequate for evaluation [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of auramine in humans. Auramine did not induce micronuclei in bone-marrow cells of mice treated *in vivo*. It transformed Syrian hamster embryo cells and induced sister chromatid exchanges and DNA strand breaks in rodent cells in culture. It caused aneuploidy, mitotic recombination and DNA damage in yeast. Auramine was mutagenic to bacteria and induced prophage [ref: 5].

**Overall evaluation**

Manufacture of auramine is *carcinogenic to humans (Group 1)*.

Auramine (technical-grade) is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 1 (1972)

**References**

1. IARC Monographs, 1, 69-73, 1972

2. Kirsch, P., Fleig, I., Frentzel-Beyme, R., Gembardt, C., Steinborn, J., Thiess, A.M., Koch, W., Seibert, W., Wellenreuther, G. & Zeller, H. 1978) Auramine. Toxicology and occupational health (Ger.). Arbeitsmed. Sozialmed. Präventivmed., 13, 1-28

3. Thiess, A.M., Link, R. & Wellenreuther, G. (1982) Mortality study of employees exposed to auramine. In: El-Attal, M., Abdel-Gelib, S., Massoud, A. & Noweir, M., eds, Proceedings of the 9th International Conference of Occupational Health in the Chemical Industry, Cairo, 1981, pp. 197-208

4. Gubéran, E., Raymond, L. & Sweetnam, P.M. (1985) Increased risk for male bladder cancer among a cohort of male and female hairdressers from Geneva. Int. J. Epidemiol., 14, 549-554

5. IARC Monographs, Suppl. 6, 83-85, 1987

### Synonyms for Auramine

- Aniline,4,4'-(imidocarbonyl)-bis(*N*,*N*'-dimethyl)-
- Apyonine auramine base
- Auramine N base
- Auramine O base
- Auramine SS
- Auramine OO
- Brilliant oil yellow
- C.I. basic yellow 2 (free base)
- 4,4'-Dimethylaminobenzophenonimide
- bis(*para*-Dimethylaminophenyl)methyleneimine
- Fat yellow A
- Glauramine
- Tetramethyl-p-diamino-imido-benzophenme
- Tetramethyldiaminodiphenylacetimine
- Yellow pyoctanine

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# AZATHIOPRINE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 119)

**CAS No.**: 446-86-6
**Chem. Abstr. Name**: 1*H*-Purine, 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Two large prospective epidemiological studies have shown that renal transplant patients, who usually receive azathioprine as an immunosuppressant, become at high risk for non-Hodgkin's lymphoma, squamous-cell cancers of the skin, hepatobiliary carcinomas and mesenchymal tumours. While this is true for each of the various etiological entities resulting in the need for a transplant, these patients also have in common heavy exposure to foreign antigens [ref: 1]. Other patients who have received azathioprine as an immunosuppressant, including those with rheumatoid arthritis, systemic lupus and other 'collagen' disorders, inflammatory bowel disease and certain skin and renal diseases, have also been studied: the same array of malignancies was found to be in excess, although to a lesser extent [ref: 1,2]. For these patients, however, the picture is still not completely clear, because patients with rheumatoid arthritis constituted the largest category in the latter study [ref: 2], and some [ref: 3], but not all studies [ref: 4], have found that this disease conveys a risk for non-Hodgkin's lymphoma in the absence of treatment.

**B. Evidence for carcinogenicity to animals** (*limited*)

Suggestive evidence was obtained that lymphomas were induced in mice after intraperitoneal, subcutaneous or intramuscular injection of azathioprine, and that thymic lymphomas and squamous-cell carcinomas of the ear duct were induced in rats after oral administration, but there were limitations in the design and reporting of these studies [ref: 1,5].

**C. Other relevant data**

There are conflicting reports of effects on the incidence of chromosomal aberrations in lymphocytes and bone-marrow cells of patients treated with azathioprine. In one study, the incidence of sister chromatid exchanges in lymphocytes of treated patients was not increased [ref: 6].

In animals treated *in vivo*, azathioprine induced dominant lethal mutations in mice; chromosomal aberrations in rabbit lymphocytes and Chinese hamster bone-marrow cells, and micronuclei in mice, rats and hamsters; it did not induce sister chromatid exchanges in Chinese hamster bone-marrow cells. Azathioprine induced chromosomal aberrations but not sister chromatid exchanges in human lymphocytes in vitro. It induced chromosomal aberrations in *Drosophila* and was weakly mutagenic to fungi and was mutagenic to bacteria [ref: 6].

**Overall evaluation**

Azathioprine is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 47-78, 1981

2. Kinlen, L.J. (1985) Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. Am. J. Med., 78 (Suppl. 1A), 44-49

3. Isomäki, H.A., Hakulinen, T. & Joutsenlahti, U. (1978) Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. J. chron. Dis., 31, 691-696

4. Fries, J.F., Bloch, D., Spitz, P. & Mitchell, D.M. (1985) Cancer in rheumatoid arthritis: a prospective long-term study of mortality. Am. J. Med., 78 (Suppl. 1A), 56-59

5. Cohen, S.M., Erturk, E., Skibba, J.L. & Bryan, G.T. (1983) Azathioprine induction of lymphomas and squamous cell carcinomas in rats. Cancer Res., 43, 2768-2772

6. IARC Monographs, Suppl. 6, 86-88, 1987

**Synonyms**

- Amuran
- Azamun
- Azathioprin
- Azatioprin
- Azothiaprine
- Azathioprene
- BW 57322
- Imuran
- Imurel
- Imurek
- Methyl-nitroimidazolylmercaptopurine
- 6-[(1-Methyl-4-nitroimidazol-5-yl)thio]purine
- 6-(1-Methyl-4-nitro-imidazole-5-yl)thiopurine
- 6-(1-Methyl-4-nitro-5-imidazolyl)mercaptopurin
- Muran
- NSC 39084

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# BENZENE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 120)

**CAS No.:** 71-43-2
**Chem. Abstr. Name:** Benzene

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Numerous case reports and series have suggested a relationship between exposure to benzene and the occurrence of various types of leukaemia [ref: 1]. Several case-control studies have also shown increased odds ratios for exposure to benzene, but mixed exposure patterns and poorly defined exposures render their interpretation difficult [ref: 1,2].

Three independent cohort studies have demonstrated an increased incidence of acute nonlymphocytic leukaemia in workers exposed to benzene [ref: 1,3]. An updating of a cohort study published earlier on benzene-exposed workers [ref: 1] confirmed the previous findings and added a further case of myelogenous leukaemia, giving a standardized mortality ratio (SMR) of 194 (95% confidence interval, 52-488), based on four cases; the difference was statistically significant when only myelogenous leukaemia was considered (4 observed, 0.9 expected; $p = 0.011$) [ref: 4]. A further cohort study found an excess of acute myeloid leukaemia (SMR, 394; 172-788) among refinery workers, based on eight cases; however, the patients had not worked in jobs identified as having the highest benzene exposure [ref: 5]. Another study of refinery workers showed no death from leukaemia (0.42 expected); however, the median exposure intensity for benzene was 0.14 ppm (0.45 mg/m$^3$), and only 16% of 1394 personal samples, taken between 1973 and 1982 inclusive, contained more than 1 ppm (3.19 mg/m$^3$). The median exposure intensity in 'benzene-related units' was 0.53 ppm (1.7 mg/m$^3$) [ref: 6].

In a Chinese retrospective cohort study, encompassing 28 460 workers exposed to benzene in 233 factories, 30 cases of leukaemia (23 acute, seven chronic) were found, as compared to four cases in a reference cohort of 28 257 workers in 83 machine production, textile and cloth factories. The mortality rate from leukaemia was 14/100 000 person-years among the exposed and 2/100 000 person-years among the unexposed (SMR, 574; $p < 0.01$). Mortality was especially high for workers engaged in organic synthesis, painting and rubber production. The mortality from leukaemia for cases that had previously had benzene poisoning was 701/100 000 person-years. 'Grab' samples of benzene in air were taken during the time of the survey in workplaces where cases of leukaemia were observed; the mean concentrations varied in a wide range from 10 to 1000 mg/m$^3$, but the range 50-500 mg/m$^3$ covered most of them [ref: 7].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Benzene was tested for carcinogenicity in mice and rats by several routes of administration. Following its oral administration at several dose levels, it induced neoplasms at multiple sites in males and females of both species [ref: 1,8-11]. After mice were exposed to benzene by inhalation, a tendency towards induction of lymphoid neoplasms was observed [ref: 1,12,13]. Exposure of rats by inhalation increased the incidence of neoplasms, mainly carcinomas, at various sites [ref: 9,10,14-16]. Skin application or subcutaneous injection of benzene to mice did not produce evidence of carcinogenicity, but most of the experiments were inadequate for evaluation [ref: 1]. In a mouse-lung tumour bioassay by intraperitoneal injection, an increase in the incidence of lung adenomas was observed in males [ref: 17].

**C. Other relevant data**

Chromosomal aberrations in human peripheral lymphocytes were associated with occupational exposure to benzene, although many of the studies are very difficult to interpret [ref: 18].

Benzene induced chromosomal aberrations, micronuclei and sister chromatid exchanges in bone-marrow cells of mice, chromosomal aberrations in bone-marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo*. It induced chromosomal aberrations and mutation in human cells *in vitro* but did not induce sister chromatid exchanges in cultured human lymphocytes except in one study in which high concentrations of an exogenous metabolic system were used. In some test systems, benzene induced cell transformation. It did not induce sister chromatid exchanges in rodent cells *in vitro*, but did induce aneuploidy and, in some studies, chromosomal aberrations in cultured Chinese hamster ovary cells. Benzene induced mutation and DNA damage in some studies in rodent cells *in vitro* [ref: 18].

In *Drosophila*, benzene was reported to be weakly positive in assays for somatic mutation and for crossing-over in spermatogonia; in single studies, it did not induce sex-linked recessive lethal mutations or translocations. It induced aneuploidy, mutation and gene conversion in fungi. Benzene was not mutagenic to bacteria [ref: 18].

**Overall evaluation**

Benzene is *carcinogenic to humans (Group 1)*

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 7 (1974); Vol. 29 (1982)

**References**

1. IARC Monographs, 29, 93-148, 391-398, 1982

2. Arp, E.W., Jr, Wolf, P.H. & Checkoway, H. (1983) Lymphocytic leukemia and exposures to benzene and other solvents in the rubber industry. J. occup. Med., 25, 598-602

3. Decouflé, P., Blattner, W.A. & Blair, A. (1983) Mortality among chemical workers exposed to benzene and other agents. Environ. Res., 30, 16-25

4. Bond, G.G., McLaren, E.A., Baldwin, C.L. & Cook, R.R. (1986) An update of mortality among chemical workers exposed to benzene. Br. J. ind. Med., 43, 685-691

5. McCraw, D.S., Joyner, R.E. & Cole, P. (1985) Excess leukemia in a refinery population. J. occup. Med., 27, 220-222

6. Tsai, S.P., Wen, C.P., Weiss, N.S., Wong, O., McClellan, W.A. & Gibson, R.L. (1983) Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries. J. occup. Med., 25, 685-692

7. Yin, S.-N., Li, G.-L., Tain, F.-D., Fu, Z.-I., Jin, C., Chen, Y.-J., Luo, S.-J., Ye, P.-Z., Zhang, J.-Z., Wang, G.-C., Zhang, X.-C., Wu, H.-N. & Zhong, Q.-C. (1987) Leukaemia in benzene workers: a retrospective cohort study. Br. J. ind. Med., 44, 124-128

8. Maltoni, C., Conti, B. & Scarnato, C. (1982) Squamous cell carcinomas of the oral cavity in Sprague Dawley rats, following exposure to benzene by ingestion. First experimental demonstration. Med. Lav., 4, 441-445

9. Maltoni, C., Conti, B. & Cotti, G. (1983) Benzene: a multi-potential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. ind. Med., 4, 589-630

10. Maltoni, C., Conti, B., Cotti, G. & Belpoggi, F. (1985) Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: current results and ongoing research. Am. J. ind. Med., 7, 415-446

11. National Toxicology Program (1986) Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N rats and B6C3F1 Mice (Gavage Studies) (NTP Technical Report 289; NIH Publ. No. 86-2545), Research Triangle Park, NC

12. Cronkite, E.P., Bullis, J.E., Inoue, T. & Drew, R.T. (1984) Benzene inhalation produces leukemia in mice. Toxicol. appl. Pharmacol., 75, 358-361

13. Cronkite, E.P., Drew, R.T., Inoue, T. & Bullis, J.E. (1985) Benzene hematotoxicity and leukemogenesis. Am. J. ind Med., 7, 447-456

14. Maltoni, C., Cotti, G., Valgimigli, L. & Mandrioli, A. (1982) Zymbal gland carcinomas in rats following exposure to benzene by inhalation. Am. J. ind. Med., 3, 11-16

15. Maltoni, C., Cotti, G., Valgimigli, L. & Mandrioli, A. (1982) Hepatocarcinomas in Sprague-Dawley rats, following exposure to benzene by inhalation. First experimental demonstration. Med. Lav., 4, 446-450

16. Snyder, C.A., Goldstein, B.D., Sellakumar, A.R. & Albert, R.E. (1984) Evidence for hematotoxicity and tumorigenesis in rats exposed to 100 ppm benzene. Am. J. ind. Med., 5, 429-434

17. Stoner, G.D., Conran, P.B., Greisiger, E.A., Stober, J., Morgan, M. & Pereira, M.A. (1986) Comparison of two routes of chemical administration on the lung adenoma response in strain A/J mice. Toxicol. appl. Pharmacol., 82, 19-31

18. IARC Monographs, Suppl. 6, 91-95, 1987

**Synonyms**

- (6)-Annulene
- Benzine
- Benzol
- Benzole
- Benzolene
- Bicarburet of hydrogen
- Carbon oil
- Coal naphtha
- Cyclohexatriene
- Mineral naphtha
- Motor benzol
- Phenyl hydride
- Polystream
- Pyrobenzol
- Pyrobenzole

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Last updated: 6 February 1998

# BENZIDINE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 123)

**Benzidine**
**CAS No.**: 92-87-5
**Chem. Abstr. Name**: (1,1'-Biphenyl)-4,4'-diamine

**Benzidine sulphate**
**CAS No.**: 531-86-2
**Chem. Abstr. Name**: (1,1'-Biphenyl)-4,4'-diamine, sulfate (1:1)

**Benzidine hydrochloride**
**CAS No.**: 14414-63-7
**Chem. Abstr. Name**: (1,1'-Biphenyl)-4,4'-diamine, Hydrochloride

**Benzidine dihydrochloride**
**CAS No.**: 531-85-1
**Chem. Abstr. Name**: (1,1'-Biphenyl)-4,4'-diamine, Dihydrochloride

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Case reports and follow-up studies of workers in many countries have demonstrated that occupational exposure to benzidine is causally associated with an increased risk of bladder cancer. In one extreme instance, all five of a group of workers continuously employed in the manufacture of benzidine for 15 years or more developed bladder cancer [ref: 1]. Earlier data suggesting that the incidence of this cancer in workers decreased after a reduction in industrial exposure [ref: 1] have been supported by a study of a cohort of workers at a US benzidine-manufacturing facility, in which major preventive measures were instituted in 1950 to minimize worker exposure. The study period covered 1945-1979, and, overall, there was a clearly significant excess of bladder cancer incidence, which, however, declined in those first employed after 1950 [ref: 2]. Although a longer follow-up is required to evaluate fully the effect of preventive measures on cancer risks, the causal association is strengthened by these two independent observations. Few other epidemiological studies have examined the cancer risk associated with exposure to benzidine alone. In a study at a dyestuffs factory in Italy, it was possible to distinguish a very high bladder cancer risk (5 deaths observed, 0.06 expected) associated with benzidine production [ref: 3]. The study was extended and updated, but the role of exposure to benzidine alone in the dramatically increased bladder cancer risk could not be examined further [ref: 4]. Of 25 benzidine 'operators' at a plant in the USA, 13 developed bladder cancer; all cases had been exposed for six years or more [ref: 5]. A surveillance programme of 179 active and 65 retired workers in a dyestuffs manufacture plant in Japan revealed nine cases of bladder cancer that occurred between 1968 and 1981; all of the cases had been engaged in benzidine production [ref: 6].

Other investigations have shown high incidences of cancer of the bladder and urinary tract after concomitant exposure to benzidine and 2-naphthylamine [ref: 7,8]. Exposure to these two compounds was also associated with an increase in the occurrence of second primary cancers at sites other than the bladder, including the liver [ref: 9].

Among 1601 workers in the chemical-dye industry in China who were exposed to benzidine, methylnaphthylamine and dianisidine, 21 cases of bladder carcinoma were found. All had a history of exposure to benzidine, while no carcinoma was found among workers exposed to methylnaphthylamine or dianisidine. Suggestions of a dose-response relationship were provided by analysis according to length of exposure [ref: 10].

Bladder cancer was also found to be increased in ecological studies of areas where benzidine (as

well as 2-naphthylamine and other compounds) was used, manufactured or stored [ref: 11,12].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Benzidine and its salts were tested for carcinogenicity by oral administration in mice, rats, hamsters and dogs and by subcutaneous and intraperitoneal injection and inhalation in rats. Following oral administration of benzidine and its hydrochloride, significant increases in the incidences of benign and malignant liver neoplasms were observed in mice and hamsters [ref: 1,13-17] and of mammary cancer in rats; benzidine induced bladder carcinomas in dogs. Following subcutaneous administration of benzidine and its sulphate to rats, a high incidence of Zymbal-gland tumours was observed. After intraperitoneal administration of benzidine to rats, a marked increase in the incidence of mammary gland and Zymbal-gland neoplasms was observed. The results of one study in rats by inhalation could not be evaluated [ref: 1].

Two metabolites of benzidine, *N*,*N'*-diacetylbenzidine and *N*-hydroxy-*N*,*N*'-diacetylbenzidine, produced mammary gland and Zymbal gland tumours in rats following their intraperitoneal injection [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of benzidine in humans.

Covalent binding products of benzidine with DNA have been described in the liver of mice and rats treated *in vivo*. Benzidine induced micronuclei, sister chromatid exchanges, DNA strand breaks and unscheduled DNA synthesis in cells of rodents treated *in vivo*. It induced unscheduled DNA synthesis in humans cells *in vitro*. It caused transformation of Syrian hamster embryo and BALB/c3T3 cells and induced chromosomal aberrations, sister chromatid exchanges, unscheduled DNA synthesis and DNA strand breaks in rodent cells *in vitro*; conflicting results were obtained for mutation. Benzidine induced aneuploidy, gene conversion and DNA damage in yeast, but not mutation. It was mutagenic to plants and bacteria [ref: 18].

**Overall evaluation**

Benzidine is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 1 (1972); Vol. 29 (1982)

**References**

1. IARC Monographs, 29, 149-183, 391-398, 1982

2. Meigs, J.W., Marrett, L.D., Ulrich, F.U. & Flannery, J.T. (1986) Bladder tumor incidence among workers exposed to benzidine: a thirty-year follow-up. J. natl Cancer Inst., 76, 1-8

3. Rubino, G.F., Scansetti, G., Piolatto, G. & Pira, E. (1982) The carcinogenic effect of aromatic amines: an epidemiological study on the role of *o*-toluidine and 4,4'-methylene bis(2-methylaniline) in inducing bladder cancer in man. Environ. Res., 27, 241-254

4. Decarli, A., Peto, J., Piolatto, G. & La Vecchia, C. (1985) Bladder cancer mortality of workers exposed to aromatic amines: analysis of models of carcinogenesis. Br. J. Cancer, 51, 707-712

5. Horton, A.W. & Bingham, E.L. (1977) Risk of bladder tumors among benzidine workers and their serum properdin levels. J. natl Cancer Inst., 58, 1225-1228

6. Yamaguchi, N., Tazaki, H., Okubu, T. & Toyama, T. (1982) Periodic urine cytology surveillance of bladder tumor incidence in dyestuff workers. Am. J. ind. Med., 3, 139-148

7. Tsuchiya, K., Okubo, T. & Ishizu, S. (1975) An epidemiological study of occupational bladder tumours in the dye industry of Japan. Br. J. ind. Med., 32, 203-209

8. Nakamura, J., Takamatsu, M., Doi, J., Ohkawa, T., Fujinaga, T., Ebisuno, S. & Sone, M. (1980) Clinical study on the occupational urinary tract tumor in Wakayama (Jpn.). Jpn. J. Urol., 71, 945-951

9. Morinaga, K., Oshima, A. & Hara, I. (1982) Multiple primary cancers following exposure to benzidine and beta-naphthylamine. Am. J. ind. Med., 3, 243-246

10. Sun, L.D. & Deng, X.M. (1980) An epidemiologic survey of bladder carcinoma in chemical dye industry (Chin.). Chin. J. Surg., 18, 491-493

11. Segnan, N. & Tanturri, G. (1976) Study on the geographical pathology of laryngeal, bladder and childhood cancer in the province of Torino (Ital.). Tumori, 62, 377-386

12. Budnick, L.D., Sokal, D.C., Falk, H., Logue, J.N. & Fox, J.M. (1984) Cancer and birth defects near the Drake superfund site, Pennsylvania. Arch. environ. Health, 39, 409-413

13. Littlefield, N.A., Nelson, C.J. & Frith, C.H. (1983) Benzidine dihydrochloride: toxicological assessment in mice during chronic exposures. J. Toxicol. environ. Health, 12, 671-685

14. Littlefield, N.A., Nelson, C.J. & Gaylor, D.W. (1984) Benzidine dihydrochloride: risk assessment. Fundam. appl. Toxicol., 4, 69-80

15. Littlefield, N.A., Wolff, G.L. & Nelson, C.J. (1985) Influence of genetic composition of test-animal populations on chronic toxicity studies used for risk estimation. J. Toxicol. environ. Health, 15, 357-367

16. Nelson, C.J., Baetcke, K.P., Frith, C.H., Kodell, R.L. & Schieferstein, G. (1982) The influence of sex, dose, time, and cross on neoplasia in mice given benzidine dihydrochloride. Toxicol. appl. Pharmacol., 64, 171-186

17. Vesselinovitch, S.D. (1983) Perinatal hepatocarcinogenesis. Biol. Res. Pregn. Perinatol., 4, 22-25

18. IARC Monographs, Suppl. 6, 96-100, 1987

**Synonyms for benzidine**

- Benzidine base
- 4,4'-Bianiline
- *para*,*para*'-Bianiline
- 4,4'-Biphenyldiamine
- 4,4'-Biphenylenediamine
- C.I. azoic diazo component 112
- 4,4'-Diaminobiphenyl
- 4,4'-Diamino-1,1'-biphenyl
- *para*,*para*'-Diaminobiphenyl
- 4,4'-Diaminodiphenyl
- *para*-Diaminodiphenyl
- 4,4'-Diphenylenediamine
- Fast Corinth base B

Last updated: 6 February 1997

# BENZIDINE-BASED DYES
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 125)

**A. Evidence for carcinogenicity to humans** (*inadequate* for benzidine-based dyes)

The epidemiological data were inadequate to evaluate the carcinogenicity of three benzidine-based dyes, Direct Black 38, Direct Blue 6 and Direct Brown 95, to humans. However, a study of silk dyers and painters who had had multiple exposure to benzidine-based and other dyes indicated that those exposures were strongly associated with the occurrence of bladder cancer [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient* for technical-grade Direct Black 38, technical-grade Direct Blue 6 and technical-grade Direct Brown 95)

Direct Black 38 was tested for carcinogenicity in mice by administration in drinking-water, producing liver and mammary tumours. Commercial Direct Black 38 produced hepatocellular carcinomas within 13 weeks after administration in the diet to rats and small numbers of carcinomas in the urinary bladder, liver and colon after administration to rats in drinking-water [ref: 1].

In a single study, commercial Direct Blue 6 produced hepatocellular carcinomas in rats within 13 weeks after its oral administration.

Commercial Direct Brown 95 produced neoplastic nodules in the livers of 4/8 female rats and a hepatocellular carcinoma in one, after its oral administration in a single study terminated after 13 weeks. The finding of preneoplastic lesions after such a short exposure prior indicates a carcinogenic effect similar to that of Direct Black 38 and Direct Blue 6 [ref: 1].

**C. Other relevant data**

Benzidine-based dyes are structurally related to benzidine, exposure to which is causally associated with cancer in humans, and commercial material may contain small amounts of benzidine. Commercial Direct Black 38 may contain small quantities of 4-aminobiphenyl and 2,4-diaminobenzene (the hydrochloride of which is chrysoidine) [ref: 1].

Benzidine has been detected in the urine of workers exposed to benzidine-based azo dyes. No data were available on the genetic and related effects of Direct Black 38, Direct Blue 6 or Direct Brown 95, in humans [ref: 1].

In experimental animals, Direct Black 38, Direct Blue 6 and Direct Brown 95 undergo reduction of the azo bonds with the appearance in the urine of benzidine and monoacetylbenzidine. The reductive cleavage of the azo bond has been attributed to the activities of intestinal microflora and/or liver azoreductases [ref: 2].

Direct Black 38 was mutagenic to bacteria. Urine from rodents treated with Direct Black 38 was mutagenic to bacteria in the presence of an exogenous metabolic system, and human intestinal microflora metabolized Direct Black 38 to highly mutagenic metabolites [ref: 2].

DNA adducts (including covalent binding products of benzidine) have been described in the livers of rats treated with Direct Blue 6 *in vivo*. Direct Blue 6 is mutagenic to bacteria only in the presence of an exogenous metabolic system and the cofactor flavine mononucleotide [ref: 2].

Direct Brown 95 induced unscheduled DNA synthesis in rat hepatocytes in an in-vivo/in-vitro assay but not in hepatocytes *in vitro*. It was mutagenic to bacteria in the presence of an exogenous

metabolic system; this activity was enhanced by the cofactor flavine mononucleotide. The urine from rats treated with Direct Brown 95 was mutagenic to bacteria in the presence of an exogenous metabolic system [ref: 2].

**Overall evaluation**

Benzidine-based dyes are *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Direct Black 38: Vol. 29 (1982); Direct Blue 6: Vol. 29 (1982); Direct Brown 95: Vol. 29 (1982)

**References**

1. IARC Monographs, 29, 295-310, 311-320, 321-330, 1982

2. IARC Monographs, Suppl. 6, 275-281, 1987

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Last updated: 11 February 1998

# BENZOYL CHLORIDE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 126)

**CAS No.**: 98-88-4

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Six cases of respiratory cancer were reported among workers in two small factories where benzoyl chloride and its chlorinated precursors were produced [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Benzoyl chloride was tested in two sets of experiments by skin application to female mice. A few skin carcinomas were observed, but their incidence was not statistically significant [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of benzoyl chloride in humans. It did not induce mutation or DNA damage in bacteria [ref: 2].

**Overall evaluation**

Benzoyl chloride is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 71 (1999)

**Also see previous evaluation**: Vol. 29 (1982)

**References**

1. IARC Monographs, 29, 83-91, 1982

2. IARC Monographs, Suppl. 6, 103-104, 1987

**Synonyms**

- Benzene carbonyl chloride
- Benzenecarbonyl chloride
- Benzoic acid, chloride
- α-Chlorobenzaldehyde

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Last updated: 9 March 1998

# BETEL QUID WITH TOBACCO (Group 1)
# and BETEL QUID WITHOUT TOBACCO (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 128)

**A. Evidence for carcinogenicity to humans** (*sufficient* for betel quid with tobacco; *inadequate* for betel quid without tobacco)

Many descriptive studies and case reports have shown an association between the habit of chewing betel quid with tobacco and oral cancer. A significant increase in the risk of oral cancer has been observed in chewers of betel quid with tobacco in several case-control studies and in one large-scale cohort study. In chewers of betel quid with tobacco, a statistically significant increase in risk was also observed for cancers of the oropharynx, hypopharynx, larynx and oesophagus [ref: 1].

Several descriptive studies from Papua-New Guinea and a number of case-control studies have suggested an association between the habit of chewing betel quid without tobacco and oral cancer. In one of the case-control studies, in which smoking was not controlled for, a statistically significant increase in risk was also observed for cancers of the oropharynx, hypopharynx, larynx and oesophagus. In another case-control study of oral cancer, in which a clear effect of chewing betel with tobacco was found, no such effect was found for chewing betel without tobacco [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited* for betel quid with and without tobacco)

Aqueous extracts of betel quid containing tobacco were tested for carcinogenicity in mice by gastric intubation, skin painting and subcutaneous injection; some malignant tumours occurred at the site of skin or subcutaneous administration. In hamsters, forestomach carcinomas occurred after painting of the cheek-pouch mucosa with aqueous extracts or implantation of wax pellets containing powdered betel quid with tobacco in the cheek pouch; carcinomas occurred in the cheek pouch following implantation of wax pellets [ref: 1].

Aqueous extracts of betel quid without tobacco were tested in mice by gastric intubation and by subcutaneous administration; an increased incidence of local tumours was observed after subcutaneous injection. In hamsters, painting of the cheek-pouch mucosa or implantation of wax pellets into the cheek pouch resulted in the induction of forestomach carcinomas; carcinomas occurred in the cheek pouch following implantation of wax pellets [ref: 1].

Aqueous or dimethyl sulphoxide extracts of areca nut with tobacco were tested in mice by skin application; a low incidence of skin tumours was reported in a study lacking controls. In hamsters, applications of such extracts to cheek-pouch mucosa produced squamous-cell carcinomas of the cheek pouch and forestomach carcinomas [ref: 1].

Areca nut and aqueous extracts of areca nut were tested in mice by oral intubation, dietary administration, skin application and intraperitoneal and subcutaneous injection. Local tumours were produced following subcutaneous injection. In rats, areca nut was inadequately tested by oral administration; aqueous extracts tested by subcutaneous injection produced local mesenchymal tumours. In hamsters, administration of areca nut and application of aqueous or dimethyl sulphoxide extracts to the cheek-pouch mucosa resulted in squamous-cell carcinomas of the cheek pouch and carcinomas of the forestomach [ref: 1]. Oral administration of a diet containing 20% betel-nut powder enhanced the incidences of preneoplastic and neoplastic lesions of the tongue in rats pretreated with 4-nitroquinoline-1-oxide and of preneoplastic liver lesions in rats pretreated with 2-acetylaminofluorene [ref: 2].

Aqueous extracts of betel leaf were tested in mice by oral intubation and by intraperitoneal injection, in hamsters by application to the cheek-pouch mucosa [ref: 1] and in rats by oral administration [ref: 3]. Betel leaf was tested in rats by dietary administration and in hamsters by implantation in beeswax pellets into the cheek pouch. All of these studies were inadequate for evaluation [ref: 1].

## C. Other relevant data

Chewing of betel quid with or without tobacco increased the frequencies of micronucleated cells in the buccal mucosa of chewers; dose-dependence was observed in relation to the number of betel quids chewed per day. Chewing of betel quid with or without tobacco increased the frequency of sister chromatid exchanges in peripheral blood lymphocytes of chewers. Increased frequencies of sister chromatid exchanges were observed in peripheral blood lymphocytes of chewers of areca nut with slaked lime and tobacco, either alone or wrapped in betel leaf, particularly among chewers who had developed oral submucous fibrosis. Extracts of urine from chewers of betel quid with tobacco were mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system [ref: 4].

An aqueous extract of betel quid (containing tobacco) induced micronuclei in bone-marrow cells of mice treated *in vivo* and was mutagenic to Chinese hamster V79 cells. No such effect was observed with extracts of betel quids not containing tobacco. Aqueous extracts of betel quids (both with and without tobacco) were mutagenic to *S. typhimurium* [ref: 4].

## Overall evaluation

Betel quid with tobacco is *carcinogenic to humans (Group 1)*.

Betel quid without tobacco is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 37 (1985)

**Subsequent evaluation**: Vol. 85 (2004)

## References


1. IARC Monographs, 37, 141-200, 1985

2. Tanaka, T., Kuniyasu, T., Shima, H., Sugie, S., Mori, H., Takahashi, M. & Hirono, J. (1986) Carcinogenicity of betel quid. III. Enhancement of 4-nitroquinoline-1-oxide and *N*-2-fluorenylacetamide-induced carcinogenesis in rats by subsequent administration of betel nut. J. natl Cancer Inst., 77, 777-781

3. Rao, A.R., Sinha, A. & Selvan, R.S. (1985) Inhibitory action of *Piper betle* on the initiation of 7,12-dimethylbenz[*a*]anthracene-induced mammary carcinogenesis in rats. Cancer Lett., 26, 207-214

4. IARC Monographs, Suppl. 6, 113, 1987


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Last updated: 6 February 1998

# *N*,*N*-BIS(2-CHLOROETHYL)-2-NAPHTHYLAMINE (CHLORNAPHAZINE) (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 130)

**CAS No.:** 494-03-1

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Among 61 patients with polycythaemia vera treated with chlornaphazine in 1954-1962 and followed until 1974, eight developed invasive carcinoma of the bladder, five developed papillary carcinomas of the bladder and eight had abnormal urinary cytology. The invasive carcinomas were seen in four of five patients treated with a cumulative dose of 200 g or moe, in two of 15 patients given 100-199 g, in one of ten patients given 50-99 g and in one of 31 patients given less than 50 g. No noncausal explanation can be suggested [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

Chlornaphazine produced lung tumours in mice following its intraperitoneal injection, and local sarcomas in rats after its subcutaneous administration [ref: 2].

**C. Other relevant data**

No data were available on the genetic and related effects of chlornaphazine in humans.

Rats administered chlornaphazine excreted metabolites of 2-naphthylamine in the urine. Chlornaphazine induced chromosomal aberrations in Chinese hamster cells, mutation in mouse lymphoma cells and unscheduled DNA synthesis in rat hepatocytes *in vitro*. A single study of cell transformation in virus-infected Syrian hamster embryo cells was inconclusive. It induced sex-linked recessive lethal mutations and chromosomal aberrations in *Drosophila* and was mutagenic to bacteria [ref: 3].

**Overall evaluation**

*N*,*N*-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine) is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**

1. Thiede, T. & Christensen, B.C. (1975) Tumours of the bladder induced by chlornaphazine (Norw.). Ugesk. Laeger, 137, 661-666

2. IARC Monographs, 4, 119-124, 1974

3. IARC Monographs, Suppl. 6, 113-115, 1987

**Synonyms**

- CB 1048
- Chlornaftina
- Chlornaphazin
- Chlornaphthin
- Chloronaftina
- Chloronaphthine
- Dichloroethyl-β-naphthylamine
- Di(2-chloroethyl)-β-naphthylamine
- Erysan
- Naphthylamine mustard
- β-Naphthyl-bis(β-chloroethyl)amine
- β-Naphthyldi-(2-chloroethyl)amine
- R 48

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Last updated: 6 February 1998

# BIS(CHLOROMETHYL)ETHER AND CHLOROMETHYL METHYL ETHER (TECHNICAL-GRADE) (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.59)

**CAS No.:** 542-88-1
**Chem. Abstr. Name:** Bis(chloromethyl)ether

**CAS No.:** 107-30-2
**Chem. Abstr. Name:** Chloromethyl methyl ether (technical-grade)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Numerous epidemiological studies [ref: 1-9] and case reports [ref: 10-13] from around the world have demonstrated that workers exposed to chloromethyl methyl ether and/or bis(chloromethyl)ether have an increased risk for lung cancer. Among heavily exposed workers, the relative risks are ten fold or more. Risks increase with duration and cumulative exposure. Histological evaluation indicates that exposure results primarily in lung cancer of the small-cell type [ref: 8]. Maximal relative risks appear to occur 15-20 years after first exposure [ref: 6], and latency is shortened among workers with heavier exposure [ref: 5,11].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Bis(chloromethyl)ether produced tumours at the site of its administration to mice after exposure by inhalation [ref: 1,14], skin application [ref: 1] or subcutaneous injection [ref: 1,15] and was an initiator of mouse skin tumours [ref: 15]; it also increased the incidence of lung tumours after its subcutaneous administration [ref: 1]. In rats, it produced tumours of the respiratory tract (lung tumours and nasal-cavity carcinoma) after exposure by inhalation [ref: 14,16-18].

Chloromethyl methyl ether produced local sarcomas in mice after its subcutaneous administration and was an initiator of mouse skin tumours [ref: 1]; in rats and hamsters, the technical grade produced a low incidence of tumours of the respiratory tract after exposure by inhalation [ref: 19].

**C. Other relevant data**

A slight increase in the incidence of chromosomal aberrations was observed in peripheral lymphocytes of workers exposed to bis(chloromethyl)ether or chloromethyl methyl ether in the preparation of ion-exchange resins [ref: 20].

Bis(chloromethyl)ether did not cause chromosomal aberrations in bone-marrow cells of rats treated *in vivo*. It induced unscheduled DNA synthesis in human fibroblasts *in vitro* and was mutagenic to bacteria [ref: 20].

Chloromethyl methyl ether enhanced virus-induced transformation of Syrian hamster embryo cells and was mutagenic to bacteria [ref: 20].

**Overall evaluation**

Bis(chloromethyl)ether and chloromethyl methyl ether (technical grade) are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**


1. IARC Monographs, 4, 231-238, 239-245, 1974

2. Albert, R.E., Pasternack, B.S., Shore, R.E., Lippmann, M., Nelson, N. & Ferris, B. (1975) Mortality patterns among workers exposed to chloromethyl ethers - a prelimary report. Environ. Health Perspect., 11, 209-214

3. DeFonso, L.R. & Kelton, S.C., Jr (1976) Lung cancer following exposure to chloromethyl methyl ether. An epidemiological study. Arch. environ. Health, 31, 125-130

4. Pasternack, B.S., Shore, R.E. & Albert, R.E. (1977) Occupational exposure to chloromethyl ethers. A retrospective cohort mortality study (1948-1972). J. occup. Med., 19, 741-746

5. Pasternack, B.S. & Shore, R.E. (1981) Lung cancer following exposure to chloromethyl ethers. In: Chwat, M. & Dror, K., eds, Proceedings of the International Conference on Critical Current Issues in Environmental Health Hazards, Tel-Aviv, Israel, pp. 76-85

6. Weiss, W. (1982) Epidemic curve of respiratory cancer due to chloromethyl ethers. J. natl Cancer Inst., 69, 1265-1270

7. McCallum, R.I., Woolley, V. & Petrie, A. (1983) Lung cancer associated with chloromethyl methyl ether manufacture: an investigation at two factories in the United Kingdom. Br. J. ind. Med., 40, 384-389

8. Weiss, W. & Boucot, K.R. (1975) The respiratory effects of chloromethyl methyl ether. J. Am. med. Assoc., 234, 1139-1142

9. Weiss, W., Moser, R. & Auerbach, O. (1979) Lung cancer in chloromethyl ether workers. Am. Rev. respir. Dis., 120, 1031-1037

10. Sakabe, H. (1973) Lung cancer due to exposure to bis(chloromethyl)ether. Ind. Health, 11, 145-148

11. Weiss, W. & Figueroa, W.G. (1976) The characteristics of lung cancer due to chloromethyl ethers. J. occup. Med., 18, 623-627

12. Reznik, G., Wagner, H.H. & Atay, Z. (1977) Long cancer following exposure to bis(chloromethyl)ether: a case report. J. environ. Pathol. Toxicol., 1, 105-111

13. Bettendorf, U. (1977) Occupational lung carcinoma after inhalation of alkylating agents. Dichlorodimethyl ether, monochlorodimethylether and dimethylsulphate (Ger.). Dtsch. med. Wochenschr., 102, 396-398

14. Leong, B.K.J., Kociba, R.J. & Jersey, G.C. (1981) A lifetime study of rats and mice exposed to vapors of bis(chloromethyl)ether. Toxicol. appl. Pharmacol., 58, 269-281

15. Zajdela, F., Croisy, A., Barbin, A., Malaveille, C., Tomatis, L. & Bartsch, H. (1980) Carcinogenicity of chloroethylene oxide, an ultimate reactive metabolite of vinyl chloride, and bis(chloromethyl)ether after subcutaneous administration and in intiation-promotion experiments in mice. Cancer Res., 40, 352-356

16. Dulak, N.C. & Snyder, C.A. (1980) The relationship between the chemical reactivity and the inhalation carcinogenic potency of direct-acting chemical agents (Abstract No. 426). Proc. Am. Assoc. Cancer Res., 21, 106

17. Kuschner, M., Laskin, S., Drew, R.T., Cappiello, V. & Nelson, N. (1975) Inhalation carcinogenicity of alpha halo ethers. III. Lifetime and limited period inhalation studies with bis(chloromethyl)ether at 0.1 ppm. Arch. environ. Health, 30, 73-77

18. Leong, B.K.J., Kociba, R.J., Jersey, G.C. & Gehring, P.J. (1975) Effects of repeated inhalation of parts per billion of bis(chloromethyl)ether in rats (Abstract No. 131). Toxicol. appl. Pharmacol., 33, 175

19. Laskin, S., Drew, R.T., Cappiello, V., Kuschner, M. & Nelson, N. (1975) Inhalation carcinogenicity of alpha halo ethers. II. Chronic inhalation studies with chloromethyl methyl ether. Arch. environ. Health, 30, 70-72

20. IARC Monographs, Suppl. 6, 119-120, 159-160, 1987

**Synonyms for Bis(chloromethyl)ether**

- BCME
- Chloro(chloromethoxy)methane
- Dichloromethyl ether
- Dimethyl-1,1'-dichloroether
- Symmetrical-dichloro-dimethyl ether
- Symmetrical-dichloromethyl ether

**Synonyms for Chloromethyl methyl ether**

- CMME
- Dimethylchloroether
- Methyl chloromethyl ether

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Last updated: 6 February 1998

# BITUMENS
# (Group 3) and
# EXTRACTS OF STEAM-REFINED AND AIR-REFINED BITUMENS
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 133)

**Bitumen**
**CAS No.**: 8052-42-4
**Chem. Abstr. Name**: Asphalt

**Bitumens, oxidized**
**CAS No.**: 64742-93-4
**Chem. Abstr. Name**: Asphalt, oxidized

**A. Evidence for carcinogenicity to humans** (*inadequate* for bitumens)

No epidemiological study of workers exposed only to bitumens is available. A cohort study of US roofers indicates an increased risk for cancer of the lung and suggests increased risks for cancers of the oral cavity, larynx, oesophagus, stomach, skin and bladder and for leukaemia. Some evidence of excess risks for lung, oral cavity and laryngeal cancers is provided by other epidemiological studies of roofers. As roofers may be exposed not only to bitumens but also to coal-tar pitches and other materials, the excess cancer risk cannot be attributed specifically to bitumens [ref: 1]. Several case reports of skin cancer among workers exposed to bitumens are available; however, exposure to coal-tars or products derived from them cannot be ruled out [ref: 1-3].

**B. Evidence for carcinogenicity to animals** (*limited* for undiluted steam-refined and cracking-residue bitumens; *inadequate* for undiluted air-refined bitumens; *sufficient* for extracts of steam-refined and air-refined bitumens)

In several studies, application to the skin of mice of various extracts of steam- and air-refined bitumens and mixtures of the two resulted in tumours at the sites of application [ref: 1,4]. Undiluted steam-refined bitumens and cracking-residue bitumens produced skin tumours when applied to the skin of mice. No skin tumour was found in mice after application of an undiluted air-refined bitumen. In limited studies, subcutaneous injection into mice and intramuscular injection into mice and rats of steam- and air-refined bitumens produced sarcomas at the injection sites [ref: 1].

**C. Other relevant data**

Antigenicity against benzo[*a*]pyrene diol epoxide-DNA adducts has been demonstrated in peripheral blood lymphocytes of roofers [ref: 5].

Both an extract of road-surfacing bitumen and its emissions were mutagenic to *Salmonella typhimurium*, whereas, in another study, 'asphalt tar' extracted from an asphalt concrete used for road surfacing was not. Bitumen-based paints for pipe coating were not mutagenic to *S. typhimurium* [ref: 5].

**Overall evaluation**

Bitumens are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Extracts of steam-refined and air-refined bitumens are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 35 (1985)

**References**

1. IARC Monographs, 35, 39-81, 1985

2. Jørgensen, N.K. (1984) Exposure to asphalt as the cause of development of skin cancer (Dan.). Ugeskr. Laeger, 146, 2832-2833

3. Tsyrkunov, L.P. (1985) Multiple basalioma in a worker laying asphalt (Russ.). Vestn. Dermatol. Venerol., 2, 48-51

4. Niemeier, R.W., Thayer, P.S., Menzies, K.T., vonThuna, P., Moss, C.E. & Burg, J. (1984) A comparison of the skin carcinogenicity of condensed roofing asphalt and coal tar pitch fumes. In: Cooke, M. & Dennis, A.J., eds, Proceedings of the 10th International Symposium on Polynuclear Aromatic Hydrocarbons, Chemistry Characterization and Carcinogenesis, Columbus, OH, Battelle, pp. 609-647

5. IARC Monographs, Suppl. 6, 121, 1987

**Synonyms for Bitumen**

- Asphaltic bitumen
- Asphaltum
- Petroleum asphalt

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Last updated 12/16/1997

# BOOT AND SHOE MANUFACTURE AND REPAIR
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 232)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Nasal adenocarcinoma has been caused by employment in boot and shoe manufacture and repair. Relative risks well in excess of ten fold have been reported from studies in the boot and shoe manufacturing industry in England and in Italy. There is also evidence that an increased risk exists for other types of nasal cancer [ref: 1-3]. A far higher risk of nasal cancer was found for people who worked in the dustiest operations, and for those classified into the category of 'heavy' exposure to leather dust, strongly suggesting a role for exposure to leather dust [ref: 2,3]. Thus, in comparison with the 'nonexposed' category, the sex-adjusted standardized odds ratio for the 'uncertain or light exposure' category was 7.5, and for the 'heavy exposure' category, 121.0. A similar, highly significant pattern was noted when only adenocarcinomas were considered. Exposure to solvents or to tobacco smoking could not account for the noted increased risk [ref: 3]. A mortality study of over 5000 men known to have been employed in the boot and shoe manufacturing industry in three towns in the UK in 1939 showed a large, significant excess of deaths from nasal cancer (10 observed, 1.9 expected). An observed:expected ratio of 14 was found among workers in the finishing room [ref: 4]. The elevated nasal cancer risk was almost totally confined to employees in the preparation and finishing rooms, where most of the dusty operations occurred. It was estimated that the risk to those men was 4.5 relative to that in other operations, and 9.8 relative to that of men resident in the area who had never been employed in the footwear industry [ref: 2].

Case reports have also suggested an association between exposure to leather, including during shoe manufacture, and mucinous adenocarcinoma of the nose and ethmoidal cancer in Switzerland and France, respectively [ref: 5,6].

One mortality study conducted in London, UK, showed no association between nasal cancer deaths occurring between 1968 and 1978 and occupation in the boot and shoe industry, as recorded on death certificates [ref: 7]. A proportionate mortality analysis of 3754 deaths among US shoeworkers revealed no death from nasal cancer, whereas 2.2 were expected on the basis of data for the general population [ref: 8]. Similar results were obtained from a study of 2798 deaths between 1954 and 1974 in a shoe and leather industry area in Massachusetts, USA; detailed occupational information was available, however, for only 289 of the deceased [ref: 9].

Early death certificate surveys showed an increased risk of bladder cancer among shoemakers and repairers. Later studies provided evidence of an increased risk associated with employment in the leather industry. Although boot and shoemakers were included in these studies, it was not possible to determine whether the risk was related to them in particular [ref: 1]. A nonsignificant increased risk for bladder cancer was reported in association with work in the boot and shoe industry in a case-control study based on deaths of male residents in certain London boroughs from 1968-1978. When data for these workers were combined with those for leather workers, the estimated risk became significant [ref: 7]. A significant association of leather work (leather or tanning industry, manufacture of leather goods, or shoemaking) with cancer of the lower urinary tract was found in a collaborative case-control study in the USA and the UK, but not in Japan [ref: 10]. A statistically significant increase was found among female shoe workers (7 deaths observed and 2.8 expected) in another, independent study in the USA. Male shoeworkers and leather workers showed no excess of bladder cancer in this study [ref: 9]. In Sweden, an increase in the incidence of bladder cancer (22 cases observed, 14.5 expected) was reported among shoe factory workers [ref: 11]. An elevated risk that was not statistically significant was also found among boot and shoe repairers in a British county. Smoking did not appear to account for the increase [ref: 12]. In another study in the UK, in a cohort of 5108 boot and shoe workers, 32 deaths from bladder cancer were observed, with 39.2 expected [ref: 13].

A possible increased risk for kidney cancer among shoe workers was suggested by a study in Sweden [ref: 11]. However, a large cohort study among boot and shoe workers in the UK did not

support this hypothesis [ref: 13]. Three cases of mesothelioma were reported among 3806 deaths in shoe workers [ref: 14]; it has further been reported that a female shoemaker (whose husband was also a shoemaker) died of mesothelioma [ref: 15].

The occurrence of leukaemia among shoemakers exposed to benzene has been well documented [ref: 1,16], and this association has been supported further by a recent mortality study in one town in the UK [ref: 4].

Surveys conducted in the The Netherlands, the UK and the USA have suggested positive associations between boot and shoe manufacture/repair and cancers of the lung, oral cavity and pharynx and stomach [ref: 1]. These suggestions were later confirmed by a mortality survey in the USA, which also showed a significant increase in the proportion of deaths due to cancers of the rectum and of the liver and gall-bladder, in people of each sex [ref: 8]. Excess mortality from rectal cancer was also found among boot and shoemakers in two towns in the UK; the excess was significant for workers in the lasting and making room, who were probably exposed to solvents, glues and leather dust [ref: 4]. Exposure to solvents, dyes or metallic compounds in the footwear industry, among nonfactory shoemakers and repairers and among operatives making leather and leather products, was deemed to be associated with the increased risk of bowel cancer noted in a US study [ref: 17]. An increased proportion of cancer of the digestive tract among male shoeworkers was found in another US study; however, it was suggested that factors other than their occupation could have been responsible for the excess noted [ref: 9]. In a study of gall-bladder cancer occurring in Sweden between 1961 and 1969, in which information on occupation was drawn from 1960 census data, the incidences of cancers of the gall-bladder and the biliary tract were found to be significantly elevated among men employed in shoemaking and repair [ref: 18]. In view of the exploratory nature and design of these studies, the findings were considered to be inadequate for a definite evaluation.

No indication of a link between Hodgkin's disease and work in 'textile, shoes, leather' industries emerged from investigations in Italy [ref: 19].

**Overall evaluation**

Boot and shoe manufacture and repair *entails exposures that are carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 25 (1981)

**References**

1. IARC Monographs, 25, 249-277, 1981

2. Acheson, E.D., Pippard, E.C. & Winter, P.D. (1982) Nasal cancer in the Northamptonshire boot and shoe industry: is it declining? Br. J. Cancer, 46, 940-946

3. Merler, E., Baldasseroni, A., Laria, R., Faravelli, P., Agostini, R., Pisa, R. & Berrino, F. (1986) On the causal association between exposure to leather dust and nasal cancer: further evidence from a case-control study. Br. J. ind. Med., 43, 91-95

4. Pippard, E.C. & Acheson, E.D. (1985) The mortality of boot and shoe makers, with special reference to cancer. Scand. J. Work Environ. Health, 11, 249-255

5. Penneau, D., Pineau, B., Dubin, J., Géraut, C., Penneau, M. & Proteau, J. (1984) Pilot retrospective study of relative risk of ethmoidal cancer in leather work and shoe manufacture (Fr.). Arch. Mal. prof., 45, 633-638

6. Rüttner, J.R. & Makek, M. (1985) Mucinous adenocarcinoma of the nose and paranasal sinuses, an occupational disease? (Ger.) Schweiz. med. Wochenschr., 115, 1838-1842

7. Baxter, P.J. & McDowall, M.E. (1986) Occupation and cancer in London: an investigation into nasal and bladder cancer using the Cancer Atlas. Br. J. ind. Med., 43, 44-49

8. Decouflé, P. & Walrath, J. (1983) Proportionate mortality among US shoeworkers, 1966-1977. Am. J. ind. Med., 4, 523-532

9. Garabrant, D.H. & Wegman, D.H. (1984) Cancer mortality among shoe and leather workers in Massachusetts. Am. J. ind. Med., 5, 303-314

10. Morrison, A.S., Ahlbom, A., Verhoek, W.G., Aoki, K., Leck, I., Ohno, Y. & Obata, K. (1985) Occupation and bladder cancer in Boston, USA, Manchester, UK, and Nagoya, Japan. J. Epidemiol. Commun. Health, 39, 294-300

11. Malker, H.R., Malker, B.K., McLaughlin, J.K. & Blot, W.J. (1984) Kidney cancer among leather workers. Lancet, i, 56

12. Cartwright, R.A. & Boyko, R.W. (1984) Kidney cancer among leather workers. Lancet, i, 850-851

13. Acheson, E.D. & Pippard, E.C. (1984) Kidney cancer among leather workers. Lancet, i, 563

14. Decouflé, P. (1980) Mesothelioma among shoeworkers. Lancet, i, 259

15. Vianna, N.J. & Polan, A.K. (1978) Non-occupational exposure to asbestos and malignant mesothelioma in females. Lancet, i, 1061-1063

16. IARC Monographs, 29, 93-148, 391-397, 1982

17. Berg, J.W. & Howell, M.A. (1975) Occupation and bowel cancer. J. Toxicol. environ. Health, 1, 75-89

18. Malker, H.R.S., McLaughlin, J.K., Malker, B.K., Stone, B.J., Weiner, J.A., Ericsson, J.L.E. & Blot, W.J. (1986) Biliary tract cancer and occupation in Sweden. Br. J. ind. Med., 43, 257-262

19. Fonte, R., Grigis, L., Grigis, P. & Franco, G. (1982) Chemicals and Hodgkin's disease. Lancet, ii, 5

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# BLEOMYCINS
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 134)

**CAS No.**: 11056-06-7
**Chem. Abstr. Name**: Bleomycin

**Bleomycin hydrochloride**
**CAS No.**: 67763-87-5

**Bleomycin sulfate**
**CAS No.**: 9041-93-4
**Chem. Abstr. Name**: Bleomycin, sulfate (salt)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of bleomycins alone was available to the Working Group. Occasional case reports of exposure to bleomycins, especially in the presence of concurrent therapy with other putative carcinogens such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1].

In a large systematic follow-up of patients with Hodgkin's disease treated with an intensive chemotherapeutic combination including bleomycins (plus adriamycin, vinblastine and dacarbazine) but no alkylating agent, preliminary evidence suggested no excess of acute nonlymphocytic leukaemia in the first decade after therapy [ref: 2].

**B. Evidence for carcinogenicity to animals** (*limited*)

Bleomycin has been tested in mice by subcutaneous and intramuscular injection and in rats transplacentally. These studies could not be evaluated because of incomplete reporting [ref: 1]. A study in rats by repeated subcutaneous injections showed that bleomycin produced renal tumours (adenomas, adenocarcinomas, sarcomas) and fibrosarcomas at the site of application at significantly dose-related incidences [ref: 3].

**C. Other relevant data**

Bleomycins induced chromosomal aberrations in lymphocytes of treated patients in one study [ref: 4].

In mice treated *in vivo*, bleomycins induced chromosomal aberrations (including heritable translocations) and sister chromatid exchanges but gave conflicting results in tests for micronuclei. It induced chromosomal aberrations and DNA strand breaks in human cells *in vitro* but gave conflicting results in tests for unscheduled DNA synthesis and sister chromatid exchange. It induced transformation of mouse C3H 10T1/2 cells, and induced aneuploidy, chromosomal aberrations, mutation and DNA damage in rodent cells *in vitro*; a weakly positive response was observed for the induction of sister chromatid exchanges. In *Drosophila*, bleomycin induced aneuploidy, chromosomal aberrations, sex-linked recessive lethal mutations, somatic mutations, genetic crossing-over and recombination, but not heritable translocations. It induced chromosomal aberrations but not sister chromatid exchanges in plants. Bleomycin was mutagenic to fungi and induced gene conversion, recombination and genetic crossing-over. It was mutagenic and caused DNA damage in bacteria [ref: 4].

**Overall evaluation**

Bleomycins are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**


1. IARC Monographs, 26, 97-113, 1981

2. Santoro, A., Viviani, S., Villarreal, C.J.R., Bonfante, V., Delfino, A., Valagussa, P. & Bonadonna, G. (1986) Salvage chemotherapy in Hodgkin's disease irradiation failures: superiority of doxorubicin-containing regimens over MOPP. Cancer Treat. Rep., 70, 343-348

3. Habs, M. & Schmähl, D. (1984) Carcinogenicity of bleomycin sulfate and peplomycin sulfate after repeated subcutaneous application to rats. Oncology, 41, 114-119

4. IARC Monographs, Suppl. 6, 121-125, 1987


**Synonyms for Bleomycin**

- Bleo
- Bleomycins
- NSC-125066

**Synonyms for Bleomycin sulfate**

- BleMomycine
- Blenoxane
- Bleocin
- Blexane

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Last updated: 27 February 1998

# BRACKEN FERN
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 135)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

In a case-control study of 98 oesophageal cancer patients and 476 controls in Japan, a relative risk of 2.7 was found for daily consumption of bracken fern. Interpretation of this study is hampered by the absence of detail about the survey and the method of selecting controls, and by failure to take account of consumption of alcohol, a risk factor for cancer of the oesophagus [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Bracken fern was tested for carcinogenicity in mice, rats, guinea-pigs, cows and toads by oral administration, producing leukaemia, intestinal tumours, lung adenomas and gastric tumours in mice, small-intestinal tumours, urinary bladder carcinomas and mammary adenocarcinomas in rats, urinary bladder tumours in guinea-pigs, alimentary-tract and bladder cancers in cows, and intestinal carcinomas and hepatomas in toads. Processed bracken fern produced intestinal tumours in rats; boiling-water extracts of bracken fern produced intestinal and bladder tumours in rats; and hot-ethanol extracts produced intestinal tumours in quails [ref: 1].

Shikimic acid isolated from bracken fern induced neoplasms of the glandular stomach in mice after a single intraperitoneal injection. Ptaquiloside derived from bracken fern induced mammary and small-intestinal carcinomas in female rats after administration by gavage [ref: 1].

Most of these studies involved small numbers of animals and were incompletely reported; however, they indicate that bracken fern is associated with cancers of the intestine and urinary bladder in many different species.

**C. Other relevant data**

No data were available on the genetic and related effects of bracken fern in humans.

An acetone extract of bracken fern was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. Light-petroleum and methanol extracts of bracken fern activated by alkaline treatment were also mutagenic to *S. typhimurium* [ref: 2].

**Overall evaluation**

Bracken fern is *possibly carcinogenic to humans (Group 2B).*

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 40 (1986)

**References**

1. IARC Monographs, 40, 47-65, 1986

2. IARC Monographs, Suppl. 6, 126, 1987

**Synonym**

- Pteridium aquilinum

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Last updated: 27 February 1998

# 1,4-BUTANEDIOL DIMETHANESULPHONATE (MYLERAN) (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.137)

**CAS No.:** 55-98-1

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Leukaemia patients who had been treated with Myleran developed many different cytological abnormalities, and some developed carcinomas [ref: 1-8]. A follow-up study of patients with bronchial carcinoma who were randomized to chemotherapy after pulmonary resection showed that of 69 who had been given Myleran and had survived five years, four developed acute nonlymphocytic leukaemia (three myelomonocytic leukaemias and one erythroleukaemia) and 15 others developed pancytopenia in the succeeding four years; among 148 other survivors at five years who had not been given Myleran, one case of pancytopenia appeared. Risk was not dose-related, although the cases were confined to those who had received no radiation and no other cytotoxic agent [ref: 9].

**B. Evidence for carcinogenicity to animals** (*limited*)

Myleran was tested for carcinogenicity by intraperitoneal injection and by intravenous injection in mice and rats and by oral administration to rats. Intraperitoneal administration of Myleran to mice did not increase the incidence of tumours in two studies [ref: 1,10], but leukaemia [ref: 11] and hypoplastic marrow [ref: 11,12] were induced in further studies and T-cell lymphoma in another, in which the effect was markedly enhanced by combined administration ofchloramphenico [ref: 13]. Leukaemia/lymphosarcoma was also reported in one study [ref: 12], but the experiment could not be evaluated due to incomplete reporting. No mammary rumour was seen in rats after intraperitoneal injection, but near-lethal doses were used and the animals were followed for only five months [ref: 14]. Intravenous administration of Myleran to mice significantly increased the incidences of thymic and ovarian tumours [ref: 1]. Intravenous administration of 7% of the $LD_{50}$ dose to rats for one year was reported to induce a variety of tumours in male rats, but the experiments could not be evaluated due to incomplete reporting [ref: 15]. Oral administration to rats of Myleran did not increase the incidence of tumours over that seen in untreated animals [ref: 1].

**C. Other relevant data**

Myleran is a bifunctional alkylating agent. Patients treated with Myleran for chronic myeloid leukaemia were found to have increased frequencies of sister chromatid exchanges and chromosomal aberrations (in a single study) in their peripheral blood lymphocytes [ref: 16].

Treatment of rodents *in vivo* with Myleran induced dominant lethal mutations and increased the frequency of chromosomal aberrations and micronuclei in bone-marrow cells; in single studies, it induced DNA damage but not mutation. Evidence for covalent binding to DNA, RNA and protein was obtained in mice treated *in vivo*. Myleran induced chromosomal aberrations and sister chromatid exchanges in human and rodent cells *in vitro*, and mutation in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations in *Drosophila* and was mutagenic to bacteria [ref: 16].

**Overall evaluation**

1,4-Butanediol dimethane sulphonate (Myleran) *is carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

## References


1. IARC Monographs, 4, 247-252, 1974

2. Waller, U. (1960) Giant nuclei after Myleran therapy and spleen irradiation for chronic myeloid leukaemia (Ger.). Pathol. Microbiol., 23, 283-290

3. Güreli, N., Denham, S.W. & Root, S.W. (1963) Cytologic dysplasia related to busulfan (Myleran) therapy. Report of a case. Obstet. Gynecol., 21, 466-470

4. Japp, H. (1974) Toxic effect of busulfan (Myleran) with irradiation for chronic myeloid leukaemia (Ger.). Schweiz. med. Wochenschr., 104, 1115-1119

5. Diamond, I., Anderson, M.M. & McCreadie, S.R. (1960) Transplacental transmission of busulfan (Myleran$^{R}$) in a mother with leukaemia. Production of fetal malformation and cytomegaly. Pediatrics, 25, 85-90

6. Feingold, M.L. & Koss, L.G. (1969) Effects of long-term administration of busulfan. Report of a patient with generalized nuclear abnormalities, carcinoma of vulva, and pulmonary fibrosis. Arch. intern. Med., 124, 66-71

7. Pezzimenti, J.F., Kim, H.C. & Lindenbaum, J. (1976) Erythroleukemia-like syndrome due to busulfan toxicity in polycythemia vera. Cancer, 38, 2242-2246

8. Dittmar, K. (1979) Acute myeloblastic leukemia with polycythemia vera treated with busulfan and phlebotomy. N.Y. State J. Med., 79, 758-760

9. Stott, H., Fox, W., Girling, D.J., Stephens, R.J. & Galton, D.A.G. (1977) Acute leukaemia after busulfan. Br. med. J., ii, 1513-1517

10. Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K. & Gori, G.B. (1973) Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Res., 33, 3069-3085

11. Chu, J., Cao, S., Ying, H. & Li, D. (1981) Experimental study of busulfan-induced leukemia in strain 615 mice (Chin.). Zhonghua Xueyexue Zazhi, 2, 10-13

12. Morley, A. & Blake, J. (1974) An animal model of chronic aplastic marrow failure. I. Late marrow failure after busulfan. Blood, 44, 49-56

13. Robin, E., Berman, M., Bhoopalam, N., Cohen, H. & Fried, W. (1981) Induction of lymphomas in mice by busulfan and chloramphenicol. Cancer Res., 41, 3478-3482

14. Philips, F.S. & Sternberg, S.S. (1975) Tests for tumor induction by antitumor agents. Recent Results Cancer Res., 52, 29-35

15. Schmähl, D. (1975) Experimental investigations with anti-cancer drugs for carcinogenicity with special reference to immunodepression. Recent Results Cancer Res., 52, 18-28

16. IARC Monographs, Suppl. 6, 129-131, 1987


## Synonyms

- 1,4-Bis(methanesulphonoxy)butane
- 1,4-Bis(methanesulphonyloxy) butane
- Busulfan
- Busulphan
- C.B.2041
- 1,4-Dimethanesulphonoxybutane
- 1,4-Dimethanesulphonoxylbutane
- 1,4-Di(methanesulphonyloxy)butane
- 1,4-Dimethylsulphonoxybutane
- 1,4-Dimethylsulphonyloxybutane
- Mablin
- Methanesulphonic acid, tetramethylene ester
- Mielevcin
- Misulban
- Mitosan
- Myeloleukon
- Myelosan
- Myleran
- Sulphabutin
- Tetramethylene bis(methanesulphonate)
- Tetramethylene dimethanesulphonate

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Last updated: 6 February 1998

# CARPENTRY AND JOINERY
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 378)

**A. Evidence for carcinogenicity to humans** (*limited*)

The epidemiological data available suggest that there may be a carcinogenic risk connected with employment as a carpenter or joiner, although some of the studies produced negative results [ref: 1].

The connection between nasal cancer other than adenocarcinoma and exposure to wood dust among carpenters and joiners, found in some studies, if true, cannot be ascribed to any specific exposure. Carpenters and joiners usually work with impregnated wood, use a variety of types of wood and are exposed to many chemicals used in carpentry [ref: 1].

Several studies raise the possibility of an increased risk of Hodgkin's disease. A number of studies suggest an association between work as a joiner and nasal adenocarcinoma, but it is possible that the workers involved may have worked in the furniture industry [ref: 1].

There is also some evidence of an association between nasal carcinomas other than adenocarcinoma and work as a carpenter. In a case-control study based on an analysis of occupational data in the hospital records of 121 men seen for nasal cancer in British Columbia, Canada, between 1939 and 1977, a relative risk of 2.5 (adjusted for smoking and ethnic origin) was associated with exposure to wood. There was an increased risk for most histological types of epithelial tumour, except for transitional tumours. Of the 28 wood workers with nasal cancer, 16 had worked in the forestry industry, seven had been carpenters, four had been construction workers and one had been a cabinet-maker [ref: 2].

A case-control study on nasal and sinonasal cancer in Denmark, Finland and Sweden found a connection with exposure to spruce, pine and birch dust and the cancers studied, especially epidermoid and anaplastic carcinomas. There were 13 cases with exposure only these types of wood *versus* four controls (relative risk, 3.2; 95% confidence interval, 1.1-9.4). Of the cases, five were in construction carpenters and one in a cabinet-maker with no exposure to hardwood; there were two construction carpenters among the controls [ref: 3].

In a Norwegian study of 70 cases of nasal carcinoma, three cases of squamous-cell carcinoma had had exposure to pine and spruce dust in joinery and carpentry *versus* 1.5 expected on the basis of the occupational distribution in Norway according to the 1946 census [ref: 4]. In France, carpenters were not found to have an increased risk of nasal cancer, but no quantitative data were given [ref: 5]. A case-control study of nasal cancer from North Carolina and Virginia, USA, showed a nonsignificant relative risk of 1.6 for carpentry [ref: 6].

In a national study of nasal cancer in England and Wales in 1963-1967, the occupations of 925 men were studied, using postal questionnaires and data from hospital and death records. Among wood workers, the standard incidence ratios (SIRs) for cabinet- and chairmakers, machinists and 'other' wood workers were 966, 616 and 293, respectively. For carpenters and joiners, the SIR was 149 [ref: 7]. Another case-control study [ref: 8] showed no significantly increased risk for 'woodworkers and carpenters' residing in certain areas of London, selected for the study because of high incidences of nasal and bladder cancer.

A Swedish register-linkage study gave a two-fold excess of adenocarcinoma, based on five cases, among carpenters and joiners but no overall excess of nasal cancer in this group [ref: 9].

A cohort study comparing the experience of 10 322 men employed in wood-working industries with that of 406 798 non-wood workers showed no excess for all cancers combined. In the subcohort of

carpenters and joiners, 36 cases of stomach cancer were found, yielding a standardized mortality ratio (SMR) of 170 ($p < 0.01$). There were 101 deaths from lung cancer, resulting in a SMR of 120 ($p < 0.05$). Nonsignificantly elevated SMRs were found for cancers of the liver, biliary ducts and gall-bladder (11 cases; SMR, 121), nonmelanocytic skin cancer (4 cases; SMR, 333) and melanoma (5 cases; SMR, 161). There were two cases of nasal cancer (SMR, 333; nonsignificant) [ref: 10].

A proportionate mortality study showed an elevated risk for death from all cancers (proportionate mortality ratio [PMR], 112; $p < 0.01$), stomach cancer (PMR, 128; $p < 0.01$) and non-Hodgkin's lymphoma (PMR, 139; $p < 0.05$) among woodworkers (including carpenters, cabinet-makers and furniture workers, lumber graders and scalers, sawyers in sawmills andwoodworkers not classified elsewhere). In this mixed category, there was no death from sinonasal cancer [ref: 11].

A Dutch case-control study [ref: 12] of 116 male patients with primary sinonasal malignancies of epithelial origin showed an increased risk of adenocarcinoma for those employed in joinery and carpentry work in factories (odds ratio, 16.3; 90% confidence interval, 2.8-85.3). This work included production of doors and window frames; hence exposure to oak dust was likely.

**Overall evaluation**

Carpentry and joinery *entail exposures that are possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 25 (1981)

**References**

1. IARC Monographs, 25, 139-156, 1981

2. Elwood, J.M. (1981) Wood exposure and smoking: association with cancer of the nasal cavity and paranasal sinuses in British Columbia. Can. med. Assoc. J., 124, 1573-1577

3. Hernberg, S., Westerholm, P., Schultz-Larsen, K., Degerth, R., Kuosma, E., Englund, A., Engzell, U., Sand Hansen, H. & Mutanen, P. (1983) Nasal and sinonasal cancer. Connection with occupational exposures in Denmark, Finland and Sweden. Scand. J. Work Environ. Health, 9, 315-326

4. Voss, R., Stenersen, T., Oppedal, B.R. & Boysen, M. (1985) Sinonasal cancer and exposure to softwood. Acta otolaryngol., 99, 172-178

5. Duclos, J.-C., Dubreuil, C., Contassot, J.C., Guinchard, R. & Arnould, G. (1979) Nasal ethmoid adenocarcinomas in woodworkers. Clinical and forensic aspects (Fr.). Arch. Mal. prof., 40, 909-917

6. Brinton, L.A., Blot, W.J., Becker, J.A., Winn, D.M., Browder, J.P., Farmer, J.C., Jr & Fraumeni, J.F., Jr (1984) A case-control study of cancers of the nasal cavity and paranasal sinuses. Am. J. Epidemiol., 119, 896-906

7. Acheson, E.D., Cowdell, R.H. & Rang, E.H. (1981) Nasal cancer in England and Wales: an occupational survey. Br. J. ind. Med., 38, 218-224

8. Baxter, P.J. & McDowall, M.E. (1986) Occupation and cancer in London: an investigation into nasal and bladder cancer using the Cancer Atlas. Br. J. ind. Med., 43, 44-49

9. Malker, H.S.R., McLaughlin, J.K., Blot, W.J., Weiner, J.A., Malker, B.K., Ericsson J.L.E. & Stone, B.J. (1986) Nasal cancer and occupation in Sweden, 1961-1979. Am. J. ind. Med., 9, 477-485

10. Stellman, S.D. & Garfinkel, L. (1984) Cancer mortality among woodworkers. Am. J. ind. Med., 5, 343-357

11. Gallagher, R.P., Threlfall, W.J., Band, P.R. & Spinelli, J.J. (1987) Cancer mortality experience of woodworkers, loggers, fishermen, farmers, and miners in British Columbia. Natl Cancer Inst. Monogr., 69, 163-167

12. Hayes, R.B., Gerin, M., Raatgever, J.W. & de Bruyn, A. (1986) Wood-related occupations, wood dust exposure, and sinonasal cancer. Am. J. Epidemiol., 124, 569-577

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Last updated: 27 February 1998

# CHLORAMBUCIL
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 144)

**CAS No.**: 305-03-3
**Chem. Abstr. Name**: Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]-

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Many case reports and a few small epidemiological studies of malignancy after therapy with chlorambucil have been reported among patients treated for breast cancer, juvenile arthritis, glomerulonephritis and ovarian cancer. Although in each study an excess of subsequent malignancy, especially acute nonlymphocytic leukaemia (ANLL), is inferred, these reports are difficult to interpret because the cases are few or because they had also received radiation or other putative carcinogens [ref: 1,2]. A randomized trial of therapy in 431 polycythemia vera patients [ref: 3] showed a significant, 13-fold increase in the incidence of ANLL in those receiving chlorambucil - 2.3 times higher than in patients receiving radioactive phosphorus. The excess was strongly related to dose and persisted throughout the first decade after treatment.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Chlorambucil has been tested for carcinogenicity in mice and rats by intraperitoneal injection and in female rats by oral gavage. It produced tumours of the lung and probably tumours of the haematopoietic system and ovaries in mice [ref: 1], and produced haematopoietic tumours in male rats and haematopoietic and lymphatic tumours in female rats [ref: 1,4]. It had an initiating effect in a two-stage skin carcinogenesis experiment in mice [ref: 1].

**C. Other relevant data**

Chlorambucil is a bifunctional alkylating agent. It induced sister chromatid exchanges in the lymphocytes of treated patients; studies of induction of chromosomal aberrations were inconclusive [ref: 5].

Chlorambucil induced chromosomal aberrations in embryo cells of rats treated *in vivo*. Sister chromatid exchanges and chromosomal aberrations were induced in human lymphocytes and sister chromatid exchanges and mutation in Chinese hamster cells *in vitro*. Chlorambucil induced sex-linked recessive lethal mutations in *Drosophila* and mutation and gene conversion in yeast. It was mutagenic to bacteria [ref: 5].

**Overall evaluation**

Chlorambucil is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 9 (1975); Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 115-136, 1981

2. Greene, M.H., Boice, J.D., Jr, Greer, B.E., Blessing, J.A. & Dembo, A.J. (1982) Acute nonlymphocytic leukemia after therapy with alkylating agents for ovarian cancer. A study of five randomized clinical trials. New Engl. J. Med., 307, 1416-1421

3. Berk, P.D., Goldberg, J.D., Silverstein, M.N., Weinfeld, A., Donovan, P.B., Ellis, J.T., Landaw, S.A., Laszlo, J., Najean, Y., Pisciotta, A.V. & Wasserman, L.R. (1981) Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. New Engl. J. Med., 304, 441-447

4. Berger, M.R., Habs, M. & Schmähl, D. (1985) Comparative carcinogenic activity of prednimustine, chlorambucil, prenisolone and chlorambucil plus prednisolone in Sprague-Dawley rats. Arch. Geschwulstforsch., 55, 429-442

5. IARC Monographs, Suppl. 6, 139-141, 1987

**Synonyms**

- Ambochlorin
- Amboclorin
- 4-[*para*-Bis(β-chloroethyl)aminophenyl]butyric acid
- CB 1348
- Chlorbutinum
- Chloroambucil
- Chloroaminophen
- Chloraminophene
- Chlorbutin
- Chlorobutin
- Chlorobutine
- *N*,*N*-Di-2-chloroethyl-gamma-p-aminophenylbutyric acid
- *para*-*N*,*N*-Di(β-chloroethyl)aminophenylbutyric acid
- Ecloril
- Elcoril
- Leukeran
- Leukersan
- Leukoran
- Linfolizin
- Linfolysin
- Lympholysin
- NSC 3088
- Phenylbutyric acid nitrogen mustard

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Last updated: 6 February 1998

# CHLORODIFLUOROMETHANE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 149)

**CAS No.**: 75-45-6

**A. Evidence for carcinogenicity to humans** (*inadequate*)

A small study of 539 refrigeration workers exposed to a mixture of chlorofluorocarbons, including chlorodifluoromethane, for at least six months with up to 30 years' follow up was uninformative with regard to the carcinogenic hazard of this chemical (6 deaths due to cancer, 5.7 expected; 2 deaths from lung cancer, 1.0 expected) [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

Chlorodifluoromethane was tested for carcinogenicity in rats by oral administration and in mice and rats by inhalation. Oral administration to rats yielded no increase in tumour incidence in one study. A study by inhalation in mice gave inconclusive results for males and negative results for females. One study by inhalation in rats was inadequate, while in another, males exposed to the highest concentration had a marginal increase in the incidence of subcutaneous fibrosarcomas and Zymbal-gland tumours and negative results were obtained for female rats [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of chlorodifluoromethane in humans. Chlorodifluoromethane did not induce dominant lethal mutations in rats or chromosomal aberrations in bone-marrow cells of mice treated *in vivo*. It did not induce unscheduled DNA synthesis in human cells *in vitro* or mutation in cultured Chinese hamster V79 cells. It did not induce mutation or mitotic gene conversion in yeast, either after direct exposure or in a host-mediated assay. It was mutagenic to plants and bacteria [ref: 2].

**Overall evaluation**

Chlorodifluoromethane is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 71 (1999)

**Also see previous evaluation**: Vol. 41 (1986)

**References**

1. IARC Monographs, 41, 237-252, 1986

2. IARC Monographs, Suppl. 6, 150-151, 1987

**Synonyms**

- Algeon 22

- Algofrene 22
- Algofrene type 6
- Arcton 22
- Arcton 4
- CFC 22
- Daiflon 22
- Difluorochloromethane
- Difluoromonochloromethane
- Dymel 22
- Electro-CF 22
- F 22
- FC 22
- Flugene 22
- Forane 22
- Freon 22
- Frigen 22
- Genetron 22
- Haltron 22
- Isceon 22
- Isotron 22
- Khaladon 22
- Monochlorodifluoromethane
- R 22
- Ucon 22

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Last updated: 13 April 1999

# CHLOROETHYL NITROSOUREAS:

# BISCHLOROETHYL NITROSOUREA (BCNU)
# (Group 2A)

# 1-(2-CHLOROETHYL)-3-CYCLOHEXYL-1-NITROSOUREA (CCNU)
# (Group 2A)

# 1-(2-CHLOROETHYL)-3-(4-METHYLCYCLOHEXYL)-1-NITROSOUREA (METHYL-CCNU)
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.150)

**Bischloroethyl nitrosourea (BCNU)**
**CAS No.:** 154-93-8
**Chem. Abstr. Name**: Urea, *N*,*N*'-bis(2-chloroethyl)-*N*-nitroso-

**1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)**
**CAS No.**: 13010-47-4
**Chem. Abstr. Name**: Urea, *N*-(2-chloroethyl)-*N*'-cyclohexyl-*N*-nitroso-

**1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU)**
**CAS No.:** 13909-09-6

**A. Evidence for carcinogenicity to humans** (*limited* for BCNU; *inadequate* for CCNU; *sufficient* for methyl-CCNU)

In seven randomized trials of treatment for brain tumours, two cases of acute nonlymphocytic leukaemia (ANLL) occurred among 1628 patients treated with BCNU (0.08 expected) within the first two years of treatment, whereas no such case occurred among 1028 patients not treated with BCNU [ref: 1].

No epidemiological study of CCNU as a single agent was available to the Working Group [ref: 2].

Adjuvant treatment with methyl-CCNU has been evaluated in 3633 patients with gastrointestinal cancer treated in nine randomized trials. Among 2067 patients treated with methyl-CCNU, 14 cases of ANLL occurred (relative risk, 12.4; 95% confidence interval, 1.7-250), whereas one occurred among 1566 patients treated with other therapies. Cumulative (actuarial) risk was 4% at six years and was not affected by concomitant radiotherapy or immunotherapy [ref: 3]. A subsequent report described a strong dose-response relationship, adjusted for survival time, giving a relative risk of almost 40 fold among patients who had received the highest dose [ref: 4].

**B. Evidence for carcinogenicity to animals** (*sufficient* for BCNU and for CCNU; *limited* for methyl-CCNU)

BCNU produced malignant tumours of the lung and an increased risk for neurogenic tumours in rats after its repeated intraperitoneal or intravenous administration, and tumours in the peritoneal cavity after its intraperitoneal administration [ref: 2,5,6]. Tests in mice by intraperitoneal administration and in rats by oral administration could not be evaluated [ref: 2]. When tested in mice by skin application together with ultraviolet B irradiation, BCNU caused an earlier appearance of skin tumours [ref: 2]. Two studies by skin painting in mice were inadequate [ref: 2,7].

CCNU produced lung tumours in rats following its intraperitoneal or intravenous injection [ref: 2,5]. When tested in mice by intraperitoneal injection, it induced a slight increase in the incidence of lymphomas. Tests in rats by oral administration could not be evaluated [ref: 2]. In one study by skin application to mice, no skin tumour was observed, but the duration of the experiment was inadequate [ref: 7].

Data on methyl-CCNU were included in a report in which a large number of cancer chemotherapeutic agents were tested for carcinogenicity by intraperitoneal injection in Sprague-Dawley and Swiss mice. In male rats injected with methyl-CCNU thrice weekly for six months, total tumour incidence was reported to be increased 1.5-2 fold over that in controls at 18 months. A slight increase in tumour incidence was reported in mice [ref: 8]. Intravenous administration of methyl CCNU to rats induced lung tumours [ref: 5].

**C. Other relevant data**

BCNU, CCNU and Me-CCNU are directly-acting, bifunctional alkylating agents [ref: 9].

No data were available on the genetic and related effects of BCNU and Me-CCNU in humans. An increased frequency of sister chromatid exchanges was observed in a single study of peripheral blood lymphocytes of patients treated with CCNU.

BCNU induced chromosomal aberrations, micronuclei and sister chromatid exchanges in cells of mice treated *in vivo*, DNA damage in human cells *in vitro*, and aneuploidy, chromosomal aberrations, sister chromatid exchanges, mutation and DNA damage in rodent cells *in vitro*. It induced sex-linked recessive lethal mutations in *Drosophila* and gene conversion in yeast. It was mutagenic and caused DNA damage in bacteria [ref: 9].

CCNU induced dominant lethal mutations in rats and DNA damage in cells of mice and rats treated *in vivo*. It induced DNA damage in human and rodent cells *in vitro* and sister chromatid exchanges and mutation in cultured Chinese hamster cells. It induced mutation and DNA damage in bacteria [ref: 9].

**Overall evaluation**

Bischloroethyl nitrosourea (BCNU) is *probably carcinogenic to humans (Group 2A)*.

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) is *probably carcinogenic to humans (Group 2A)*.

1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU) is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: BCNU: Vol. 26 (1981) (p. 89); CCNU: Vol. 26 (1981) (p. 144)

**References**

1. Greene, M.H., Boice, J.D., Jr & Strike, T.A. (1985) Carmustine as a cause of acute nonlymphocytic leukemia. New Engl. J. Med., 313, 579

2. IARC Monographs, 26, 79-95, 137-149, 1981

3. Boice, J.D., Jr, Greene, M.H., Killen, J.Y., Jr, Ellenberg, S.S. & Fraumeni, J.F., Jr (1986) Leukemia after adjuvant chemotherapy with semustine (methyl-CCNU). Evidence of a dose-response effect. New Engl. J. Med., 314, 119-120

4. Boice, J.D., Jr, Greene, M.H., Killen, J.Y., Jr, Ellenberg, S.S., Keehn, R.J., McFadden, E., Chen, T.T. & Fraumeni, J.F., Jr (1983) Leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU). New Engl. J. Med., 309, 1079-1084

5. Habs, M. & Schmahl, D. (1984) Long-term toxic and carcinogenic effects of cytostatic drugs. Dev. Oncol., 15, 201-209

6. Eisenbrand, G. (1984) Anticancer nitrosoureas: investigations on antineoplastic, toxic and neoplastic activities. In: O'Neill, I.K., von Borstel, R.C., Miller, C.T., Long J. & Bartsch, H., eds, N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer (IARC Scientific Publications No. 57), Lyon, International Agency for Research on Cancer, pp. 695-708

7. Zackheim, H.S. & Smuckler, E.A. (1980) Tumorigenic effect of topical mechlorethamine, BCNU and CCNU in mice. Experientia, 36, 1211-1212

8. Weisburger, E.K. (1977) Bioassay program for carcinogenic hazards of cancer chemotherapeutic agents. Cancer, 40, 1935-1951

9. IARC Monographs, Suppl. 6, 116-118, 152-154, 1987

**Synonyms for Bischloroethyl nitrosourea (BCNU)**

- BiCNU
- 1,3-Bis(2-chloroethyl)-1-nitrosourea
- Bis(2-chloroethyl)nitrosourea
- 1,3-Bis(2-chloroethyl)nitrosourea
- 1,3-Bis(β-chloroethyl)-1-nitrosourea
- Carmustin
- Carmustine
- 1,3-Di(2-chloroethyl)-1-nitrosourea
- Nitrumon
- NSC 409962

**Synonyms for 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU)**

- Belustine
- Cee NU
- Chloroethylcyclohexylnitrosourea
- 1-(2-Chloroethyl)-3-cyclohexylnitrosourea
- ICIG 1109
- Lomustine
- NSC 79037

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Last updated: 6 February 1998

# CHLOROFORM
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 152)

**CAS No.**: 67-66-3
**Chem. Abstr. Name:** Trichloromethane

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Two studies of trihalomethane levels in drinking-water supplies and community-based rates of cancer mortality have been reported. Correlations were found between these levels and various site-specific cancer mortality rates, especially those for bladder cancer, but also those for cancers of the rectum/large intestine, brain and kidney and lymphoma [ref: 1,2]. In one study in which trihalomethane levels in drinking-water at place of residence were compared directly for 395 matched pairs of female teachers with regard to colorectal cancer, no association with trihalomethane exposure was observed [ref: 3]. A mortality study of anaesthesiologists who worked at the time chloroform was used provided no significant information [ref: 4].

Several investigations have attempted to assess the effects of trihalomethanes in drinking-water indirectly by comparing risks of cancers at various sites with extent of chlorination. Although excesses of some cancers have been found, it is not possible to evaluate any effect of chloroform from such studies [ref: 5-16].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Chloroform produced benign and malignant tumours of the liver and kidney in mice following oral gavage [ref: 17,18]. Administration in drinking-water to female mice did not increase the incidence of liver tumours [ref: 19]. Administration of chloroform to rats by gavage or in drinking-water increased the incidences of kidney [ref: 17,19] and thyroid tumours [ref: 17] and of neoplastic nodules of the liver [ref: 20]. Chloroform was tested inadequately by subcutaneous and intraperitoneal injection in mice [ref: 17]. A study by oral administration in dogs gave negative results [ref: 21]. Oral administration of chloroform did not enhance the incidences of liver and lung tumours induced in mice by intraperitoneal injection of *N*-ethyl-*N*-nitrosourea [ref: 22], but it enhanced the incidence of liver preneoplastic foci in rats treated with a single dose of *N*-nitrosodiethylamine [ref: 23].

**C. Other relevant data**

No adequate data were available on the genetic and related effects of chloroform in humans.

Chloroform did not induce micronuclei in bone-marrow cells of mice or DNA damage in liver or kidney cells of rats treated *in vivo*. It did not induce chromosomal aberrations, sister chromatid exchanges or unscheduled DNA synthesis in human lymphocytes *in vitro*. Chloroform enhanced virus-induced cell transformation of Syrian hamster embryo cells. It did not induce sister chromatid exchanges or mutation in Chinese hamster cells or DNA damage in rat hepatocytes *in vitro*. Chloroform did not induce sex-linked recessive lethal mutations in *Drosophila* or aneuploidy, mutation or somatic segregation in *Aspergillus*. Chloroform induced DNA damage but not mutation, aneuploidy, mitotic recombination or gene conversion in *Saccharomyces cerevisiae*, whereas mutation, mitotic recombination and gene conversion were induced in *S. cerevisiae* under conditions in which endogenous levels of cytochrome P450 were enhanced. Chloroform did not induce mutation or DNA damage in bacteria [ref: 24].

**Overall evaluation**

Chloroform is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 73 (1999)

**Also see previous evaluations**: Vol. 1 (1972); Vol. 20 (1979)

**References**


1. Hogan, M.D., Chi, P.-Y., Hoel, D.G. & Mitchell, T.J. (1979) Association between chloroform levels in finished drinking water supplies and various site-specific cancer mortality rates. J. environ. Pathol. Toxicol., 2, 873-887

2. Cantor, K.P., Hoover, R., Mason, T.J., McCabe, L.J. (1978) Association of cancer mortality with halomethanes in drinking water. J. natl Cancer Inst., 61, 979-985

3. Lawrence, C.E., Taylor, P.R., Trock, B.J. & Reilly, A.A. (1984) Trihalomethanes in drinking water and human colorectal cancer. J. natl Cancer Inst., 72, 563-568

4. Linde, H.W. & Mesnick, P.S. (1980) Causes of Death of Anesthesiologists from the Chloroform Era (PB 80-125172 (EPA/600/1-79-043)), Springfield VA, National Technical Information Service

5. Cantor, K.P. (1982) Epidemiological evidence of carcinogenicity of chlorinated organics in drinking water. Environ. Health Perspect., 46, 187-195

6. Carlo, G.L. & Mettlin, C.J. (1980) Cancer evidence and trihalomethane concentrations in a public drinking water system. Am. J. publ. Health, 70, 523-525

7. Craun, G.F. (1985) Epidemiologic studies of organic micropollutants in drinking water. Sci. total Environ., 47, 461-472

8. DeRouen, T.A. & Diem, J.E. (1977) Relationships between cancer mortality in Louisiana drinking-water source and other possible causative agents. In: Hiatt, H.H., Watson, J.D. & Winsten, J.A., eds, Origins of Human Cancer, Book A, Incidence of Cancer in Humans, Cold Spring Harbor, NY, CSH Press, pp. 331-345

9. Gottlieb, M.S., Carr, J.K. & Morris, D.T. (1981) Cancer and drinking water in Louisiana: colon and rectum. Int. J. Epidemiol., 10, 117-125

10. Alavanja, M., Goldstein, I. & Susser, M. (1978) A case control study of gastrointestinal and urinary tract cancer mortality and drinking water chlorination. In: Jolley, R.L., Gorchev, H. & Hamilton, D.H., Jr, eds, Water Chlorination, Environmental Impact and Health Effects, Vol. 2, Ann Arbor, MI, Ann Arbor Science, pp. 395-409

11. Brenniman, G.R., Vasilomanolakis-Lagos, J., Amsel, J., Namekata, T. & Wolff, A.H. (1980) Case-control study of cancer deaths in Illinois communities served by chlorinated or nonchlorinated water. In: Jolly, R.J., Brungs, W.A., Cumming, R.B. & Jacobs, V.A., eds, Water Chlorination, Environmental Impact and Health Effects, Vol. 3, Ann Arbor, MI, Ann Arbor Science, pp. 1043-1057

12. Crump, K.S. & Guess, H.A. (1982) Drinking water and cancer: review of recent epidemiological findings and assessment of risks. Am. Rev. publ. Health, 3, 339-357

13. Gottlieb, M.S., Carr, J.K. & Clarkson, J.R. (1982) Drinking water and cancer in Louisiana. A retrospective mortality study. Am. J. Epidemiol., 116, 652-667

14. Young, T.B., Kanarek, M.S. & Tsiatis, A.A. (1981) Epidemiologic study of drinking water chlorination and Wisconsin female cancer mortality. J. natl Cancer Inst., 67, 1191-1198

15. Kanarek, M.S. & Young, T.B. (1982) Drinking water treatment and risk of cancer death in Wisconsin. Environ. Health Perspect., 46, 179-186

16. Wilkins, J.R., III & Comstock, G.W. (1981) Source of drinking water at home and site-specific cancer incidence in Washington county, Maryland. Am. J. Epidemiol., 114, 178-190

17. IARC Monographs, 20, 401-427, 1979

18. Roe, F.J.C., Palmer, A.K., Worden, A.N. & Van Abbé, N.J. (1979) Safety evaluation of toothpaste containing chloroform. I. Long-term studies in mice. J. environ. Pathol. Toxicol., 2, 799-819

19. Jorgenson, T.A., Meierhenry, E.F., Rushbrook, C.J., Bull, R.J. & Robinson, M. (1985) Carcinogenicity of chloroform in drinking water to male Osborne-Mendel rats and female B6C3$F_1$ mice. Fundam. appl. Toxicol., 5, 760-769

20. Tumasonis, C.F., McMartin, D.N. & Bush, B. (1985) Lifetime toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. Ecotoxicol. environ. Saf., 9, 233-240

21. Heywood, R., Sortwell, R.J., Noel, P.R.B., Street, A.E., Prentice, D.E., Roe, F.J.C., Wadsworth, P.F., Worden, A.N. & Van Abbe, N.J. (1979) Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J. environ. Pathol. Toxicol., 2, 835-851

22. Pereira, M.A., Knutsen, G.L. & Herren-Freund, S.L. (1985) Effect of subsequent treatment of chloroform or phenobarbital on the incidence of liver and lung tumors initiated by ethylnitrosourea in 15 day old mice. Carcinogenesis, 6, 203-207

23. Deml, E. & Oesterle, D. (1985) Dose-dependent promoting activity of chloroform in rat liver foci bioassay. Cancer Lett., 29, 59-63

24. IARC Monographs, Suppl. 6, 155-158, 1987

**Synonyms**

- Formyl trichloride
- Freon 20
- Methane trichloride
- Methenyl chloride
- Methenyl trichloride
- Methyl trichloride
- R 20
- Trichloroform

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Last updated: 30 September 1999

**CHLOROPHENOXY HERBICIDES**
**(Group 2B)**

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.156)

**2,4-D and esters**
**CAS No.:** 94-75-7
**Chem. Abstr. Name:** (2,4-Dichlorophenoxy) acetic acid

**2,4,5-T and esters**
**CAS No.**: 93-76-5
**Chem. Abstr. Name**: (2,4,5-Trichlorophenoxy) acetic acid

**MCPA**
**CAS No.:** 94-74-6
**Chem. Abstr. Name:** (4-Chloro-2-methyl-phenoxy) acetic acid

**2,4-DP**
**CAS No.**: 120-36-5
**Chem. Abstr. Name**: 2-(2,4-Dichlorophenoxy) propanoic acid

**Silvex**
**CAS No.**: 93-72-1
**Chem. Abstr. Name**: 2-(2,4,5-Trichlorophenoxy) propanoicacid

**MCPP**
CAS No.: 93-65-2
**Chem. Abstr. Name**: 2-(4-Chloro-2-methylphenoxy) propanoicacid

**A. Evidence for carcinogenicity to humans** (*limited*for chlorophenoxy herbicides)

In a Danish cohort study of chemical workers exposed to chlorophenoxy herbicides [particularly (4-chloro-2-methylphenoxy) acetic acid (MCPA), 2-(4-chloro-2-methylphenoxy)propanoic acid (mecoprop), 2,4-dichlorophenoxyacetic acid (2,4-D) and 2-(2,4-

dichlorophenoxy)propanoic acid (dichlorprop)], as well as other chemicals, no overall increase in cancer incidence rate was observed, but there were significantly increased risks for soft-tissue sarcoma and lung cancer cancer in some subcohorts, which were not necessarily those with the highest exposures to chlorophenoxy herbicide preparations [ref: 1].

A recently reported cohort of 5784 male employees in a UK company that manufactured, formulated and sprayed MCPA and other pesticides but only small amounts of 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) had no general excess mortality from cancer. Three potentially exposed workers died from nasal carcinoma, however. One death due to soft-tissue sarcoma approximately equalled the expected rate. No excess of lymphoma was seen [ref: 2].

A Finnish cohort study of brush control workers with short follow-up time showed no increased cancer risk. A small Swedish cohort study of railroad workers who sprayed herbicides showed an increased risk of cancers at all sites combined for those exposed to chlorophenoxy herbicide preparations and other herbicides. An excess incidence of all cancers was also reported from a very small cohort of Swedish forestry foremen exposed to chlorophenoxy herbicide preparations and other herbicides. A study of long-term pesticide applicators in the German Democratic Republic, heavily exposed to a number of chemicals, including 2,4-D and MCPA, demonstrated an increased risk of bronchial carcinoma [ref: 1].

Two population-based case-control studies conducted in northern and southern Sweden, respectively, showed a statistically significant association between exposure to chlorophenoxy herbicides, especially in forestry and agriculture, and the occurrence of soft-tissue sarcomas. An increased risk of soft-tissue sarcoma was described among highly exposed Italian rice weeders in a population-based case-control study. However, a case-control study from New Zealand did not demonstrate any increased risk of soft-tissue sarcoma in people exposed to chlorophenoxy herbicides [ref: 1]. Nor did a recently reported population-based case-control study of soft-tissue sarcoma and

lymphoma in Kansas, USA, find any association between soft-tissue sarcoma and exposure to 2,4-D [ref: 3].

A statistically significant association between malignant lymphoma (Hodgkin's and non-Hodgkin's) and exposure to chlorophenoxy herbicides was found in a Swedish case-control study [ref: 1]. The population-based case-control study of soft-tissue sarcoma and Hodgkin's and non-Hodgkin's lymphoma in Kansas showed that use of 2,4-D was associated with non-Hodgkin's lymphoma, especially among farmers who had been exposed for more than 20 days per year, among whom there was an approximately six-fold excess, and among those who had mixed or applied the herbicides themselves. Hodgkin's lymphoma was not, however, found to be associated with herbicide exposure [ref: 3]. No significant or consistent association was seen in a case-control study of these tumours from New Zealand, and in a Danish cohort of chemical workers exposed to chlorophenoxy herbicides there was also no significantly increased risk of malignant lymphoma [ref: 1,4]. Farmers and forestry workers in Washington State, USA, with exposure to phenoxy herbicides had a significantly increased risk of non-Hodgkin's lymphoma. People of Scandinavian descent in the area had an increased risk of soft-tissue sarcoma in connection with phenoxy herbicide exposure, but no increased risk of non-Hodgkin's lymphoma [ref: 5].

Three Swedish case-control studies of colon, liver and nasal and nasopharyngeal cancer, which used the same study design and methods as in the studies on soft-tissue sarcoma and malignant lymphoma, did not demonstrate significantly increased risks, although a risk ratio of 2.1 was reached for nasal and nasopharyngeal cancer [ref: 1].

A record-linkage study using census data on occupation and cancer registry information in Sweden did not reveal any excess of soft-tissue sarcoma among agricultural and forestry workers [ref: 6,7]. However, on the basis of occupational titles, the elevated risks seen in Swedish case-control studies of soft-tissue sarcoma and lymphoma were reduced to 1.4 or less [ref: 8]. A UK study based on data from cancer registration showed a slightly but significantly increased risk of soft-

tissue sarcoma among farmers, farm managers and market gardeners, but not in other subgroups in forestry and farming [ref: 9]. No association with soft-tissue sarcoma has been found with military service in Viet Nam, despite potential exposure to phenoxy herbicides [ref: 1,10], although there is a case report in this respect [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate* for 2,4-D and 2,4,5-T)

2,4-D and several of its esters were tested in rats and mice by oral administration and in mice by subcutaneous administration. All of these studies had limitations, due either to inadequate reporting or to the small number of animals used. Therefore, although increased incidences of tumours were observed in one study in which rats received 2,4-D orally and in another in which mice received its isooctyl ester by subcutaneous injection, no evaluation of the carcinogenicity of this compound could be made [ref: 11].

2,4,5-T was tested in mice by oral and subcutaneous administration. All of the studies had limitations due to the small numbers of animals used. Therefore, although an increased incidence of tumours at various sites was observed in one study in which 2,4,5-T (containing less than 0.05 mg/kg chlorinated dibenzodioxins) was given orally, no evaluation of the carcinogenicity of this compound could be made on the basis of the available data [ref: 12]. In rats fed diets containing three different concentrations of 2,4,5-T, the incidences of all tumour types were comparable to those in the control groups, with the exception that the incidence of interfollicular C-cell adenomas of the thyroid was increased significantly in female rats receiving the lowest dose. This increase was not considered to be related to treatment since it was not dose-related and the female control group had an unusually low incidence of thyroid adenomas [ref: 13].

A study of the incidence of small-intestinal adenocarcinoma in groups of sheep from different farms showed an association with use of phenoxy herbicides, as elicited by farmers' responses to a questionnaire. However, other herbicides were in use, and there was no

documentation of exposures [ref: 14].

No adequate data were available on the carcinogenicity of MCPA [ref: 15].

**C. Other relevant data**

In single studies, lymphocytes of persons occupationally exposed to chlorophenoxy herbicides, including 2,4-D, did not show increased frequencies of sister chromatid exchanges or chromosomal aberrations. Other studies could not be assessed since workers were also exposed to other formulations. A single study of herbicide and pesticide sprayers exposed to 2,4,5-T, in which a small increase in the incidence of sister chromatid exchanges was reported, could not be assessed since workers were also exposed to other formulations. Persons occupationally exposed to MCPA did not have increased frequencies of sister chromatid exchanges (one study) or chromosomal aberrations in their lymphocytes [ref: 16].

2,4-D did not induce dominant lethal mutations, micronuclei or sister chromatid exchanges in rodents treated *in vivo*. Pure 2,4-D did not induce chromosomal aberrations in human lymphocytes *in vitro*, whereas a commercial formulation did. 2,4-D induced sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*. It did not induce sister chromatid exchanges but did induce mutation and inhibited intercellular communication in Chinese hamster cells *in vitro*, 2,4-D induced somatic mutation in *Drosophila*, but conflicting results were obtained for induction of sex-linked recessive lethal mutations; it did not induce aneuploidy. 2,4-D caused chromosomal aberrations and was mutagenic in plants. It induced mutation, gene conversion and mitotic recombination in yeast. It was not mutagenic to bacteria or bacteriophage. The *n*-butyl and iso-octyl esters of 2,4-D were also not mutagenic to bacteria [ref: 16].

2,4,5-T induced chromosomal aberrations in bone-marrow cells of Mongolian gerbils, but not in spermatogonia of Chinese hamsters, and aneuploidy in oocytes of rats treated *in vivo*. It did not induce

micronuclei in mice or dominant lethal mutations in mice or rats *in vivo*. 2,4,5-T inhibited intercellular communication in Chinese hamster V79 cells *in vitro*. There was weak evidence for the induction of sex-linked recessive lethal mutations in *Drosophila*; it did not induce aneuploidy or somatic mutation. It induced chromosomal aberrations in plants. It was mutagenic to yeast, but neither 2,4,5-T nor the *n*-butyl-, iso-butyl or iso-octyl ester of 2,4,5-T was mutagenic to bacteria [ref: 16].

MCPA did not induce structural chromosomal aberrations or micronuclei in mice treated *in vivo*; weakly positive results were obtained for sister chromatid exchanges in cells of Chinese hamsters treated *in vivo* and *in vitro*. It was weakly active in inducing sex-linked recessive lethal mutations but did not induce aneuploidy in *Drosophila*. MCPA and its methyl ester were mutagenic to yeast but not to bacteria [ref: 16].

**Overall evaluation**

Chlorophenoxy herbicides are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 41 (1986)

**References**

1. IARC Monographs, 41, 357-406, 1986

2. Coggon, D., Pannett, B., Winter, P.D., Acheson, E.D. & Bonsall, J. (1986) Mortality of workers exposed to 2-methyl-4-chlorophenoxyacetic acid. Scand. J. Work Environ. Health, 12, 448-454

3. Hoar, S.K., Blair, A., Holmes, F.F., Boysen, C.D., Robel, R.J., Hoover, R. & Fraumeni, J.F., Jr (1986) Agricultural herbicide use and

risk of lymphoma and soft-tissue sarcoma. J. Am. med. Assoc., 256, 1141-1147

4. Pearce, N.E., Sheppard, R.A., Smith, A.H. & Teague, C.A. (1987) Non-Hodgkin's lymphoma and farming: an expanded case-control study. Int. J. Cancer, 39, 155-161

5. Woods, J.S., Polissar, L., Severson, R.K., Heuser, L.S. & Kulander, B.G. (1987) Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. J. natl Cancer Inst., 78, 899-910

6. Wirklund, K. & Holm, L.-E. (1986) Soft tissue sarcoma risk in Swedish agricultural and forestry workers. J. natl Cancer Inst., 76, 229-234

7. Wirklung, K., Holm, L.-E. & Dich, J. (1987) Soft tissue sarcoma risk among agricultural and forestry workers in Sweden. Chemosphere (in press)

8. Hardell, L. & Axelson, O. (1986) Phenoxyherbicides and other pesticides in the etiology of cancer: some comments on Swedish experiences. In: Becker, C.E. & Coye, M.J., eds, Cancer Prevention. Strategies in the Workplace, Washington DC, Hemisphere, pp. 107-119

9. Balarajan, R. & Acheson, E.D. (1984) Soft tissue sarcomas in agriculture and forestry workers. J. Epidemiol. Commun. Health, 38, 113-116

10. Kang, H.K., Weatherbee, L., Breslin, P.P., Lee, Y. & Shepard, B.M. (1986) Soft tissue sarcomas and military service in Vietnam: a case comparison group analysis of hospital patients. J. occup. Med., 28, 1215-1218

11. IARC Monographs, 15, 111-138, 1977

12. IARC Monographs, 15, 273-299, 1977

13. Kociba, R.J., Keyes, D.G., Lisowe, R.W., Kalnins, R.P., Dittenber, D.D., Wade, C.E., Gorzinski, S.J., Mahle, N.H. & Schwetz, B.A. (1979) Results of a two-year chronic toxicity and oncogenic study of rats ingesting diets containing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Food Cosmet. Toxicol., 17, 205-221

14. Newell, K.W., Ross, A.D. & Renner, R.M. (1984) Phenoxy and picolinic acid herbicides and small intestinal adenocarcinoma in sheep. Lancet, ii, 1301-1305

15. IARC Monographs, 30, 255-269, 1983

16. IARC Monographs, Suppl. 6, 161-163, 233-236, 538-540, 1987

**Synonyms for 2,4-D and esters**

- Abco W.K-67 2,4-D Weed Killer (butyl ester of 2,4-D)
- Abco W.K-DT 133 (isooctyl esters of 2,4-D and 2,4,5-T)
- Abco WKS-65 Brush Killer (isooctyl esters of 2,4-D, 2,4,5-Tand silvex [2-(2,4,5-trichloro-phenoxy)propionic acid])
- Acetic acid, (2,4-dichlorophenoxy)-
- Acide dichloro-2,4 phenoxyacetique
- Acido(2,4-dicloro-fenossi)-acetico
- Acme Poison Ivy Killer (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Acme Vegetation Killer (2,4-D + prometone [2-methoxy-4,6-bis(isopropylamino)-s-triazine])
- Acme Weed-No-More Spotter (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Agent Orange (n-butyl esters of 2,4-D and 2,4,5-T)
- Agent Purple (n-butyl esters of 2,4-D and 2,4,5-T + isobutylester of 2,4,5-T)
- Agent White (triisopropanolamine salt of 2,4-D + triisopropanolamine)
- Agrotect (2,4-D, form unspecified)
- Agway 2,4-D and Silvex Lawn and Weed Killer (2-

ethylhexylester of 2,4-D + butoxyethanol ester of silvex [2-(2,4,5-trichlorophenoxy)propionicacid])

- Agway Weed Killer "66" Improved (triethanolaminesalt of 2,4-D)
- Allied Chemical Low Volatile 1-1/3-2/3 Brush Killer (2,4-D+ 2,4,5-T + isooctyl esters of 2,4-D and 2,4,5-T
- Amchem 2,4-D 2,4,5-T Low Volatile Ester Brush Killer (isooctylesters of 2,4-D and 2,4,5-T)
- Amchem 6DT. Low Volatile Ester Brush Killer (isooctyl estersof 2,4-D and 2,4,5-T)
- Amchem Amine 2,4-D Low Volatile Ester Weed Killer (isooctylester of 2,4-D)
- Amchem Emulsamine Brush Killer (alkyl $C_{12}$ + $C_{14}$ aminesalts of 2,4-D and 2,4,5-T)
- Amchem Emulsamine E-3 (dodecylamine salts of 2,4-D + tetradecylaminesalts of 2,4-D)
- Amchem Isooctyl-DT (isooctyl esters of 2,4-D and 2,4,5-T)
- Amchem Isooctyl-DT6 (isooctyl esters of 2,4-D and 2,4,5-T)
- Amchem Super D Weed one (diethanolamine salts of 2,4-D anddicamba [3,6-dichloro-2-methoxy-benzoic acid])
- Amchem Weed Killer 650 (isopropyl ester of 2,4-D)
- Amoco 2,4-D LV Ester (isooctyl ester of 2,4-D)
- Amoco 2,4-D Weed Killer No. 3-E-M (butyl and isopropyl estersof 2,4-D)
- Amoco 2,4-D Weed Killer No. 3E (butyl and isopropyl estersof 2,4-D)
- Amoco 2,4-D Weed Killer No. 5 (butyl and isopropyl estersof 2,4-D)
- Amoco 2,4-D Weed Killer No. 5-M (butyl ester of 2,4-D)
- Amoco 2,4-D Weed Killer No. 6B (butyl ester of 2,4-D)
- Amoco Brush Killer (isooctyl esters of 2,4-D and 2,4,5-T)
- Amoxone (triethanolamine salt of 2,4-D)
- Ansar 290D (triethanolamine salt of 2,4-D + triethanolaminemethanearsonate)
- Antrol 2,4-D and 2,4,5-T Weed and Brush Killer (alkanolaminesalts [of the ethanol and ispropanol series] of 2,4-D

+ triethylaminesalts of 2,4,5-T)

- Antrol Jet Stream Weed Killer (alkanolamine salts [of theethanol and isopropanol series] of 2,4-D + butoxypolypropoxypropylesters of silvex [2-(2,4,5-trichlorophenoxy)propionic acid])
- Antrol Squeeze'N Weed (alkanolamine salts [of the ethanoland isopropanol series] of 2,4-D + butoxypolypropoxypropyl estersof silvex [2-(2,4,5-trichlorophenoxy)propionic acid])
- Antrol Wide Stream Chickweed and Clover Killer (alkanolaminesalts [of the ethanol and isopropanol series] of 2,4-D + butoxypolypropoxypropylesters of silvex [2-(2,4,5-trichlorophenoxy)propionic acid])
- Aptrex (monuron trichloroacetate [3-(p-chlorophenyl)-1,1-dimethylureatrichloracetate] + isooctyl ester of 2,4-D)
- Aqua-Kleen (butoxyethanol ester of 2,4-D)
- Asgrow Weed-Nix Lawn Food and Weed Killer with 2,4-D and silvex(dimethylamine 2,4-dichlorophenoxy-acetate + isooctyl ester ofsilvex [2-(2,4,5-trichlorophenoxy)propionic acid])
- Associated Sales 4-Pound 2,4-D Ester Weed Killer (butyl esterof 2,4-D)
- Atlacide with 2,4-D (sodium chlorate + 2,4-D)
- Balcom's G-K-20 (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Balcom's T-D Special Weed Killer (isooctyl esters of 2,4-Dand 2,4,5-T)
- Barber's 2,4-D Ester Weed Killer (butyl ester of 2,4-D)
- Barber's Weed Killer (Amine Formulation) (dimethylamine saltof 2,4-D)
- Barber's Weed Killer (Ester Formulation) (isopropyl esterof 2,4-D)
- Barco Weed Killer (Ester Formulation) (butyl ester of 2,4-D)
- Best 4 Servis Brand Lawn Weed Killer (dimethylamine salt of2,4-D)
- Blitz 64 (dimethylamine salts of 2,4-D)
- Bonide Crabgrass and Broadleaf Weed Killer (dodecylammoniumand octylammonium methanearsonate + octylammonium salt of 2,4-D)

- Bonide Dioweed 40% Liquid (triethanolamine salt of 2,4-D)
- Bonide Dioweed Dust (triethanolamine salt of 2,4-D)
- Bonide Dioweed Liquid (triethanolamine salt of 2,4-D + 2,4-D)
- Bonus Type B (2,4-D + 2-[2-methyl-4-chlorophenoxy]propionicacid)
- Breck's Lawn Weed Killer (butoxyethoxypropanol esters of 2,4-Dand 2,4,5-T)
- Bridgeport Spot Weed Killer (isopropyl ester of 2,4-D)
- Brulin's 2,4-D Liquid Weed Killer-20% (triethanolamine saltof 2,4-D)
- Brulin's Brush Killer (butyl esters of 2,4-D and 2,4,5-T)
- Brush Killer 155 (dimethylamine salts of trichlorobenzoicacids + triethanolamine salts of 2,4-D and 2,4-dichlorophenoxypropionicacid)
- Brush Killer 170 (butoxyethanol esters of 2,4-dichlorophenoxypropionicacid and 2,4-D)
- Brush Killer 171 (butoxyethanol esters of 2,4-dichlorophenoxypropionicacid and 2,4-D)
- Brush Killer 50-50 (butyl esters of 2,4-D and 2,4,5-T)
- Brush Killer X (isooctyl esters of 2,4-D and 2,4,5-T)
- Brush-O-Cide (isooctyl esters of 2,4-D + 2,4,5-T)
- Brush-Off No. 438 Conc. 2-2 LV Brush Killer (isooctyl estersof 2,4-D and 2,4,5-T)
- Brush-Rhap A-2D-2T (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Brush-Rhap Amine A-2D-2T (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Brush-Rhap B-1.33D - 0.67T (butyl esters of 2,4-D and 2,4,5-T)
- Brush-Rhap B-2-2 (2,4-D + 2,4,5-T)
- Brush-Rhap B-2D-2T (butyl esters of 2,4-D and 2,4,5-T)
- Brush-Rhap Injection Fluid Low Volatile 2D-2T (2-ethylhexylesters of 2,4-D and 2,4,5-T)
- Brush-Rhap Injection Fluid Low Volatile 3D-3T (2-ethylhexylesters of 2,4-D and 2,4,5-T)
- Brush-Rhap Low Volatile 2D-2T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)

- Brush-Rhap Low volatile 3D-2T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Brush-Rhap Low Volatile 3D-3T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Brush-Rhap LV 2D-2T (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Brush-Rhap LV-2-2-0 (2,4-D + 2,4,5-T)
- Butoxyethanol ester of (2,4-dichlorophenoxy) acetic acid
- Butoxyethyl 2,4-dichlorophenoxyacetate
- Butyl (2,4-dichlorophenoxy)acetate
- Butyl 2,4-D
- Butyl 400 (butyl ester of 2,4-D)
- Butyl dichlorophenoxyacetate
- Butyl ester of dichlorophenoxyacetic acid
- Certified C-300 Selective Weed Killer (isooctyl esters of2,4-D and 2,4,5-T)
- Chem-Pels Plus (isooctyl esters of 2,4-D and 2,4,5-T)
- Chemform Butoxy Brush Killer (butoxyethoxypropanol estersof 2,4-D and 2,4,5-T)
- Chemical Insecticide's Isopropyl Ester of 2,4-D Liquid Concentrate(isopropyl ester of 2,4-D)
- Chempar Low Volatile Brush Killer No. 2 (2,4,5-T + 2,4-D)
- Chipco Turf Herbicide "D" (2,4-D, form unspecified)
- Chipco Turf Herbicide "D" and "T" (dimethylaminesalt of 2,4-D + triethylamine salt of 2,4,5-T)
- Chipco Turf Kleen (diethanolamine salts of 2-(2-methyl-4-chlorophenoxy)propionicacid and 2,4-D)
- Chipman 2,4-D Amine 80 (2,4-D, form unspecified)
- Chipman 2,4-D Amine No. 4 (dimethylamine salt of 2,4-D)
- Chipman 2,4-D Butyl Ester 334E
- Chipman 2,4-D Butyl Ester 4E
- Chipman 2,4-D Butyl Ester 6 (n-butyl ester of 2,4-D)
- Chipman 2,4-D Butyl Ester 6E
- Chipman 2,4-D Ester 128 (2,4-D ester, form unspecified)
- Chipman 2,4-D Ester 5% Dust (2,4-D ester, form unspecified)
- Chipman 2,4-D Ester 64 (2,4-D ester, form unspecified)
- Chipman 2,4-D Ester 80 L.V. (2,4-D ester, form unspecified)

- Chipman 2,4-D Gran 20 (isooctyl ester of 2,4-D)
- Chipman 2,4-D Low Volatile Ester 4L (isooctyl ester of 2,4-D)
- Chipman 2,4-D Low Volatile Ester 6 (isooctyl ester of 2,4-D)
- Chipman 2,4-D Low Volatile Ester 6L (isooctyl ester of 2,4-D)
- Chipman Amine Brush Killer (triethylamine salts of 2,4-D and2,4,5-T)
- Chipman Brush Killer 128 (2,4-D + 2,4,5-T, forms unspecified)
- Chipman Brush Killer 128 L.V. (2,4-D + 2,4,5-T, forms unspecified)
- Chipman Brush Killer 128 Regular (2,4-D + 2,4,5-T, forms unspecified)
- Chipman Brush Killer 76 (isooctyl esters of 2,4-D and 2,4,5-T)
- Chipman Lawn Weed Killer (2,4-D [form unspecified] + d-isomerof mecoprop [2-(4-chloro-2-methylphenoxy)propionic acid])
- Chipman Low Volatile Brush Killer No. 2 (isooctyl esters of2,4-D and 2,4,5-T)
- Chipman Low Volatile Brush Killer No. 3 (isooctyl esters of2,4-D and 2,4,5-T)
- Chlorocrotyl ester of 2,4-D
- Chloroxone (2,4-D, form unspecified)
- Commercial Brush Killer (isooctyl esters of 2,4-D and 2,4,5-T)
- Crop Rider "45" (2-ethylhexyl ester of 2,4-D)
- Crop Rider 2.67D (butyl ester of 2,4-D)
- Crop Rider 20% Agua Granular (2-ethylhexyl ester of 2,4-D)
- Crop Rider 20% Terra Granular (2-ethylhexyl ester of 2,4-D)
- Crop Rider 3-34D-2 (isopropyl ester of 2,4-D)
- Crop Rider 3.34D (isopropyl ester of 2,4-D)
- Crop Rider 6D Weed Killer (butyl ester of 2,4-D)
- Crop Rider 6D-OS Weed Killer (butyl ester of 2,4-D)
- Crop Rider LV-6D (2-ethylhexyl ester of 2,4-D)
- Crop-Guard (isobutyl and n-butyl esters of 2,4-D)
- Cross Country Organic Lawn Food with Weed Killer (sodium saltof 2,4-D)
- Cross Country Poison Ivy Killer (butoxyethoxypropanol estersof 2,4-D and 2,4,5-T)

- Cross Country Weed Killer Spray (alkanolamine salts of 2,4-D)
- Cross Country Weedeath (isopropyl and triethylamine saltsof 2,4-D)
- Crotilin (chlorocrotyl ester of 2,4-D)
- Crotylin (chlorocrotyl ester of 2,4-D)
- (2,4-Dichloor-fenoxy)azijnzuur
- (2,4-Dichlor-phenoxy)essigsaure
- (2,4-Dichlorophenoxy)acetic acid, butyl ester
- (2,4-Dichlorophenoxy)acetic acid, crotyl ester
- (2,4-Dichlorophenoxy)acetic acid, dimethylamine salt
- (2,4-Dichlorophenoxy)acetic acid, isooctyl ester
- (2,4-Dichlorophenoxy)acetic acid, isopropyl ester
- (2,4-Dichlorophenoxy)acetic acid, sodium salt
- 006 Shrub-A-Dub (isooctyl ester of 2,4-D + bromacil [5-bromo-3-sec-butyl-6-methyluracil]+ pentachlorophenol + other chlorophenols)
- 006 Weed Killer (isooctyl ester of 2,4-D + bromacil [5-bromo-3-sec-butyl-6-methyluracil]+ pentachlorophenol + other chloropenols)
- 2,4-D + Bromacil [5-bromo-3-sec-butyl-6-methyluracil] + pentachlorophenol+ other phenols)
- 2,4-D acid
- 2,4-D amine (dimethylamine salt of 2,4-D)
- 2,4-D, alpha-chlorocrotyl ester
- 2,4-D, butyl ester
- 2,4-D, dimethylamine salt
- 2,4-D, isooctyl ester
- 2,4-D, isopropyl ester
- 2,4-Dichlorophenoxyacetic acid
- 2,4-Dichlorophenoxyacetic acid, 2-butenyl ester
- 2,4-Dichlorophenoxyacetic acid, 4-chlorocrotonyl alcohol ester
- 2,4-Dichlorophenoxyacetic acid, 4-chlorocrotonyl ester
- 2,4-Dichlorophenoxyacetic acid, butoxyethyl ester
- 2,4-Dichlorophenoxyacetic acid, butyl ester
- 2,4-Dichlorophenoxyacetic acid, isooctyl ester
- 2,4-Dichlorophenoxyacetic acid, isopropyl ester

- 2,4-Dichlorophenoxyacetic acid, sodium salt
- 2,4-Dichlorphenoxyacetic acid
- 2,4-Dow Weed Killer Formula 40 (alkanolamine salt of 2,4-D)
- 2,4-Dow Weed Killer Formula 40 (alkanolamine salts [of theethanol and isopropanol series] of 2,4-D)
- 2,4-Dwuchlorofenoksyoctowy Kwas
- D 50 (2,4-D, form unspecified)
- D-Weed-O (isooctyl ester of 2,4-D + Bromacil [5-bromo-3-sec-butyl-6-methyluracil]+ pentachlorophenol + other chlorophenols)
- Dacamine (N-oleyl 1,3-propylenediamine salts of 2,4-D and2,4,5-T)
- Dacamine 1D/1T (N-oleyl 1,3-propylenediamine salts of 2,4-Dand 2,4,5-T)
- Dacamine 2D/2T (N-oleyl 1,3-propylenediamine salts of 2,4-Dand 2,4,5-T)
- Dacamine 4D (N-oleyl 1,3-propylenediamine salt of 2,4-D)
- Dal-E-Rad + 2 Powder (disodium methanearsonate [hexahydrate]+ sodium 2,4-dichlorophenoxy acetate monohydrate)
- DB Granular (disodium tetraborate pentahydrate and decahydrate+ 2,4-D)
- De Witt S-77 Weed Killer (dimethylamine salts of 2,4-D and2,4,5-T)
- De-Pester Ded-Weed for Lawns (2,4-D + 2,4,5-T + Kerosene)
- De-Pester Ded-Weed LV-2 (2,4-D)
- De-Pester Ded-Weed ME-4 (butyl ester of 2,4-D)
- De-Pester Ded-Weed ME-5 (butyl ester of 2,4-D)
- De-Pester Ded-Weed ME-6 (butyl ester of 2,4-D)
- De-Pester Ded-Weed ME-9 (butyl ester of 2,4-D)
- Decamine (2,4-D, form unspecified)
- Ded-weed for Lawns, New Improved (isooctyl esters of 2,4-Dand 2,4,5-T)
- Ded-weed LV-69 (2,4-D, form unspecified)
- Del SK 40 Heavy Duty Weed Killer (alkanolamine salts [of theethanol and isopropanol series] of 2,4-D)
- Del-Kill Weed Killer 400 Liquid (mixed aliphatic hydrocarbons+

isooctyl ester of
- Destruxol Weed Killer "D" (isooctyl esters of 2,4-Dand 2,4,5-T)
- Di-Met Chickweed and Weed Killer (isooctyl esters of 2,4-Dand silvex [2-(2,4,5-trichlorophenoxy) propionic acid])
- Di-Met Plus-2, Liquid for Crabgrass and Lawn Weeds (dodecylammonium methanearsonate + octyl ammonium methanearsonate + octylammonium salt of 2,4-D)
- Di-Met Plus-2, Liquid for Dallis Grass and Lawn Weeds (dodecylammonium methanearsonate + octyl ammonium methanearsonate + octylammonium salt of 2,4-D)
- Diamond Alkali Chemicals 2-2 2-Ethyl Hexyl Brush Killer (2-ethylhexylesters of 2,4-D and 2,4,5-T)
- Diamond Alkali Chemicals 4 2-Ethyl Hexyl D Weed Killer (2-ethylhexylester of 2,4-D)
- Diamond Alkali Chemicals 4-Mixed Amine-D Weed Killer (alkyland dialkanolamine salts of 2,4-D)
- Diamond Alkali Chemicals Crop Rider Amine 4-D (alkyl and dialkanolaminesalts of 2,4-D)
- Diamond Alkali Chemicals Crop Rider and Line Rider LV-4D (2-ethylhexyester of 2,4-D)
- Diamond Alkali Chemicals Technical 2-Ethyl Hexyl-D (2-ethylhexylester of 2,4-D)
- Diamond Alkali Chemicals The Line Rider (2-ethylhexyl estersof 2,4-D and 2,4,5-T)
- Diamond Shamrock Amine 2D/2T (dimethylamine salts of 2,4-Dand 2,4,5-T)
- Diamond Shamrock Amine 6D (dimethylamine salt of 2,4-D)
- Diamond Shamrock Butyl 4D (butyl ester of 2,4-D)
- Diamond Shamrock Butyl 6D Weed Killer (butyl ester of 2,4-D)
- Diamond Shamrock Dormant Cane LV 3D/3T-OS (isooctyl estersof 2,4-D and 2,4,5-T)
- Diamond Shamrock LO-VOL 2D/2T (isooctyl esters of 2,4-D and2,4,5-T)
- Diamond Shamrock LO-VOL 4D (isooctyl ester of 2,4-D)
- Diamond Shamrock LO-VOL 6D (isooctyl ester of 2,4-D)
- Dichlorophenoxyacetic acid

- Dichlorophenoxyacetic acid, butyl ester
- Dikonirt (sodium salt of 2,4-D)
- Dimethylamine, (2,4-dichlorophenoxy) acetate
- Dimethylammonium 2,4-dichlorophenoxy acetate
- Dinoxol (butoxyethanol esters of 2,4-D and 2,4,5-T)
- Dinoxol 64 (butoxyethanol esters of 2,4-D and 2,4,5-T)
- Dinoxol Super-6 (butoxyethanol esters of 2,4-D and 2,4,5-T)
- DMA-4 (dimethylamine salt of 2,4-D)
- Dolge E.W.T. Amine Type 2,4-D Weed Killer (diethanolaminesalt of 2,4-D)
- Dormone (2,4-D, form unspecified)
- Dow 2,4-ccDichlorophenoxyacetic Acid, Sodium Salt (monohydratesodium salt of 2,4-D)
- Dow Brush Killer 50-50 (butyl esters of 2,4-D and 2,4,5-T)
- Dow Brush Killer X (isooctyl esters of 2,4-D and 2,4,5-T)
- Dow Butyl 265 (butyl ester of 2,4-D)
- Dow Butyl 400 (butyl ester of 2,4-D)
- Dow DMA-4 (dimethylamine salt of 2,4-D)
- Dow Formula 40 (alkanolamine salt of 2,4-D)
- Dow Weed Killer X (butoxypropyl ester of 2,4-D)
- Dragon Lawn Weed Killer (2,4-D + dicamba [3,6-dichloro-2-methoxybenzoicacid])
- DRO 2,4-D Concentrate (diethylamine salt of 2,4-D)
- Dro Weedtrol Concentrate (disodium monomethyl creonate pentahydrate+ sodium monohydrate of 2,4-D)
- Droweed Spot Treatment Kills Law Weeds (propylene glycol andbutyl ether esters of 2,4-D)
- Du Pont Lawn Weed Killer (dimethylamine salt of 2,4-D)
- Du Pont Turf Food with Weed Killer (dimethylamine salt of2,4-D)
- Du Pont Weed Killer No. 2 (dimethylamine salt of 2,4-D)
- Dupont Lawn Weeder (propylene glycol and butyl ether estersof 2,4-D)
- Emulsamine Brush Killer (dodecyl- and tetradecylamine saltsof 2,4-D and 2,4,5-T)
- Emulsamine E-3 (dodecyl- and tetradecylamine salts of 2,4-D)

- Emulsavert 100 (2,4-D + 2,4,5-T + N,N-dimethyloleylamine saltsof 2,4-D and 2,4,5-T)
- Emulsavert 248 (2,4-D + 2,4,5-T + N,N-dimethyloleylamine saltsof 2,4-D and 2,4,5-T)
- Emulsavert-D (2,4-D, form unspecified)
- Envert-171 (2,4-D, form unspecified)
- Envert-DT (butoxyethanol esters of 2,4-D and 2,4,5-T)
- Esso Herbicide 10 (butyl ester of 2,4-D)
- Estasol (isopropyl ester of 2,4-D)
- Esteron 44 (isopropyl ester of 2,4-D)
- Esteron 44 Improved Weed Killer (butyl ester of 2,4-D)
- Esteron 44 Weed Killer (isopropyl and butyl esters of 2,4-D)
- Esteron 6E Herbicide (isooctyl ester of 2,4-D)
- Esteron 76 (isopropyl and butyl esters of 2,4-D)
- Esteron 76 BE (butyl ester of 2,4-D)
- Esteron 76 BE Herbicide (butyl ester of 2,4-D)
- Esteron 76-E Weed Killer (isopropyl and butyl esters of 2,4-D)
- Esteron 99 Concentrate (butoxyethanol ester of 2,4-D)
- Esteron 99 Weed Killer (propylene glycol butyl ether esterof 2,4-D)
- Esteron 99 Weed Killer Concentrate (propylene glycol butylether esters of 2,4-D)
- Esteron Brush Killer (old formulation) (isopropyl esters of2,4-D and 2,4,5-T)
- Esteron Brush Killer (propylene glycol butyl ether estersof 2,4-D and 2,4,5-T)
- Esteron Brush Killer O.B. (propylene glycol butyl ether estersof 2,4-D and 2,4,5-T)
- Esteron Ten-Ten (propylene glycol butyl ether esters of 2,4-D)
- Estone (ethyl ester of 2,4-D)
- Feed No Weed (triethylamine salts of 2,4-D and 2,4,5-T)
- Felco Butyl Ester 600 2,4-D Weed Killer (butyl ester of 2,4-D)
- Felco HV2 Weed Killer (butyl ester of 2,4-D)
- Felco HV4 Weed Killer (butyl ester of 2,4-D)
- Felco Low Volatile Ester 600 (isooctyl ester of 2,4-D)
- Felco LV 400 Weed Killer (isooctyl ester of 2,4-D)

- Felco Super Brush Killer (butyl esters of 2,4-D and 2,4,5-T)
- Fenac Plus (dimethylamine salts of 2,4-D and 2,3,6-trichlorophenylaceticacid)
- Fence Painter Weed Out (monuron [3-(p-chlorophenyl)-1,1-dimethylurea]+ sodium salt of 2,4-D + sodium tetraborate)
- Fence Rider "45" (isooctyl esters of 2,4-D and 2,4,5-T)
- Fence Rider 22 (butyl esters of 2,4-D and 2,4,5-T)
- Fence Rider LV-22 (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Fence Rider LV-3D/3T (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Fernesta (2,4-D, form unspecified)
- Fernimine (ethanol and ispropyl esters of 2,4-D)
- Fernoxene (sodium salt of 2,4-D)
- Fernoxone (2,4-D, form unspecified)
- Ferxone (2,4-D, form unspecified)
- Field-Clean (isooctyl ester of 2,4-D)
- Floratox 4 LB.LV 2,4-D Weed Killer (isooctyl ester of 2,4-D)
- Floratox 428 4-Pound 2,4-D Ester Weed Killer (butyl esterof 2,4-D)
- Floro Tox 2,4-D Amine Weed Killer (dimethylamine salt of 2,4-D)
- Foredex 75 (2,4-D, form unspecified)
- Foremost All Season Weed Killer (mixed aliphatic hydrocarbons+ isooctyl ester of 2,4-D + pentachlorophenol + other chlorophenols+ bromacil[5-bromo-3-sec-butyl-6-methyluracil])
- Formula 40 (ethanol and isopropyl esters of 2,4-D)
- FS Amine 400 Weed Killer (dimethylamine salt of 2,4-D)
- FS Ester 400 Weed Killer (butyl ester of 2,4-D)
- FS LV 400 Weed Killer (isooctyl ester of 2,4-D)
- G.L.F. Weed Killer 66 Sequestered (2,4-D, form unspecified)
- GCC-165 Weed Killer (isooctyl ester of 2,4-D + bromacil [5-bromo-3-sec-butyl-6-methyluracil]+ pentachlorophenol + other chlorophenols)
- GCC-425 (isooctyl esters of 2,4-D, 2,4,5-T and 2-(2,4,5-trichlorophenoxy)propionicacid)

- GCC-429 (isooctyl esters of 2,4-D, 2,4,5-T and 2-(2,4,5-trichlorophenoxy)propionicacid)
- General Chemical 2,4-D 3.34 Butyl Ester Weed Killer
- General Chemical 2,4-D 4-Butyl Ester Weed Killer
- General Chemical 2,4-D 6.00 Butyl Ester Weed Killer
- General Chemical 2,4-D Butyl Ester Weed Killer
- Good-Life Weed Woe (diethanolamine salts of 2-(2-methyl-4-chlorophenoxy)propionicacid, 2,4-D and dicamba [3,6-dichloro-2-methoxy benzoic acid])
- Gormel's Brush Killer (propylene glycol butyl ether estersof 2,4-D and 2,4,5-T)
- Gormel's Weed and Clover Killer (isooctyl esters of 2,4-Dand 2,4,5-T)
- Gormel's Weed Kil (alkanolamine salts [of the ethanol andisopropanol series] of 2,4-D)
- Green Cross Commercial Weed Killer "96" (2,4-D +butyl ester of 2,4-D)
- Green Cross Ester Weed Killer (2,4-D)
- Green Cross Roadside 2,4-D Low Volatile Weed Killer (isooctylester of 2,4-D)
- Green Cross Vegetation Killer (monuron [3-(p-chlorophenyl)-1,1-dimethylurea]+ 2,4-D + 2,4,5-T)
- Green Cross Weed-No-More "80" (2,4-D)
- Green Cross Weed-No-More (butyl ester of 2,4-D)
- Green Light 2,4-D, 2,4,5-T Weed Killer (isooctyl esters of2,4-D and 2,4,5-T)
- Green Light Broadleaf Weed Killer (alkanolamine salts [ofthe ethanol and isopropanol series] of 2,4-D)
- Green Light Weed Killer (alkanolamine salts [of the ethanoland isopropanol series] of 2,4-D + triethylamine salt of 2,4,5-T)
- Greenfield Broadleaf Weed and Crab Grass Killer (trifluralin[alpha,alpha,alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine]+ disodium methylarsonate + sodium salts of 2,4-D and 2,4,5-T)
- Greenfield Crab Grass and Broadleaf Weed Killer (trifluralin[alpha,alpha,alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-

toluidine]+ disodium methylarsonate hexahydrate + isooctyl esters of 2,4-Dand 2,4,5-T)

- Greenfield Crabgrass and Dandelion Killer (disodium methanearsonate+ trifluralin [alpha,alpha,alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine]+ sodium salts of 2,4-D and 2,4,5-T)
- Greenfield Dandelion and Broadleaf Weed Killer (isooctyl estersof 2,4-D and silvex [2-(2,4,5-trichlorophenoxy)propionic acid])
- Greenfield Dandelion and Chickweed Killer (isooctyl estersof 2,4-D and silvex [2-(2,4,5-trichlorophenoxy)propionic acid])
- Greenfield Two-Way green Power (isooctyl esters of 2,4-D andsilvex [2-(2,4,5-trichlorophenoxy) propionic acid] + nitrogen+ phosphoric acid + soluble potash)
- Greenfield Weeds As It Feeds For Lawns (isooctyl esters of2,4-D and 2,4,5-T)
- Greever's 2,4-D Low Volatile Ester Weed Killer (isooctyl esterof 2,4-D)
- Greever's Low Volatile Brush Killer (isooctyl esters of 2,4-Dand 2,4,5-T)
- Halts Plus With Dandelion Control (S-(0,0-diisopropyl phosphorodithioate)ester of N-(2-mercaptoethyl) benzenesulphonamide + 2,4-D + 2(2-methyl-4-chlorophenoxy)propionicacid)
- Hedonal (isooctyl ester of 2,4-D)
- Hedonal (The Herbicide) (2,4-D, form unspecified)
- Hedonol (2,4-D, form unspecified)
- Henry Field's Lawn Weed Killer (isooctyl ester of 2,4-D)
- Herbate Ester 128 (2,4-D, form unspecified)
- Herbate Ester 80 (isooctyl ester of 2,4-D)
- Home Use Weed Killer (alkanolamine salts [of the ethanol andisopropanol series] of 2,4-D)
- Hormit (sodium salt of 2,4-D)
- Hormoslyr 64 (2,4-D + 2,4,5-T)
- Hub States Selective Weed and Brush Killer Amine Formula 400(diethylethanolamine salts of 2,4-D and 2,4,5-T)

- Instemul DA 120 Concentrate (oleyl amine salt of 2,4-D)
- Instemul DA 40 (oleyl amine salt of 2,4-D)
- Instemul DTA 22 (oleyl amine salt of 2,4-D + oleyllinoleylamine salt of 2,4,5-T)
- Instemul DTA 66 Concentrate (oleyl amine salt of 2,4-D + oleyllinoleylamine salt of 2,4,5-T)
- Isooctyl 2,4-dichlorophenoxyacetate (isooctyl ester of 2,4-D)
- Isooctyl alcohol, (2,4-dichlorophenoxy) acetate (isooctylester of 2,4-D)
- Jet-Weed Killer Power Pellets (2,4-D + silvex [2-(2,4,5-trichlorophenoxy)propionicacid])
- Kansel (2,4-D + dicamba [2-methoxy-3,6-dichlorobenzoic acid])
- Kilbrush 8-16 Ester (butyl esters of 2,4-D and 2,4,5-T)
- Knoxweed (eptam [S-ethyl dipropylthiocarbamate] + 10 E 2,4-D)
- Kro-Foot-Kil (dimethylamine salts of 2,4-D + phenylmercuricacetate)
- Krotilin (chlorocrotyl ester of 2,4-D)
- Krotiline (chlorocrotyl ester of 2,4-D)
- Lawn Weed Killer (triethanolamine salt of 2,4-D)
- Lawn Weed-Rhap (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Lawn-Keep (2,4-D, form unspecified)
- Lebanon Deluxe Weed and Feed with 2,4-D and Banvel D (dimethylaminesalts of 2,4-D, dicamba [3,6-dichloro-2-methoxy-benzoic acid]and related acids)
- Lebanon Weedeth (dimethylamine salt of 2,4-D, dimethylaminesalt of dicamba [3,6-dichloro-2-methoxy-benzoic acid] and relatedacid)
- Limit (chloro-N,N-diallylacetamide + 2,4-D)
- Line Rider 22 (butyl esters of 2,4-D and 2,4,5-T)
- Line Rider Invert D/T (isooctyl esters of 2,4-D and 2,4,5-T)
- Line Rider Invert D/T Concentrate (isooctyl esters of 2,4-Dand 2,4,5-T)
- Line Rider LV-21 (isooctyl esters of 2,4-D and 2,4,5-T)
- Line Rider LV-4D (isooctyl ester of 2,4-D)
- Line Rider LV-6D (isooctyl ester of 2,4-D)
- Liqweedate (2-methoxy-4,6-bis(isopropylamine)-s-triazine

+isooctyl esters of 2,4-D and 2,4,5-T)
- Liqweedate-2 (2-methoxy-4,6-bis(isopropylamine)-s-triazine+ isooctyl ester of 2,4-D)
- Lironox (butyl ester of 2,4-D)
- Lithate 2,4-D (lithium salt of 2,4-D)
- Lo-Estasol (butoxyethanol ester of 2,4-D)
- Machete (alkanolamine salts [of the ethanol and isopropanolseries] of 2,4-D)
- Macondray (2,4-D, form unspecified)
- Manco Kill-Weed (dimethylamine salt of 2,4-D)
- Manco Super Kill-Weed (isooctyl esters of 2,4-D and 2,4,5-T)
- Mecopar (diethanolamine salts of MCPP [2-(2-methyl-4-chlorophenoxy)propionicacid] and 2,4-D)
- MFA 40% Butyl Ester Weed Killer (butyl ester of 2,4-D)
- MFA LO-V Super Brush Killer (octyl esters of 2,4-D and 2,4,5-T)
- MFA LO-V Super Brush Killer (octyl esters of 2,4-D and 2,4,5-T)
- MFA No. 4 Weed Killer (butyl ester of 2,4-D)
- MFA No. 6 Weed Killer (butyl ester of 2,4-D)
- MFA Super Brush Kill (butyl esters of 2,4-D and 2,4,5-T)
- Miller's 4# Ester (butyl ester of 2,4-D)
- Miller's 6# Ester (butyl ester of 2,4-D)
- Miller's Lo Vol 4# 2,4-D (isooctyl ester of 2,4-D)
- Milorganite Plus 2,4-D (2,4-D, form unspecified)
- Miracle (2,4-D, form unspecified)
- Monosan (2,4-D, form unspecified)
- Monsanto 2,4-D 2,4,5-T Amine brush Killer (dimethylamine saltof 2,4-D + triethylamine salt of 2,4,5-T)
- Monsanto 2,4-D 2,4,5-T Amine Brush Killer (triethylamine saltsof 2,4-D and 2,4,5-T)
- Monsanto 2,4-D 2,4,5-T Butyl Ester Brush Killer
- Monsanto 2,4-D 2,4,5-T Low Volatile Ester Brush Killer (isooctylesters of 2,4-D and 2,4,5-T)
- Monsanto 2,4-D Amine (dimethylamine salt of 2,4-D)
- Monsanto 2,4-D Butyl Ester

- Monsanto 2,4-D Butyl Ester Concentrate
- Monsanto 2,4-D Granular (isooctyl ester of 2,4-D)
- Monsanto 2,4-D Isopropyl Ester
- Monsanto 2,4-D Low Volatile Ester (isooctyl ester of 2,4-D)
- Morselect (dimethylamine salt of 2,4-D)
- Moxone (2,4-D, form unspecified)
- Munichem Muni-Kill (mixed aliphatic hydrocarbons + isooctylester of 2,4-D + bromacil [5-bromo-3-sec-butyl-6-methyluracil]+ pentachlorophenol + other chlorophenols)
- Naco LV-4D Weed Killer (isooctyl ester of 2,4-D)
- Nalkil Weed Killer 400 Liquid (isooctyl ester of 2,4-D + bromacil[5-bromo-3-sec-butyl-6-methyluracil] + pentachlorophenol + otherchlorophenols)
- Navy Brand WKB-15 (isooctyl esters of 2,4-D and 2,4,5-T)
- Navy Brand WKB-28 (butoxyethoxypropanol esters of 2,4-D and2,4,5-T)
- Niagara 2,4-D Weed Killer (Amine Form) (ethanol and propanolaminesalts of 2,4-D)
- Niagara Brush-Killer (Ester Form) (butoxyethanol esters of2,4-D and 2,4,5-T)
- Niagara Commercial Brush Killer (isooctyl esters of 2,4-Dand 2,4,5-T)
- Niagara Estasol (isopropyl ester of 2,4-D)
- NSC 423 (2,4-D, form unspecified)
- Nutro Dandelion and Turf Weed Killer (2,4-D + dicamba [3,6-dichloro-2-methoxybenzoicacid])
- Nutro Turf Weed Killer (ethylhexyl ester of 2,4-D and silvex[2-(2,4,5-trichlorophenoxy) propionic acid])
- Nutro Weed Bomb (2,4-D + MCPP [2-methyl-4-chloro-phenoxy)propionicacid])
- Olin Butyl Ester 22 Brush Killer (butyl esters of 2,4-D and2,4,5-T)
- Olin Butyl Ester D267 Weed Killer (butyl ester of 2,4-D)
- Olin Butyl Ester D4 Weed Killer (butyl ester of 2,4-D)
- Olin Butyl Ester D6 Weed Killer (butyl ester of 2,4-D)
- Olin Isopropyl Ester D334 Weed Killer (isopropyl ester of2,4-D)

- Olin LV Ester 22 Brush Killer (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Olin LV Ester D4 Weed Killer (2-ethylhexyl ester of 2,4-D)
- Ortho 2,4-D LV Ester 4 (isooctyl ester of 2,4-D)
- Ortho Brush Killer (isooctyl esters of 2,4-D and 2,4,5-T)
- Pacific Cooperatives P 2,4-D Amine Weed Killer (dimethylaminesalt of 2,4-D)
- Parsons 2,4-D Weed Killer (dimethylamine salt of 2,4-D)
- Parsons 2,4-D Weed Killer Butyl Ester
- Parsons 2,4-D Weed Killer Isopropyl Ester
- Parsons 2,4-D Weed Killer No. 40 (dimethylamine salt of 2,4-D)
- Parsons Corn-Tal Weed Killer (butyl, isopropyl and isooctylesters of 2,4-D)
- Parsons Poison Ivy and Brush Killer No. 2 (isooctyl estersof 2,4-D and 2,4,5-T)
- Patterson's Hi-Test Butyl Ester 2,4-D Weed Killer
- Patterson's Lawn Weed Killer (isooctyl esters of 2,4-D and2,4,5-T)
- Patterson's Super Brush Killer (butyl esters of 2,4-D and2,4,5-T)
- Patterson's Super Brush Killer Low Volatile (isooctyl estersof 2,4-D and 2,4,5-T)
- Pax Action Weed'N Feed 18-4-4 (alkanolamine salt of 2,4-D+ dimethylamine salt of dicamba [3,6-dichloro-2-methoxybenzoicacid] + nitrogen + phosphoric acid + soluble potash)
- Pax Total For Lawns 10-6-4 (N-Oleyl 1,3-propylenediamine saltof 2,4-D + dimethylamine salt of 2-(2-methyl-4-chlorophenoxy)propionicacid + dimethyl ester of tetrachloroterephthalic acid + disodiummethanearsonate hexahydrate + heptachlor + related c
- Pennamine (2,4-D, form unspecified)
- Pennamine D (heptylamine salt of 2,4-D)
- Phenox (2,4-D, form unspecified)
- Pielik (2,4-D, form unspecified)
- Pielik E (sodium salt of 2,4-D)
- Pill Kill Kartridges for Dandelions and Broadleaf Weeds (2,4-D+

silvex [2-(2,4,5-trichlorophenoxy)propionic acid])
- PL Devastate Non-Selective Weed Killer (isooctyl ester of2,4-D + bromacil [5-bromo-3-sec-butyl-6-methyl-uracil] + pentachlorophenol+ other chlorophenols)
- PL Liqui-date (isooctyl esters of 2,4-D, 2,4,5-T and silvex[2-(2,4,5-trichlorophenoxy) propionic acid])
- Planotox (butoxyethyl ester of 2,4-D)
- Plantgard (2,4-D, form unpecified)
- Plus 2 for Grass (2,4-D + 2-(2-methyl-4-chlorophenoxy) propionicacid)
- Pratt Lawn Weed Killer (2,4-D + 2,4,5-T)
- Pratt's Crabgrass and Broadleaf Weed Killer (octyl ammoniummethyl arsonate + 2,4-D) )
- Proturf Broad Spectrum Weedicide (2,4-D + dicamba [3,6-dichloro-2-methoxybenzoicacid])
- Proturf Broad Spectrum Weedicide II (2,4-D + 2-(2-methyl-4-chlorophenoxy)propionicacid)
- Proturf Fertilizer Plus Dicot Weed Control (2,4-D + dicamba[3,6-dichloro-2-methoxybenzoic acid])
- Proturf Fertilizer Plus Dicot Weed Control II (2,4-D + 2-(2-methyl-4-chlorophenoxy)propionicacid)
- R-H Weed Rhap 20 (2,4-D)
- Real-Kill Spot Weed Killer (amine salts of 2,4-D, dicamba[3,6-dichloro-2-methoxybenzoic acid] and MCPP [2-(2-methyl-4-chlorophenoxy)propionic acid])
- Real-Kill Spot Weed Killer (amine salts of 2,4-D, dicamba[3,6-dichloro-2-methoxybenzoic acid] and 2,4,5-T)
- Reasor-Hill Brush Rhap (2,4-D + 2,4,5-T)
- Red Devil Dry Weed Killer (2,4-D)
- Rhodia 2,4-D Butyl Ester 6L
- Rhodia 2,4-D Low Volatile Ester 4L (isooctyl ester of 2,4-D)
- Rhodia Low Volatile Brush Killer No. 2 (2,4-D + 2,4,5-T)
- Rid-O-Weed (isopropyl and diisopropanol amine salts of 2,4-D)
- Robot Gardener Weed and Crabgrass Killer (potassium cyanate+ 2,4-D)
- Roundup Granular (2-chloro-N-isopropylacetanilide +

isooctylester of 2,4-D)
- Roundup Wettable Powder (2-chloro-N-isopropylacetanilide +2,4-D)
- S.I.R.-Ester (isooctyl esters of 2,4-D and 2,4,5-T)
- Salvik (2,4-D, form unspecified)
- Salvo (2,4-D, form unspecified)
- Science Lawn Weed-Killer (isooctyl esters of 2,4-D + 2,4,5-T)
- Scott's 4-XD Weed Control (2,4-D)
- Security Lawn Weed Killer (N-oleyl 1,3-propylenediamine saltof 2,4-D)
- Shell 40 (butyl ester of 2,4-D)
- Sodium 2,4-D
- Sodium 2,4-dichlorophenoxyacetate
- Spontox (2,4-D, or 2,4,5-T, forms unspecified)
- Spritz-Hormit (sodium salt of 2,4-D)
- Stull's Low Volatile Brush Killer No. 4 (isooctyl esters of2,4-D and 2,4,5-T)
- Stull's Low Volatile Weed Killer (isooctyl ester of 2,4-D)
- Stull's Stu-Ester Low Volatile (isooctyl ester of 2,4,5-T)
- Super Crab-E-Rad + 2 (dodecylammonium methanearsonate + octylammoniummethanearsonate + octylammonium salt of 2,4-D)
- Super D Weedone (diethylamine salts of 2,4-D and dicamba [3,6-dichloro-2-methoxybenzoicacid])
- Super Dal-E-Rad + 2 (dodecylammonium methanearsonate + octylammoniummethanearsonate + octylammonium salt of 2,4-D)
- Sure Death 2,4-D Amine Weed Killer (dimethylamine salt of2,4-D)
- Sure Death 40% Butyl Ester Type Weedkiller (butyl ester of2,4-D)
- Sure Death Lawn Weed Killer (2-ethyl 4-methylpentanol and2-ethylhexanol esters of 2,4-D and 2,4,5-trichlorophenoxypropionicacid)
- Sure Death No. 4 Butyl Ester Weed Killer (butyl ester of 2,4-D)
- Sure Death No. 6 Butyl Ester Weed Killer (butyl ester of 2,4-D)

- Sure Death No. 6-D Low Vol 2,4-D (2-ethyl 4 methylpentanoland 2-ethylhexanol esters of 2,4-D)
- Sure-Death Low-Vol 2,4-D #4 (2-ethylpentanol and 2-ethylhexanolesters of 2,4-D)
- Swift's Gold Bear 2-2 Brush Kill (isooctyl esters of 2,4-Dand 2,4,5-T)
- Swift's Gold Bear 40 (triethylamine salt of 2,4-D)
- Swift's Gold Bear 44 Ester (isopropyl ester of 2,4-D)
- Swift's Gold Bear Woody Plant Control (isooctyl esters of2,4-D and 2,4,5-T)
- T-H Ded-Weed ME-6 (butyl ester of 2, 4-D)
- T-H Ded-Weed ME-9 (butyl ester of 2,4-D)
- Techne 2,4-D Amine Weed Killer (dimethylamine salt of 2,4-D)
- Techne 40% Butyl Ester type Weed Killer (butyl ester of 2,4-D)
- Techne Butyl Ester Weed Killer No.4 (butyl ester of 2,4-D)
- Techne Butyl Ester Weed Killer No.6 (butyl ester of 2,4-D)
- Techne Low-Vol 2,4-D No.4 (2-ethylpentanol and 2-ethylhexanolesters of 2,4-D)
- Termicide 5-15 (triethanolamine salt of 2,4-D + triethanolaminemethanearsonate)
- The Andersons Broadleaf Weed Killer (dimethylamine salt of2,4-D + isooctyl ester of silvex [2-(2,4,5-trichlorophenoxy)propionicacid])
- The Andersons Weed and Feed (dimethylamine salt of 2,4-D +isooctyl ester of silvex [2-(2,4,5-trichlorophenoxy)propionicacid])
- The Crop Rider (butyl ester of 2,4-D)
- The Line Rider (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Thorokil (2,4-D + bromacil [5-bromo-3-sec-butyl-6-methyluracil]+ pentachlorophenol)
- Tobacco States Brand Ester 210 (isooctyl ester of 2,4-D)
- Tobacco States Brand Ester 410 Concentrate (2-ethylhexyl esterof 2,4-D)
- Tobacco States Brand Ester Brush Killer 2-2 (butyl estersof 2,4-D and 2,4,5-T)
- Tobacco States Brand Low-Vol Brush Killer 2-20 (isooctyl

estersof 2,4-D and 2,4,5-T)
- Tordon 101 Mixture (triisopropanol amine salts of 2,4-D and4-amino-3,5,6-trichloropicolinic acid)
- Transamine OA-1.5D-1.5T (N,N-dimethyloleyllinoleylamine saltsof 2,4-D and 2,4,5-T)
- Transamine OA-3D (N,N-dimethyloleyllinoleylamine salt of 2,4-D)
- Tributon (2,4-D + 2,4,5-T, forms unspecified)
- Triple Tonic (dimethylamine salts and propylene glycol butylether esters of 2,4-D + nitrogen + phosphoric acid + soluble potash)
- Turf Builder Plus 2 (2,4-D + 2-(2-methyl-4-chlorophenoxy)-propionicacid
- U 46 (2,4-D + 2,4,5-T, forms unspecified)
- U 46 DP (2,4-D, form unspecified)
- U 46 Spezial (2,4-D + 2,4,5-T, forms unspecified)
- U-5043 (2,4-D, form unspecified)
- Unico 2,4-D Ester Weed Killer (butyl ester of 2,4-D)
- Unico 2,4-D Lo-V Ester Weed Killer (2-ethylhexyl ester of2,4-D)
- Unico Brush Killer (butyl esters of 2,4-D and 2,4,5-T)
- Unico Brush Killer A (butyl ester of 2,4-D + isooctyl esterof 2,4,5-T)
- Unico Lo-V Brush Killer (2-ethylhexyl esters of 2,4-D and2,4,5-T)
- Unico Turf Treeter Lawn Weed Killer (dimethylamine salts of2,4-D and dicamba [3,6-dichloro-2-methoxy-benzoic acid])
- Utility Brush Killer No. 2 (isooctyl esters of 2,4-D and 2,4,5-T)
- Vaughan's Liquid K.O. (octyl ammonium salt of 2,4-D + octyland dodecyl ammonium methylarsonate)
- Veg-I-Kill (isooctyl ester of 2,4-D + bromacyl [5-bromo-3-sec-butyl-6-methyluracyl]+ pentachlorophenol + others chlorophenols)
- Veon BK (dimethylamine salts of 2,4-D and 2,4,5-T)
- Vergemaster (2,4-D, form unspecified)
- Verton 2-D (2,4,-D, form unspecified)
- Verton 2D (propylene glycol butyl ether ester of 2,4-D)

- Verton 4D (propylene glycol butyl ether ester of 2,4-D)
- Verton CE (propylene glycol butyl ether esters of 2,4-D and2,4,5-T)
- Verton CE Herbicide (propylene glycol butyl ether esters of2,4-D and 2,4,5-T)
- Verton D (2,4-D, form unspecified)
- Vi-Par (diethanolamine salts of 2-(2-methyl-4-chlorophenoxy)-propionicacid and 2,4-D)
- Vidon 638 (2,4-D, unspecified)
- Visko-Rhap 2,4-D Low Volatile Ester 4L (isooctyl ester of2,4-D)
- Visko-Rhap A-1D (oleylamine salt of 2,4-D)
- Visko-Rhap A-3D (N,N-dimethyl oleyllinoleylamine salt of 24-D)
- Visko-Rhap Low Drift Herbicides (2,4-D, form unspecified)
- Visko-Rhap Low Volatile 1.5D-1.5T (2-ethylhexyl esters of2,4-D and 2,4,5-T)
- Visko-Rhap Low Volatile 1D-1T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Visko-Rhap Low Volatile 4L (2,4-D, form unspecified)
- Visko-Rhap Low Volatile Ester 1D-1T (2-ethylhexyl esters of2,4-D and 2,4,5-T)
- Visko-Rhap Low Volatile Ester 2D (2-ethylhexyl ester of 2,4-D)
- Visko-Rhap Oil-Soluble Amine A-3D (N,N-dimethyloleyllinoleylaminesalt of 2,4-D)
- Wasco Brush Killer (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Weed and Brush Off Amine Formula 400 (diethylethanolaminesalts of 2,4-D and 2,4,5-T)
- Weed Broom (anhydrous disodium methanearsonate + lithium saltof bromacil [5-bromo-3-sec-butyl-6-methyluracil] + anhydrous sodiumsalt of 2,4-D)
- Weed Killer 646 (butyl ester of 2,4-D)
- Weed-Ag-Bar (2,4-D, form unspecified)
- Weed-B-Gon (2,4-D, form unspecified)
- Weed-Ban (amines [form unspecified] of 2,4-D and dicamba [3,6-dichloro-2-methoxybenzoicacid])
- Weed-Bane Amine (2,4-D, form unspecified)

- Weed-Bane Ester (2,4-D, form unspecified)
- Weed-Nix Lawn Food with 2,4-D and Banvel D (dimethylaminesalts of 2,4-D, dicamba [3,6-dichloro-2-methoxy-benzoic acid]and related acids)
- Weed-No-More (2,4-D ester, form unspecified)
- Weed-Out Lawn Weed Control with 2,4-D and Silvex (dimethylaminesalt of 2,4-D + isooctyl ester of silvex [2-(2,4,5-trichlorophenoxy)propionicacid])
- Weed-Rhap (2,4-D, form unspecified)
- Weed-Rhap A-4 (2,4-D)
- Weed-Rhap A-4D (dimethylamine salt of 2,4-D)
- Weed-Rhap B-2.67D (butyl ester of 2,4-D)
- Weed-Rhap B-266 (2,4-D)
- Weed-Rhap B-4 (2,4-D)
- Weed-Rhap B-4D (butyl ester of 2,4-D)
- Weed-Rhap B-6D (butyl ester of 2,4-D)
- Weed-Rhap I-3.34 (2,4-D)
- Weed-Rhap I-3.34D (isopropyl ester of 2,4-D)
- Weed-Rhap Low Volatile 4D (2-ethylhexyl ester of 2,4-D)
- Weed-Rhap Low Volatile 5D (2-ethylhexyl ester of 2,4-D)
- Weed-Rhap Low Volatile F4D For Mixing with Fertilizer (2-ethylhexylester of 2,4-D)
- Weed-Rhap Low Volatile-Granular D (2-ethylhexyl ester of 2,4-D)
- Weed-Rhap LV-4-0 (2,4-D)
- Weed-Rhap LV-4D (butoxyethanol ester of 2,4-D)
- Weedar (2,4-D or 2,4,5-T, forms unspecified)
- Weedar 64 (dimethylamine salt of 2,4-D)
- Weedar Amine Brush Killer (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Weedez Wonder Bar (triethylamine salt of 2,4-D)
- Weedone (2,4-D or 2,4,5-T, forms unspecified)
- Weedone 48 (2,4-D, form unspecified)
- Weedone 638 (2,4-D)
- Weedone 638 (butoxyethanol ester of 2,4-D)
- Weedone Aero-Concentrate 96 (butyl ester of 2,4-D)

- Weedone Aero-Concentrate E (butyl ester of 2,4-D)
- Weedone Brush Killer 32 (butoxyethanol esters of 2,4-D and2,4,5-T)
- Weedone Brush Killer 64 (butoxyethanol esters of 2,4-D and2,4,5-T)
- Weedone Brush Killer 977 (butoxyethanol esters of 2,4-D and2,4,5-T)
- Weedone Brush Killer 977 Concentrate (butoxyethanol estersof 2,4-D and 2,4,5-T)
- Weedone Concentrate 48 (ethyl ester of 2,4-D)
- Weedone Industrial Brush Killer (butoxyethanol esters of 2,4-Dand 2,4,5-T)
- Weedone LV-6 (butoxyethanol ester of 2,4-D)
- Weedone LV4 (butoxyethanol ester of 2,4-D)
- Weedone-170 (2,4-D, form unspecified)
- Woodbury Pre-Merge Granular 20 2,4-D (2-ethylhexanol esterof 2,4-D)
- Woodbury Woodkill Ester Conc. (butyl esters of 2,4-D and 2,4,5-T)
- Woodkill Ester Concentrate (butyl esters of 2,4-D and 2,4,5-T)
- Zehrung 2,4-D Selective Amine Weed Killer (dimethylamine saltof 2,4-D)
- Zehrung Weed Blitz (triethanolamine salts of 2,4-D and 2,4,5-T)
- Zep R-61 Weed Killer (dimethylamine salts of 2,4-D and 2,4,5-T)

**Synonyms for 2,4,5-T and esters**

- Abco Improved W.K-245 (isooctyl ester of 2,4,5-T)
- Abco W.K-DT 133 (isooctyl esters of 2,4-D and 2,4,5-T)
- Abco WKS-65 Brush Killer (isooctyl esters of 2,4-D, 2,4,5-Tand silvex [2-(2,4,5-trichloro-phenoxy)propionic acid])
- Acetic acid, (2,4,5-trichlorophenoxy)-
- Acide trichloro-2,4,5 phenoxyacetique
- Acido(2,4,5-tricloro-fenossi)-acetico
- Acme Poison Ivy Killer (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)

- Acme Weed-No-More Spotter (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Agent Orange (n-butyl esters of 2,4-D and 2,4,5-T)
- Agent Purple (n-butyl esters of 2,4-D and 2,4,5-T + isobutylester of 2,4,5-T)
- Allied Chemical Low Volatile 1-1/3-2/3 Brush Killer (2,4-D+ 2,4,5-T + isooctyl esters of 2,4-D and 2,4,5-T)
- Amchem 2,4,5-T Low Volatile Ester Brush Killer (isooctyl esterof 2,4,5-T)
- Amchem 2,4-D 2,4,5-T Low Volatile Ester Brush Killer (isooctylesters of 2,4-D and 2,4,5-T)
- Amchem 6DT. Low Volatile Ester Brush Killer (isooctyl estersof 2,4-D and 2,4,5-T)
- Amchem 6T Low Volatile Ester Brush Killer (isooctyl esterof 2,4,5-T)
- Amchem Amine 2,4,5-T for Rice (triethylamine salt of 2,4,5-T)
- Amchem Emulsamine Brush Killer (alkyl C_1_2 + C_1_4 aminesalts of 2,4-D and 2,4,5-T)
- Amchem Isooctyl-DT (isooctyl esters of 2,4-D and 2,4,5-T)
- Amchem Isooctyl-DT6 (isooctyl esters of 2,4-D and 2,4,5-T)
- Amchem Isooctyl-T (isooctyl ester of 2,4,5-T)
- Amchem Isooctyl-T6 (isooctyl ester of 2,4,5-T)
- Amine 4T (2,4,5-T, form unspecified)
- Amine 4T2 (triethylamine salt of 2,4,5-T)
- Amoco 2,4,5-T Amine (triethylamine salt of 2,4,5-T)
- Amoco 2,4,5-T LV Ester (isooctyl ester of 2,4,5-T)
- Amoco Brush Killer (isooctyl esters of 2,4-D and 2,4,5-T)
- Antrol 2,4-D and 2,4,5-T Weed and Brush Killer (alkalonaminesalts [of the ethanol and isopropanol series] of 2,4-D + triethylaminesalt of 2,4,5-T)
- Associated Sales Low Volatile 2,4,5-T Brush Killer (isooctylester of 2,4,5-T)
- Balcom's Brush Killer Number 4 (isooctyl ester of 2,4,5-T)
- Balcom's G-K-20 (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Balcom's T-D Special Weed Killer (isooctyl esters of 2,4-Dand 2,4,5-T)

- Breck's Lawn Weed Killer (butoxyethoxypropanol esters of 2,4-Dand 2,4,5-T)
- Brulin's Brush Killer (butyl esters of 2,4-D and 2,4,5-T)
- Brush Killer 50-50 (butyl esters of 2,4-D and 2,4,5-T)
- Brush Killer T (butyl esters of 2,4,5-T)
- Brush Killer TX (isooctyl esters of 2,4,5-T)
- Brush Killer X (isooctyl esters of 2,4-D and 2,4,5-T)
- Brush-Blitz (isooctyl ester of 2,4,5-T)
- Brush-O-Cide (isooctyl esters of 2,4-D + 2,4,5-T)
- Brush-Off 445 Low Volatile Brush Killer (2,4,5-T, form unspecified)
- Brush-Off No. 438 Conc. 2-2 LV Brush Killer (isooctyl estersof 2,4-D and 2,4,5-T)
- Brush-Rhap A-2D-2T (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Brush-Rhap A-4T (triethylamine salt of 2,4,5-T)
- Brush-Rhap Amine A-2D-2T (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Brush-Rhap B-1.33D - 0.67T (butyl esters of 2,4-D and 2,4,5-T)
- Brush-Rhap B-2-2 (2,4-D + 2,4,5-T)
- Brush-Rhap B-2D-2T (butyl esters of 2,4-D and 2,4,5-T)
- Brush-Rhap B-4 (2,4,5-T)
- Brush-Rhap B-4T (butyl ester of 2,4,5-T)
- Brush-Rhap Injection Fluid Low Volatile 2D-2T (2-ethylhexylesters of 2,4-D and 2,4,5-T)
- Brush-Rhap Injection Fluid Low Volatile 3D-3T (2-ethylhexylesters of 2,4-D and 2,4,5-T)
- Brush-Rhap Injection Fluid Low Volatile 4T (2-ethylhexyl esterof 2,4,5-T)
- Brush-Rhap Injection Fluid-B (2,4,5-T)
- Brush-Rhap Low Volatile 2D-2T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Brush-Rhap Low volatile 3D-2T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Brush-Rhap Low Volatile 3D-3T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)

- Brush-Rhap Low Volatile 4T (2-ethylhexyl ester of 2,4,5-T)
- Brush-Rhap Low Volatile 5T (2-ethylhexyl ester of 2,4,5-T)
- Brush-Rhap Low Volatile 6T (2-ethylhexyl ester of 2,4,5-T)
- Brush-Rhap LV 2D-2T (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Brush-Rhap LV Injection Fluid-0 (2,4,5-T)
- Brush-Rhap LV-2-2-0 (2,4-D + 2,4,5-T)
- Brush-Rhap LV-4-0 (2,4,5-T)
- Brush-Rhap LV-40 (isooctyl esters of 2,4,5-T)
- Brush-Rhap LV-4T (2-ethylhexyl ester of 2,4,5-T)
- Brush-Rhap LV-6T (2-ethylhexyl ester of 2,4,5-T)
- Brush-Rhap LV-OXY-4T (2,4,5-T, form unspecified)
- Brush-Rhap OXY-4T (butoxyethanol ester of 2,4,5-T)
- Butyl 2,4,5-trichlorophenoxyacetate
- Certified C-300 Selective Weed Killer (isooctyl esters of2,4-D and 2,4,5-T)
- Chem-Pels Plus (isooctyl esters of 2,4-D and 2,4,5-T)
- Chem-Weed 2,4,5-T (butoxyethoxypropanol ester of 2,4,5-T +2,4,5-T)
- Chemform Butoxy Brush Killer (butoxyethoxypropanol estersof 2,4-D and 2,4,5-T)
- Chempar Low Volatile Brush Killer No. 2 (2,4,5-T + 2,4-D)
- Chipco Turf Herbicide "D" and "T" (dimethylaminesalt of 2,4-D + triethylamine salt of 2,4,5-T)
- Chipco Turf Herbicide "T" (triethylamine salt of2,4,5-T)
- Chipman 2,4,5-T 76 (L.V.) (2,4,5-T, form unspecified)
- Chipman 2,4,5-T Amine 4L (triethylamine salt of 2,4,5-T)
- Chipman 2,4,5-T Low Volatile Ester 4L (isooctyl ester of 2,4,5-T)
- Chipman 2,4,5-T Low Volatile Ester 6L (isooctyl ester of 2,4,5-T)
- Chipman Amine Brush Killer (triethylamine salts of 2,4-D and2,4,5-T)
- Chipman Brush Killer 128 (2,4-D + 2,4,5-T, forms unspecified)
- Chipman Brush Killer 128 L.V. (2,4-D + 2,4,5-T, forms unspecified)
- Chipman Brush Killer 128 Regular (2,4-D + 2,4,5-T, forms

unspecified)
- Chipman Brush Killer 76 (isooctyl esters of 2,4-D and 2,4,5-T)
- Chipman Low Volatile Brush Killer No. 2 (isooctyl esters of2,4-D and 2,4,5-T)
- Chipman Low Volatile Brush Killer No. 3 (isooctyl esters of2,4-D and 2,4,5-T)
- Chipman LVE-4L (isooctyl esters of 2,4,5-T)
- Chipman LVE-6L (isooctyl esters of 2,4,5-T)
- Clover Killer (butoxyethanol ester of 2,4,5-T)
- Commercial Brush Killer (isooctyl esters of 2,4-D and 2,4,5-T)
- Crop Rider 248 (2-ethylhexyl ester of 2,4-D)
- Crop Rider Amine 4T (triethylamine salt of 2,4,5-T)
- Crop Rider Amine 4T-2 (triethylamine salt of 2,4,5-T)
- Cross Country Poison Ivy Killer (butoxyethoxypropanol estersof 2,4-D and 2,4,5-T)
- Dacamine (N-oleyl 1,3-propylenediamine salts of 2,4-D and2,4,5-T)
- Dacamine 1D/1T (N-oleyl 1,3-propylenediamine salts of 2,4-Dand 2,4,5-T)
- Dacamine 2D/2T (N-oleyl 1,3-propylenediamine salts of 2,4-Dand 2,4,5-T)
- Dacamine 4T (N-oleyl 1,3-propylenediamine salt of 2,4,5-T)
- Dacamine T (N-oleyl 1,3-propylenediamine salt of 2,4,5-T)
- De Witt S-77 Weed Killer (dimethylamine salts of 2,4-D and2,4,5-T)
- De-Pester Ded-Weed 50-50 Brush-Kil (2,4,5-T)
- De-Pester Ded-Weed for Lawns (2,4-D + 2,4,5-T + Kerosene)
- De-Pester Ded-Weed LV-6 (2,4,5-T)
- De-Pester Ded-Weed LV-9 (2,4,5-T)
- De-Pester Ded-Weed T6 Brush Kil (amyl ester of 2,4,5-T)
- Ded-weed Brush Killer (2,4,5-T, form unspecified)
- Ded-weed for Lawns, New Improved (isooctyl esters of 2,4-Dand 2,4,5-T)
- Ded-weed LV-6 Brush Kil (2,4,5-T, form unspecified)
- Destruxol Weed Killer "D" (isooctyl esters of 2,4-Dand 2,4,5-T)
- Diamond Alkali Chemicals 2-2 2-Ethyl Hexyl Brush Killer (2-

ethylhexylesters of 2,4-D and 2,4,5-T)
- Diamond Alkali Chemicals Technical 2-Ethyl Hexyl-T (2-ethylhexylester of 2,4,5-T)
- Diamond Alkali Chemicals The Line Rider (2-ethylhexyl estersof 2,4-D and 2,4,5-T)
- Diamond Shamrock Amine 2D/2T (dimethylamine salts of 2,4-Dand 2,4,5-T)
- Diamond Shamrock Amine 4T (triethylamine salt of 2,4,5-T)
- Diamond Shamrock Dormant Cane Concentrate LV-6T-OS (isooctylester of 2,4,5-T)
- Diamond Shamrock Dormant Cane LV 3D/3T-OS (isooctyl estersof 2,4-D and 2,4,5-T)
- Diamond Shamrock LO-VOL 2D/2T (isooctyl esters of 2,4-D and2,4,5-T)
- Diamond Shamrock LO-VOL 4T (isooctyl ester of 2,4,5-T)
- Diamond Shamrock LO-VOL 6T (isooctyl ester of 2,4,5-T)
- Dinoxol (butoxyethanol esters of 2,4-D and 2,4,5-T)
- Dinoxol 64 (butoxyethanol esters of 2,4-D and 2,4,5-T)
- Dinoxol Super-6 (butoxyethanol esters of 2,4-D and 2,4,5-T)
- Dormant Cane Concentrate (2-ethylhexyl ester of 2,4,5-T)
- Dow 2,4,5-T Amine Weed Killer (triethylamine salt of 2,4,5-T)
- Dow Brush Killer 50-50 (butyl esters of 2,4-D and 2,4,5-T)
- Dow Brush Killer TX (butoxypropyl esters of 2,4,5-T)
- Dow Brush Killer X (isooctyl esters of 2,4-D and 2,4,5-T)
- Emulsamine 2,4,5-T (dodecyl- and tetradecylamine salts of2,4,5-T)
- Emulsamine Brush Killer (dodecyl- and tetradecylamine saltsof 2,4-D and 2,4,5-T)
- Emulsavert 100 (2,4-D + 2,4,5-T + N,N-dimethyloleylamine saltsof 2,4-D and 2,4,5-T)
- Emulsavert 248 (2,4-D + 2,4,5-T + N,N-dimethyloleylamine saltsof 2,4-D and 2,4,5-T)
- Envert-DT (butoxyethanol esters of 2,4-D and 2,4,5-T)
- Envert-T (butoxyethanol ester of 2,4,5-T)
- Estercide T-2 (2,4,5-T, form unspecified)
- Estercide T-245 (2,4,5-T, form unspecified)

- Esteron 245 (old formulation) (isopropyl and mixed amyl estersof 2,4,5-T)
- Esteron 245 (propylene and polypropylene butyl ether estersof 2,4,5-T)
- Esteron 245 Concentrate (propylene glycol butyl ether estersof 2,4,5-T)
- Esteron 245 Herbicide (propylene and polypropylene glycolbutyl ether esters of 2,4,5-T)
- Esteron 245 O.S. (propylene glycol butyl ether esters of 2,4,5-T)
- Esteron Brush Killer (old formulation) (isopropyl esters of2,4-D and 2,4,5-T)
- Esteron Brush Killer (propylene glycol butyl ether estersof 2,4-D and 2,4,5-T)
- Esteron Brush Killer O.B. (propylene glycol butyl ether estersof 2,4-D and 2,4,5-T)
- Feed No Weed (triethylamine salts of 2,4-D and 2,4,5-T)
- Felco 2,4,5-T Brush Killer (butyl ester of 2,4,5-T)
- Felco Super Brush Killer (butyl esters of 2,4-D and 2,4,5-T)
- Fence Rider "45" (isooctyl esters of 2,4-D and 2,4,5-T)
- Fence Rider 22 (butyl esters of 2,4-D and 2,4,5-T)
- Fence Rider 3.34-T Brush Killer (isopropyl ester of 2,4,5-T)
- Fence Rider 4T Brush Killer (butyl ester of 2,4,5-T)
- Fence Rider 6T Brush Killer (butyl ester of 2,4,5-T)
- Fence Rider LV-22 (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Fence Rider LV-3D/3T (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Fence Rider LV-4T Brush Killer (2-ethylhexyl ester of 2,4,5-T)
- Fence Rider LV-6T Brush Killer (2-ethylhexyl ester of 2,4,5-T)
- Forron (2,4,5-T, form unspecified)
- Fortex (2,4,5-T, form unspecified)
- Fruitone A (2,4,5-T)
- GCC-425 (isooctyl esters of 2,4-D, 2,4,5-T and 2-(2,4,5-trichlorophenoxy)propionicacid)
- GCC-429 (isooctyl esters of 2,4-D, 2,4,5-T and 2-(2,4,5-trichlorophenoxy)propionicacid)
- General Chemical 2,4,5-T Amine (triethylamine salt of 2,4,5-T)

- Gormel's Brush Killer (propylene glycol butyl ether estersof 2,4-D and 2,4,5-T)
- Gormel's Weed and Clover Killer (isooctyl esters of 2,4-Dand 2,4,5-T)
- Green Cross Celatox 50/30 (2,4,5-T + MCP [(4-chloro-2-methyl-phenoxy)aceticacid])
- Green Cross Vegetation Killer (monuron [3-(p-chlorophenyl)-1,1-dimethylurea]+ 2,4-D + 2,4,5-T)
- Green Light 2,4-D, 2,4,5-T Weed Killer (isooctyl esters of2,4-D and 2,4,5-T)
- Green Light Weed Killer (alkanolamine salts [of the ethanoland isopropanol series] of 2,4-D + triethylamine salt of 2,4,5-T)
- Greenfield Broadleaf Weed and Crab Grass Killer (trifluralin[alpha,alpha,alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine]+ disodium methylarsonate + sodium salts of 2,4-D and 2,4,5-T)
- Greenfield Crab Grass and Broadleaf Weed Killer (trifluralin[alpha,alpha,alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine]+ disodium methylarsonate hexahydrate + isooctyl esters of 2,4-Dand 2,4,5-T)
- Greenfield Crabgrass and Dandelion Killer (disodium methanearsonate+ trifluralin [alpha,alpha,alpha-trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine]+ sodium salts of 2,4-D and 2,4,5-T)
- Greenfield Weeds As It Feeds For Lawns (isooctyl esters of2,4-D and 2,4,5-T)
- Greever's Low Volatile Brush Killer (isooctyl esters of 2,4-Dand 2,4,5-T)
- Hercules (isooctyl esters of 2,4,5-T)
- HH Poison Ivy Killer (triethylamine salt of 2,4,5-T)
- Hormoslyr 64 (2,4-D + 2,4,5-T)
- Hub States Selective Weed and Brush Killer Amine Formula 400(diethylethanolamine salts of 2,4-D and 2,4,5-T)
- Instemul DTA 22 (oleyl amine salt of 2,4-D + oleyllinoleylamine salt of 2,4,5-T)
- Instemul DTA 66 Concentrate (oleyl amine salt of 2,4-D +

oleyllinoleylamine salt of 2,4,5-T)
- Instemul TA 120 Concentrate (oleyllinoleyl amine salt of 2,4,5-T)
- Instemul TA 40 (oleyllinoleyl amine salt of 2,4,5-T)
- Inverton 245 (2,4,5-T, form unspecified)
- Kansel (2,4,5-T + propylene glycol butyl ether esters of 2,4,5-T)
- Kilbrush 8-16 Ester (butyl esters of 2,4-D and 2,4,5-T)
- Kilex 3 (butyl ester of 2,4,5-T)
- L.V. Brush Rhap-4 (isooctyl ester of 2,4,5-T)
- Lawn Weed-Rhap (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Line Rider 22 (butyl esters of 2,4-D and 2,4,5-T)
- Line Rider 4T (butyl ester of 2,4,5-T)
- Line Rider Amine 4T-2 (alkyl amine salt of 2,4,5-T)
- Line Rider Invert D/T (isooctyl esters of 2,4-D and 2,4,5-T)
- Line Rider Invert D/T Concentrate (isooctyl esters of 2,4-Dand 2,4,5-T)
- Line Rider Invert T (isooctyl ester of 2,4,5-T)
- Line Rider Invert T Concentrate (isooctyl ester of 2,4,5-T)
- Line Rider LV-21 (isooctyl esters of 2,4-D and 2,4,5-T)
- Line Rider LV-4T (2-ethylhexyl ester of 2,4,5-T)
- Line Rider LV-6T (2-ethylhexyl ester of 2,4,5-T)
- Liqweedate (2-methoxy-4,6-bis(isopropylamine)-s-triazine +isooctyl esters of 2,4-D and 2,4,5-T)
- LO-VOL 4T (2,4,5-T, form unspecified)
- Manco Super Kill-Weed (isooctyl esters of 2,4-D and 2,4,5-T)
- MFA 2,4,5-T Butyl Ester
- MFA LO-V 2,4,5-T (octyl ester of 2,4,5-T)
- MFA LO-V Super Brush Killer (octyl esters of 2,4-D and 2,4,5-T)
- MFA Super Brush Kill (butyl esters of 2,4-D and 2,4,5-T)
- Monsanto 2,4,5-T Amine (triethylamine salt of 2,4,5-T)
- Monsanto 2,4,5-T Butyl Ester (isobutyl and n-butyl estersof 2,4,5-T)
- Monsanto 2,4,5-T Low Volatile Ester (isooctyl ester of 2,4,5-T)
- Monsanto 2,4-D 2,4,5-T Amine Brush Killer (dimethylamine saltof 2,4-D + triethylamine salt of 2,4,5-T)

- Monsanto 2,4-D 2,4,5-T Amine Brush Killer (triethylamine saltsof 2,4-D and 2,4,5-T)
- Monsanto 2,4-D 2,4,5-T Butyl Ester Brush Killer
- Monsanto 2,4-D 2,4,5-T Low Volatile Ester Brush Killer (isooctylesters of 2,4-D and 2,4,5-T)
- n-Butyl(2,4,5-trichlorophenoxy)acetate
- n-Butylester Kyselini 2,4,5-trichlorfenoxyoctove
- Navy Brand WKB-15 (isooctyl esters of 2,4-D and 2,4,5-T)
- Navy Brand WKB-28 (butoxyethoxypropanol esters of 2,4-D and2,4,5-T)
- Niagara Brush-Killer (Ester Form) (butoxyethanol esters of2,4-D and 2,4,5-T)
- Niagara Commercial Brush Killer (isooctyl esters of 2,4-Dand 2,4,5-T)
- Olin Butyl Ester 22 Brush Killer (butyl esters of 2,4-D and2,4,5-T)
- Olin LV Ester 22 Brush Killer (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Ortho Brush Killer (isooctyl esters of 2,4-D and 2,4,5-T)
- Parsons 2,4,5-T Brush Killer (2,4,5-T)
- Parsons Poison Ivy and Brush Killer No. 2 (isooctyl estersof 2,4-D and 2,4,5-T)
- Patterson's 2,4,5-T Low Volatile and Brush Killer (isooctylester of 2,4,5-T)
- Patterson's Lawn Weed Killer (isooctyl esters of 2,4-D and2,4,5-T)
- Patterson's Super Brush Killer (butyl esters of 2,4-D and2,4,5-T)
- Patterson's Super Brush Killer Low Volatile (isooctyl estersof 2,4-D and 2,4,5-T)
- Phorfox (2,4,5-T, form unspecified))
- PL Liqui-date (isooctyl esters of 2,4-D, 2,4,5-T and silvex[2-(2,4,5-trichlorophenoxy) propionic acid])
- Pratt Lawn Weed Killer (2,4-D + 2,4,5-T)
- Real-Kill Spot Weed Killer (amine salts of 2,4-D, dicamba[3,6-dichloro-2-methoxybenzoic acid] and 2,4,5-T)
- Reasor-Hill Brush Rhap (2,4-D + 2,4,5-T)

- Reddon (propylene glycol butyl ether esters of 2,4,5-T)
- Reddox (2,4,5-T, form unspecified)
- Rhodia Low Volatile Brush Killer No. 2 (2,4-D + 2,4,5-T)
- S.I.R.-Ester (isooctyl esters of 2,4-D and 2,4,5-T)
- Science Lawn Weed-Killer (isooctyl esters of 2,4-D + 2,4,5-T)
- Stull's Hardwood Spray (isooctyl ester of 2,4,5-T)
- Stull's Low Volatile Brush Killer No. 4 (isooctyl esters of2,4-D and 2,4,5-T)
- Sure Death 2,4,5-T Conc. #4 (butyl ester of 2,4,5-T)
- Sure Death 2,4,5-T Conc. (2-ethyl 4-methylpentanol and 2-ethylhexanolesters of 2,4,5-T)
- Swift's Gold Bear 2-2 Brush Kill (isooctyl esters of 2,4-Dand 2,4,5-T)
- Swift's Gold Bear 55 Brush Kill (isooctyl ester of 2,4,5-T)
- Swift's Gold Bear Woody Plant Control (isooctyl esters of2,4-D and 2,4,5-T)
- 2,4,5-T Amine (dimethylamine salt of 2,4,5-T)
- 2,4,5-T Low Volatile Ester 6L (2,4,5-T, form unspecified)
- 2,4,5-T, butoxyethanol ester
- 2,4,5-T, butyl ester
- 2,4,5-T, isooctyl esters
- 2,4,5-T, oleic-1,3-propylenediamine salt
- 2,4,5-T, propyleneglycol butyl ether esters
- 2,4,5-T, triethylamine salt
- 2,4,5-T-dimethylamine salt
- 2,4,5-Trichlorophenoxyacetic acid
- T-5 Brush Kil (2,4,5-T, form unspecified)
- T-H Ded-Weed LV-6 (2,4,5-T)
- T-H Ded-Weed LV-9 (2,4,5-T)
- Techne 2,4,5-T Concentrate No.4 (butyl ester of 2,4,5-T)
- The Line Rider (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Tobacco States Brand Ester Brush Killer 2-2 (butyl estersof 2,4-D and 2,4,5-T)
- Tobacco States Brand Low-Vol Brush Killer 2-20 (isooctyl estersof 2,4-D and 2,4,5-T)
- Tormona (2,4,5-T, form unspecified)

- Transamine OA-1.5D-1.5T (N,N-dimethyloleyllinoleylamine saltof 2,4-D and 2,4,5-T)
- Transamine OA-3T (N,N-dimethyloleyllinoleylamine salt of 2,4,5-T)
- Trelease (butoxyethanol ester of 2,4,5-T)
- Tributon (2,4-D + 2,4,5-T, forms unspecified)
- (2,4,5-Trichloor-fenoxy)-azunzuur
- (2,4,5-Trichlor-phenoxy)-essigsaevre
- (2,4,5-Trichlorophenoxy)acetic acid
- Trinixol (2,4,5-T, form unspecified)
- Trinoxol (butoxyethanol ester of 2,4,5-T)
- Trinoxol Super-6 (butoxyethanol ester of 2,4,5-T)
- Trioxon (2,4,5-T, form unspecified)
- Trioxone (butyl ester of 2,4,5-T)
- U 46 (2,4-D + 2,4,5-T, forms unspecified)
- U 46 Spezial (2,4-D + 2,4,5-T, forms unspecified)
- Unico 2,4,5-T Lo-V Ester Brush Killer (2-ethylhexyl esterof 2,4,5-T)
- Unico Brush Killer (butyl esters of 2,4-D and 2,4,5-T)
- Unico Brush Killer A (butyl ester of 2,4-D + isooctyl esterof 2,4,5-T)
- Unico Lo-V Brush Killer (2-ethylhexyl esters of 2,4-D and2,4,5-T)
- Utility Brush Killer No. 2 (isooctyl esters of 2,4-D and 2,4,5-T)
- Veon (2,4,5-T, form unspecified)
- Veon 100 (triethylamine salt of 2,4,5-T)
- Veon 245 (triethylamine salt of 2,4,5-T)
- Veon BK (dimethylamine salts of 2,4-D and 2,4,5-T)
- Verton 2-T (2,4,5-T, form unspecified)
- Verton 2T (2,4,5-T, form unspecified)
- Verton 2T Herbicide (propylene glycol butyl ether esters of2,4,5-T)
- Verton CE (propylene glycol butyl ether esters of 2,4-D and2,4,5-T)
- Verton CE Herbicide (propylene glycol butyl ether esters of2,4-D and 2,4,5-T)

- Verton T (propylene glycol butyl ether esters of 2,4,5-T)
- Visko-Rhap H Low Volatile 2T (2-ethylhexyl ester of 2,4,5-T)
- Visko-Rhap Low Volatile 1.5D-1.5T (2-ethylhexyl esters of2,4-D and 2,4,5-T)
- Visko-Rhap Low Volatile 1D-1T (2-ethylhexyl esters of 2,4-Dand 2,4,5-T)
- Visko-Rhap Low Volatile 2T (2-ethylhexyl ester of 2,4,5-T)
- Visko-Rhap Low Volatile 3T (2-ethylhexyl ester of 2,4,5-T)
- Visko-Rhap Low Volatile Ester 1D-1T (2-ethylhexyl esters of2,4-D and 2,4,5-T)
- Visko-Rhap Low Volatile Ester 2T (2-ethylhexyl ester of 2,4,5-T)
- Wasco Brush Killer (2-ethylhexyl esters of 2,4-D and 2,4,5-T)
- Weed and Brush Off Amine Formula 400 (diethylethanolaminesalts of 2,4-D and 2,4,5-T)
- Weed-Rhap A-4T (triethylamine salt of 2,4,5-T)
- Weedar (2,4-D or 2,4,5-T, forms unspecified)
- Weedar 2,4,5-T (triethylamine salt of 2,4,5-T)
- Weedar Amine Brush Killer (dimethylamine salt of 2,4-D + triethylaminesalt of 2,4,5-T)
- Weedone (2,4-D or 2,4,5-T, forms unspecified)
- Weedone (butoxyethanol ester of 2,4,5-T)
- Weedone 2,4,5-T (2,4,5-T, form unspecified)
- Weedone 2,4,5-T Special Air Spray Formula (butoxyethanol esterof 2,4,5-T)
- Weedone Brush Killer 32 (butoxyethanol esters of 2,4-D and2,4,5-T)
- Weedone Brush Killer 64 (butoxyethanol esters of 2,4-D and2,4,5-T)
- Weedone Brush Killer 977 (butoxyethanol esters of 2,4-D and2,4,5-T)
- Weedone Brush Killer 977 Concentrate (butoxyethanol estersof 2,4-D and 2,4,5-T)
- Weedone Industrial Brush Killer (butoxyethanol esters of 2,4-Dand 2,4,5-T)
- Woodbury Woodkill Ester Conc. (butyl esters of 2,4-D and 2,4,5-

T)
- Woodkill Ester Concentrate (butyl esters of 2,4-D and 2,4,5-T)
- Zehrung 2,4,5-T blackberry Vine Killer (isopropyl ester of2,4,5-T)
- Zehrung Weed Blitz (triethanolamine salts of 2,4-D and 2,4,5-T)
- Zep R-61 Weed Killer (dimethylamine salts of 2,4-D and 2,4,5-T)

**Synonyms for MCPA**

- (4-Chloro-ortho-toloxy)acetic acid
- (4-Chloro-ortho-tolyloxy)acetic acid
- [(4-Chloro-ortho-tolyl)oxy]acetic acid
- 2,4-MCPA
- 2-Methyl-4-chlorophenoxyacetic acid
- 2M-4CH
- 2M4KH
- 4-Chloro-ortho-cresoxyacetic acid
- Agritox
- Agroxon
- Agroxone
- AK-2M
- Anicon kombi
- Anicon M
- B-Selektonon M
- Banlene plus
- Banvel M
- Basagran-M
- BH MCPA
- Bordermaster
- Brominal M
- Brominal plus
- Bronate
- Cambilene
- Cekherbex
- Chiptox
- Chlorotoloxyacetic acid
- Chwastox

- Cornox M
- Ded-Weed
- Dicopur-M
- Dicotex
- Dikotes
- Dow MCP amine weed killer
- Emcepan
- Empal
- Empral
- Hedapur M52
- Hedarex M
- Hedonal M
- Herbicide M
- Hormotuho
- Hormotuho X super
- Hornotuha
- Kilsem
- Krezone
- Legumex DB
- Leuna M
- Leyspray
- Linormore
- M40
- MCP
- Mephanac
- Metaxon
- Methoxone
- Netazol
- Okultin M
- Phenoxylene plus
- Phenoxylene super
- Raphone
- Razol dock killer
- Rhomenc
- Rhomene
- Rhonox

- Seppic MMD
- Trasan
- U 46
- U 46 M-Fluid 4
- U 46 M-Fluid 6
- Ustinex
- Verdone
- Vesakontuho MCPA
- Weed-Rhap
- Weedar
- Weedar MCPA concentrate
- Weedar sodium MCPA
- Weedone MCPA ester
- Zelan

**Synonyms for 2,4-DP**

- 2-(2,4-Dichlorophenoxy)-propionic acid
- Dichlorprop

**Synonyms for Silvex**

- Fenoprop
- 2-(2,4,5-Trichlorophenoxy)propionic acid
- 2,4,5-TP

**Synonyms for MCPP**

- 2-(4-Chloro-ortho-tolyloxy)propionic acid
- Mecoprop

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Last updated: 2 March 1998

# CHOLESTEROL
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 161)

**CAS No.**: 57-88-5
**Chem. Abstr. Name**: Cholest-5-en-ol (3β)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Intake of dietary cholesterol was greater in premenopausal cases than controls in a case-control study of diet and breast cancer; however, this finding was not statistically significant, and the association was less strong than that with dietary fat [ref: 1]. In a reanalysis of the same data, dietary cholesterol did not have an effect independent of saturated fat intake [ref: 2]. Further, in a cohort study of 89 538 US nurses, there was no increased risk of breast cancer associated with dietary fat or dietary cholesterol [ref: 3]. Dietary cholesterol intake was greater in cases than in controls in a case-control study of colorectal cancer, but the risk ratios were lower than for saturated fat intake [ref: 4]. Risk ratios were also elevated for dietary cholesterol and colon cancer in a second case-control study, although they were lower for rectal cancer and risk ratios were elevated to a greater extent for dietary protein [ref: 5]. In a study in which cholesterol intake of Seventh-Day Adventists was compared with that of lacto-ovo-vegetarians and nonvegetarians, differences for colon cancer risk were not 'striking' [ref: 6]. However, a study using food disappearance data from 20 countries showed that, when dietary cholesterol was controlled for, the partial correlations of dietary fat and fibre with colon cancer mortality were no longer significant. Cross-classification showed a significant, main effect for cholesterol but not for fat or fibre [ref: 7].

Dietary cholesterol was associated with increased risk of lung cancer in a case-control study. The association was found in all subjects, in smoking subjects and in males, but not in females [ref: 8]. Dietary cholesterol was also found to be slightly associated with increased risk of bladder cancer in a further case-control study [ref: 9]. These studies involved the use of relatively restricted dietary questionnaires, and it was not possible to determine whether the association with dietary cholesterol was part of a stronger association with other dietary factors with which the intake of cholesterol is associated.

Dietary cholesterol was analysed in relation to cancer mortality in a ten-year follow-up of the Honolulu Heart Program in the USA. There was no significant association, but data for individual cancer sites were not reported [ref: 10].

The available data on serum cholesterol levels and cancer have been considered [ref: 11], and subsequently reported independently [ref: 12]. It was concluded that observational studies afford substantial evidence that preclinical cancer causes a lowering of blood cholesterol, and limited, but biologically plausible evidence that males with naturally low blood cholesterol levels are at increased risk of colon cancer. Since then, there have been reports of seven studies primarily related to follow-up of cohorts established for the study of cardiovascular disease [ref: 13-20]. A study of 4035 residents of California, USA, aged 40-89, showed no association between plasma cholesterol and cancer morbidity or mortality over a seven-year period for either men or women for any cancer site [ref: 13]. In a five-year follow-up of 10 940 participants in the Hypertension Detection and Follow-up Program in the USA, a small but statistically significant inverse relationship was found between baseline serum cholesterol level and cancer incidence. When cases diagnosed in the first two years were excluded, the association was similar in magnitude but no longer statistically significant. The numbers of cases did not permit analysis by cancer site [ref: 14]. Up to six years of follow-up (mean, three years) were reported for 10 000 middle-aged men in the Malmö; Preventive Program in Sweden [ref: 15]. Serum cholesterol was inversely related to cancer mortality (44 deaths) - a relationship seen also for the 25 cancer deaths that occurred more than 2.5 years after screening [ref: 15]. Serum urate levels at screening were correlated with early but not late (more than 2.5 years after screening) cancer mortality. As urate levels might indicate proliferation of cancer cells, the association of raised serum cholesterol with late deaths may be due to another mechanism than cancer present at the time of screening [ref: 16].

In the Busselton community study in Western Australia, 1564 subjects have been followed for 13 years. In men aged 60-74, but not in men aged 40-59 or in women, a negative association between serum cholesterol level and cancer mortality was found [ref: 17]. It was not indicated if the association persisted when early cancer deaths were excluded. In New Zealand, 630 Maoris aged 25-74 were followed for over 17 years. A significant inverse relationship between cancer mortality and serum cholesterol was found for men and women considered together. The relative risk in the pooled data, derived by comparing the approximate 10th and 90th percentiles of serum cholesterol concentration, decreased from 3.0 to 2.4 after excluding deaths in the first five years [ref: 18]. Fifteen years of follow-up of 11 325 healthy men aged 40-59 in the Seven Countries Study has also been reported. Among 477 cancer deaths five or more years after cholesterol measurement, there was a significant excess of deaths from lung cancer in the lower 20% of the cholesterol distribution in the populations. Nevertheless, regional comparisons of cancer mortality showed highest cancer rates in northern Europe, where the cholesterol levels were highest [ref: 19]. In contrast, in a cohort study in Sweden of 92 000 subjects less than 75 years old examined in 1963-1965 and followed by linkage to the Swedish Cancer Registry until 1979, there was a positive association between serum cholesterol level and risk of rectal cancer in men. When serum cholesterol and β-lipoprotein levels were considered together, the risk for men with elevated serum cholesterol (equal or higher than 2.5 g/l) and β-lipoprotein (equal or higher than 2.2 g/l), relative to those with lower levels, was 1.6 for colon cancer (95% confidence interval, 1.2-2.2) and 1.7 for rectal cancer (1.2-2.4) [ref: 20]. In the largest study so far reported, the incidence of cancer was determined in 160 135 male and female members of a prepaid health plan in California, USA, for whom serum cholesterol levels were determined as part of a multiphasic health examination. Follow-up was for eight to 16 years. No consistent association of low cholesterol with cancer incidence was found, although cancer incidence was highest in those in the lowest quintile of serum cholesterol levels in the first two years after the measurement [ref: 21].

Five case-control studies have been reported in which serum cholesterol was assessed [ref: 22-26]. A case-control study of 37 cases of primary brain tumours and two controls per case found elevated levels of serum cholesterol in the cases compared to the controls. The difference was not reduced by controlling for potential confounders (including weight) [ref: 22]. In the second study, serum cholesterol was measured in 244 patients with adenomatous polyps of the colon, 182 patients with Dukes' A or B colon cancer and 688 hospital controls. The mean serum cholesterol levels were lower for the Dukes' B cases, accounting for most of the difference. There was no difference in mean levels between those with adenomatous polyps and their controls. After adjustment for nutritional status using serum albumin level, however, there was no difference between any of the groups [ref: 23]. In a nested case-control study within a cohort, 245 newly-diagnosed cases of large-bowel cancer in members of a prepaid health care plan and five matched controls for each case were compared, on the basis of serum cholesterol measurements performed as part of a multiphasic health examination prior to the diagnosis of the cases. No direct or inverse relationship between serum cholesterol and large-bowel cancer was found [ref: 24]. A fourth case-control study was based on a cohort of 18 995 people examined at a health centre between 1970-1973, where medical records were found for 100 of 176 cancer cases who had died by 1979, for 393 of 900 control subjects still alive in 1979, and for 69 of 153 people who had died of cardiovascular disease in the same period. Serum cholesterol levels in the cancer cases were significantly lower than those in controls only in the two-year period prior to death and were inconsistently depressed three to six or seven to 16 years prior to death [ref: 25]. In a fifth study, a positive association was found between serum cholesterol levels and the prevalence of adenomatous polyps at colonoscopy performed in 842 patients. The odds ratio for large-bowel adenoma between the highest and lowest quintiles of serum cholesterol was 1.9 (95% confidence interval, 1.1-3.5) after adjustment for age and 2.0 (1.1-3.6) after adjustment for body-mass index [ref: 26]. Serum cholesterol was assessed in relation to disease-free survival of 279 colon cancer patients. There was an 11% (nonsignificant) lower cumulative disease-free survival at five years in those with serum cholesterol levels below the median than in those with levels above the median [ref: 27]. In a further study, family history of cancer was found to be positively associated with serum cholesterol levels in young adults [ref: 28].

Thus, although studies of cohorts assembled to study cardiovascular disease risk continue to show associations of low serum cholesterol with cancer incidence and mortality, the studies designed specifically to assess the relationship do not in general confirm the association. When site-specific data are available, they are not consistent. Nevertheless, a plausible mechanism exists - namely, that those who maintain a low serum cholesterol in face of a possibly elevated fat intake increase the concentration of cholesterol metabolites (especially bile acids) in the intestine and thus increase their risk for colon cancer [ref: 29].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Cholesterol was tested for carcinogenicity in mice by administration in the diet, by subcutaneous administration and by bladder implantation. These studies were all inadequate for evaluation. Cholesterol has also been tested in combination with various carcinogens, but the results were inadequate to assess the carcinogenesis-enhancing potential of the compound [ref: 11]. Feeding of cholesterol to rats exposed to a mammary carcinogen did not affect the incidence of mammary tumours [ref: 30], while feeding after administration of a colon carcinogen resulted in a lower incidence of colon tumours [ref: 31].

**C. Other relevant data**

No data were available on the genetic and related effects of cholesterol in humans. Cholesterol did not transform Syrian hamster embryo cells and was not mutagenic to bacteria [ref: 32].

**Overall evaluation**

Cholesterol is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 10 (1976); Vol. 31 (1983)

**References**

1. Miller, A.B., Kelley, A., Choi, N.W., Matthews, V., Morgan, R.W., Munan, L., Burch, J.D., Feather, J., Howe, G.R. & Jain, M. (1978) A study of diet and breast cancer. Am. J. Epidemiol., 107, 499-509

2. Howe, G.R. (1985) The use of polytomous dual response data to increase power in case-control studies: an application to the association between dietary fat and breast cancer. J. chron. Dis., 38, 663-670

3. Willett, W.C., Stampfer, M.J., Colditz, G.A., Rosner, B.A., Hennekens, C.H. & Speizer, F.E. (1987) Dietary fat and the risk of breast cancer. New Engl. J. Med., 316, 22-28

4. Jain, M., Cook, G.M., Davis, F.G., Grace, M.G., Howe, G.R. & Miller, A.B. (1980) A case-control study of diet and colo-rectal cancer. Int. J. Cancer, 26, 757-768

5. Potter, J.D. & McMichael, A.J. (1986) Diet and cancer of the colon and rectum: a case-control study. J. natl Cancer Inst., 76, 557-569

6. Turjman, N., Calkins, B., Phillips, R., Goodman, G.T. & Nair, P.P. (1984) Dietary intake of plant sterols and cholesterol among population groups at different risks for colon cancer (Abstract No. 3330). Fed. Proc., 43, 855

7. Liu, K., Stamler, J., Moss, D., Garside, D., Persky, V. & Soltero, I. (1979) Dietary cholesterol, fat and fibre, and colon-cancer mortality. An analysis of international data. Lancet, ii, 782-785

8. Hinds, M.W., Kolonel, L.N., Hankin, J.H. & Lee, J. (1983) Dietary cholesterol and lung cancer risk in a multiethnic population in Hawaii. Int. J. Cancer, 32, 727-732

9. Risch, H.A., Burch, J.D., Miller, A.B., Hill, G.B., Steele, R. & Howe, G.R. (1987) Dietary factors and the incidence of cancer of the urinary bladder. Am. J. Epidemiol. (in press)

10. McGee, D., Reed, D., Stemmerman, G., Rhoads, G., Yano, K. & Feinleib, M. (1985) The relationship of dietary fat and cholesterol to mortality in 10 years: the Honolulu Heart Program. Int. J. Epidemiol., 14, 97-105

11. IARC Monographs, 31, 95-132, 1983

12. McMichael, A.J., Jensen, O.M., Parkin, D.M. & Zaridze, D.G. (1984) Dietary and endogenous cholesterol and human cancer. Epidemiol. Rev., 6, 192-216

13. Wingard, D.L., Criqui, M.H., Holdbook, M.J. & Barrett-Connor, E. (1984) Plasma cholesterol and cancer morbidity and mortality in an adult community. J. chron. Dis., 37, 401-406

14. Morris, D.L., Borhani, N.O., Fitzsimons, E., Hardy, R.J., Hawkins, C.M., Kraus, J.F., Labarthe, D.R., Mastbaum, L. & Payne, G.H. (1983) Serum cholesterol and cancer in the hypertension detection and follow-up program. Cancer, 52, 1754-1759

15. Petersson, B. & Trell, E. (1983) Premature mortality in middle-aged men: serum cholesterol as risk factor. Klin. Wochenschr., 63, 795-801

16. Petersson, B. & Trell, E. (1983) Raised serum urate concentration as risk factor for premature mortality in middle aged men: Relation to death from cancer. Br. med. J., 287, 7-9

17. Cullen, K., Stenhouse, N.S., Wearne, K.L. & Welborn, T.A. (1983) Multiple regression analysis of risk factors for cardiovascular disease and cancer mortality in Busselton, Western Australia - 13-year study. J. chron. Dis., 36, 371-377

18. Salmond, C.E., Beaglehole, R. & Prior, I.A.M. (1985) Are low cholesterol values associated with excess mortality? Br. med. J., 290, 422-424

19. Keys, A., Aravanis, C., Blackburn, H., Buzina, R., Dontas, A.S., Fidanza, F., Karvonen, M.J., Menotti, A., Nedeljkovic, S., Punsar, S. & Toshima, H. (1985) Serum cholesterol and cancer mortality in the Seven Countries Study. Am. J. Epidemiol., 121, 870-883

20. Törnberg, S.A., Holm, L.-E., Cartensen, J.M. & Eklund, G.A. (1986) Risks of cancer of the colon and rectum in relation to serum cholesterol and beta-lipoprotein. New Engl. J. Med., 315, 1629-1633

21. Hiatt, R.A. & Fireman, B.H. (1986) Serum cholesterol and the incidence of cancer in a large cohort. J. chron. Dis., 39, 861-870

22. Abramson Z.H. & Kark, J.D. (1985) Serum cholesterol and primary brain tumours: a case-control study. Br. J. Cancer, 52, 93-98

23. Neugut, A.I., Johnsen, C.M. & Fink, D.J. (1986) Serum cholesterol levels in adenomatous polyps and cancer of the colon. A case-control study. J. Am. med. Assoc., 255, 365-367

24. Sidney, S., Friedman, G.D. & Hiatt, R.A. (1986) Serum cholesterol and large bowel cancer. A case-control study. Am. J. Epidemiol., 124, 33-38

25. Gerhardsson, M., Rosenqvist, U., Ahlbom, A. & Carlson, L.A. (1986) Serum cholesterol and cancer - a retrospective case-control study. Int. J. Epidemiol., 15, 155-159

26. Mannes, G.A., Maier, A., Thieme, C., Wiebecke, B. & Paumgartner, G. (1986) Relation between the frequency of colorectal adenoma and the serum cholesterol level. New Engl. J. Med., 315, 1634-1638

27. Tartter, P.I., Slater, G., Papatestas, A.E. & Aufses, A.H., Jr (1984) Cholesterol, weight, height, Quetelet's index, and colon cancer recurrence. J. surg. Oncol., 27, 232-235

28. Reed, T., Wagener, D.K., Donahue, R.P. & Kuller, L.H. (1986) Family history of cancer related to cholesterol level in young adults. Genet. Epidemiol., 3, 63-71

29. Broitman, S.A. (1981) Cholesterol excretion and colon cancer. Cancer Res., 41, 3738-3740

30. Cohen, L.A. & Chan, P.-C. (1982) Dietary cholesterol and experimental mammary cancer development. Nutr. Cancer, 4, 99-106

31. Cohen, B.I., Raicht, R.F. & Fazzini, E. (1982) Reduction of N-methyl-N-nitrosourea-induced colon tumors in the rat by cholesterol. Cancer Res., 42, 5050-5052

32. IARC Monographs, Suppl. 6, 166-167, 1987

**Synonyms**

- (-)-Cholesterol
- 5,6-Cholesten-3β-ol
- 5-Cholesten-3β-ol
- Cholest-5-en-3β-ol
- Cholesterin
- Cholesterine
- Cholesterol base H
- Cholesteryl alcohol
- Cordulan
- $\Delta^5$(-cholesten-3β-ol)
- Dusoline
- Dusoran
- Dythol
- β-Hydroxycholest-5-ene
- Hydrocerin
- Kathro
- Lanol
- Nimco cholesterol base H
- Nimco cholesterol base No. 7l2
- Provitamin D
- Super hartolan
- Tegolan

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Last updated: 9 March 1998

# CHRYSOIDINE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 169)

**CAS No.**: 532-82-1
**Chem. Abstr. Name**: 4-(Phenylazo)-1,3-benzenediamine, monohydrochloride

**A. Evidence for carcinogenicity to humans** (*inadequate*)

A report of bladder cancer in three amateur anglers with exposure to chrysoidine-dyed maggots [ref: 1] stimulated reports of four further cases [ref: 2,3] and two case-control studies [ref: 4,5]. A study in Yorkshire, UK, used an existing large-scale bladder cancer case-control study (over 900 pairs) and made further enquiries regarding fishing, maggots and dyes used on or in the maggots. The relative risks were 0.7 (95% confidence interval, 0.2-2.3) based on five exposed cases for the use of bronze (surface-coloured) maggots, and 2.0 (0.6-6.2) based on nine exposed cases for yellow maggots (ready or self-coloured) [ref: 4]. A study in the West Midlands, UK, was smaller (202 pairs) but showed a higher percentage of use of dyed maggots (14% of cases, 8% of controls). A three-fold excess risk was noted for the use of bronze maggots for more than five years [ref: 5]. This study almost certainly included five cases from the previous case reports that stimulated the case-control studies, but this factor is unlikely to remove the statistically significant excess risk.

**B. Evidence for carcinogenicity to animals** (*limited*)

Chrysoidine was tested for carcinogenicity in single experiments in mice and rats by oral administration only. In mice, it produced liver-cell adenomas and carcinomas, leukaemia and reticulum-cell sarcomas. The experiment on rats was inadequately reported [ref: 6].

**C. Other relevant data**

No data were available on the genetic and related effects of chrysoidine in humans. It was mutagenic to bacteria [ref: 7].

**Overall evaluation**

Chrysoidine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 8 (1975)

**References**

1. Searle, C.E. & Teale, J. (1982) Chrysoidine-based bait: a possible carcinogenic hazard to anglers? Lancet, i, 564

2. Massey, J.A., Feneley, R.C.L. & Abrams, P.H. (1984) Maggots dyed with chrysoidine. Br. med. J., 289, 1451-1452

3. Sole, G.M. (1984) Maggots dyed with chrysoidine: a possible risk to anglers. Br. med. J., 289, 1043-1044

4. Cartwright, R.A., Robinson, M.R.G., Glashan, R.W., Gray, B.K., Hamilton-Stewart, P., Cartwright, S.C. & Barnham-Hall, D. (1983) Does the use of stained maggots present a risk of bladder cancer to coarse fishermen? Carcinogenesis, 4, 111-113

5. Sole, G. & Sorahan, T. (1985) Coarse fishing and risk of urothelial cancer. Lancet, i, 1477-1479

6. IARC Monographs, 8, 91-96, 1975

7. IARC Monographs, Suppl. 6, 176-177, 1987

**Synonyms**

- 2,4-Diaminoazobenzene hydrochloride
- 4-(Phenylazo)-*m*-phenylenediamine, hydrochloride
- 4-(Phenylazo)-*m*-phenylenediamine, monohydrochloride
- Astra chrysoidine R
- Basic Orange 2
- Basic Orange 2, monohydrochloride
- Brasilazina Orange Y
- Brilliant oil Orange Y base
- Calcozine chrysoidine Y
- Calcozine Orange YS
- Chrysoidin
- Chrysoidin FB
- Chrysoidin YN
- Chrysoidine [II]
- Chrysoidine A
- Chrysoidine B
- Chrysoidine C crystals
- Chrysoidine crystals
- Chrysoidine G
- Chrysoidine GN
- Chrysoidine GS
- Chrysoidine HR
- Chrysoidine J
- Chrysoidine M
- Chrysoidine Orange
- Chrysoidine PRL
- Chrysoidine PRR
- Chrysoidine SL
- Chrysoidine special [biological stain and indicator]
- Chrysoidine SS
- Chrysoidine Y
- Chrysoidine Y base new
- Chrysoidine Y crystals
- Chrysoidine Y ex
- Chrysoidine Y special
- Chrysoidine YGH
- Chrysoidine YL
- Diazocard chrysoidine G
- Elcozine chrysoidine Y
- Leather Orange HR
- Nippon kagaku chrysoidine
- Pure chrysoidine YBH
- Pure chrysoidine YD
- Pyracryl Orange Y
- Solvent Orange 3
- Sugai chrysoidine
- Tertrophene brown CG

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# CISPLATIN
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 170)

**CAS No.:** 15663-27-1
**Chem. Abstr. Name:** Platinum, diamminedichloro-, (SP-4-2)-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of cisplatin as a single agent was available to the Working Group. Occasional case reports of exposure to cisplatin, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1-3].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Multiple intraperitoneal administrations of cisplatin to mice significantly increased the incidence and number of lung adenomas. Similar treatments caused a significant increase in the incidence of skin papillomas in mice given promoting treatment of croton oil applied to the skin. The incidences of epidermoid carcinomas and of both malignant and benign tumours in internal organs were increased by the same treatment, but were not significantly different from those in controls [ref: 1,4]. In two studies, multiple intraperitoneal injections of cisplatin to rats induced leukaemia [ref: 5,6].

**C. Other relevant data**

In one study, cisplatin-adriamycin combination chemotherapy induced sister chromatid exchanges in peripheral blood lymphocytes of patients treated with this agent. In another study, antigenicity against cisplatin-DNA adducts was demonstrated in blood cells of treated patients [ref: 7].

Cisplatin induced structural chromosomal aberrations and sister chromatid exchanges in cells of rodents treated *in vivo*, but it did not induce dominant lethal mutations in mice. It transformed Syrian hamster embryo cells; it induced chromosomal aberrations, micronuclei and sister chromatid exchanges in both human and rodent cells *in vitro*, and mutation and DNA damage (including DNA cross-links) in rodent cells *in vitro*. In *Drosophila*, cisplatin induced aneuploidy and dominant lethal and sex-linked recessive lethal mutations. It induced chromosomal aberrations and mutation in plants. Cisplatin induced mutation, gene conversion and DNA damage in fungi and mutation and DNA damage in bacteria [ref: 7].

**Overall evaluation**

Cisplatin is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 151-164, 1981

2. Mead, G.M., Green, J.A., Macbeth, F.R., Williams, C.J., Whitehouse, J.M.A. & Buchanan, R. (1983)

Second malignancy after cisplatin, vinblastin, and bleomycins (PVB) chemotherapy: a case report. Cancer Treat. Rep., 67, 410

3. Pedersen-Bjergaard, J., Rørth, M., Avnstrøm, S., Philip, P. & Hou-Jensen, K. (1985) Acute nonlymphocytic leukemia following treatment of testicular cancer and gastric cancer with combination chemotherapy not including alkylating agents: report of two cases. Am. J. Hematol., 18, 425-429

4. Leopold, W.R., Batzinger, R.P., Miller, E.C., Miller, J.A. & Earhart, R.H. (1981) Mutagenicity, tumorigenicity, and electrophilic complexes of 1,2-diaminocyclohexane. Cancer Res., 41, 4368-4377

5. Kempf, S.R. & Ivankovic, S. (1986) Chemotherapy-induced malignancies in rats after treatment with cisplatin as single agent and in combination: preliminary results. Oncology, 43, 187-191

6. Kempf, S.R. & Ivankovic, S. (1986) Carcinogenic effect of cisplatin(*cis*-diammine-dichloroplatinum(II), CDDP) in BD IX rats. J. Cancer Res. clin. Oncol., 111, 133-136

7. IARC Monographs, Suppl. 6, 178-181, 1987

**Synonyms**

- CDDP
- Cisplatyl
- DDP
- *cis*-DDP
- *cis*-Diamminedichloroplatinum
- *cis*-Diaminodichloroplatinum [II]
- *cis*-Diamminedichloroplatinum [II]
- *cis*-Diammineplatinum [II]-chloride
- *cis*-Dichlorodiaminoplatinum
- *cis*-Dichlorodiaminoplatinum [II]
- *cis*-Dichlorodiammineplatinum
- *cis*-Dichlorodiammineplatinum [II]
- NSC 119875
- PDD
- Platinol
- *cis*-Platinous diaminodichloride
- *cis*-Platinum
- *cis*-Platinum diaminodichloride
- *cis*-Platinum[II] diaminodichloride
- *cis*-Platinum diamminedichloride
- *cis*-Platinum[II] diamminedichloride
- Platinum diamminodichloride

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Last updated: 11 February 1998

# CLOMIPHENE CITRATE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 172)

**Clomiphene**
**CAS No.**: 911-45-4
**Chem. Abstr. Name**: 2-[4-(2-Chloro-1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethylethanamine

**Clomiphene citrate**
**CAS No.**: 50-41-9
**Chem. Abstr. Name**: 2-[4-(2-Chloro-1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethylethanamine-2-hydroxy-1,2,3-propanetricarboxylate (1:1)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Only case reports of benign and malignant tumours occurring at various sites are available [ref: 1-5]. These include testicular tumours in three young men who had received clomiphene as part of hormonal treatment for oligospermia [ref: 2], a hepatoblastoma in a female infant whose mother had received clomiphene citrate as treatment for infertility [ref: 3], a liver-cell adenoma in a woman who had received clomiphene citrate for oligomenorrhoea [ref: 4], and unilateral testicular neoplasms in two of 650 oligospermic men who had received monthly treatments with clomiphene citrate (daily for three weeks followed by a week of rest) for six to 12 months [ref: 5].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Clomiphene citrate was tested in an inadequate experiment in newborn rats by single subcutaneous injection; reproductive-tract abnormalities, including uterine and ovarian tumours, were reported [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of clomiphene citrate in humans. It did not induce chromosomal aberrations or micronuclei in bone-marrow cells of mice treated *in vivo* [ref: 6].

**Overall evaluation**

Clomiphene citrate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 21 (1979)

**References**

1. IARC Monographs, 21, 551-561

2. Neoptolemos, J.P., Locke, T.J. & Fossard, D.P. (1981) Testicular tumour associated with hormonal treatment for oligospermia. Lancet, ii, 754

3. Melamed, I., Bujanover, Y., Hammer, J. & Spirer, Z. (1982) Hepatoblastoma in an infant born to

a mother after hormonal treatment for steriligy. New Engl. J. Med., 307, 820

4. Carrasco, D., Barrachina, M., Prieto, M. & Berenguer, J. (1983) Clomiphene citrate and liver cell adenoma. New Engl. J. Med., 310, 1120-1121

5. Nilsson, A. & Nilsson, S. (1985) Testicular germ cell tumors after clomiphene therapy for subfertility. J. Urol., 134, 560-562

6. IARC Monographs, Suppl. 6, 184-185, 1987

**Synonyms for Clomiphene**

- Chloramiphene
- 2-*para*-(2-Chloro-1,2-diphenylvinyl)-phenoxy]triethylamine
- 2-*para*-(β-Chloro-α-phenylstyryl)phenoxy]triethylamine
- Clomifene
- Clomiphene B

**Synonyms for Clomiphene citrate**

- Clomiphene dihydrogen citrate
- 2-[*p*-(2-Chloro-1,2-diphenylvinyl)phenoxy]triethylamine citrate (1:1)
- Clomid
- Clomifeno
- Clomivid
- Clomphid
- Chloramiphene
- Dyneric
- Genozym
- Ikaclomin
- Mer-41
- MRL 41
- MRL/41
- NSC 35770
- Omifin
- Racemic clomiphene citrate

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Last updated: 9 March 1998

# COAL GASIFICATION
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 173)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Case reports of tumours of the skin (including the scrotum), bladder and respiratory tract in association with employment in industries involving the destructive distillation of coal suggested a link between work in that industry and human cancer. Descriptive epidemiological studies based on death certificates corroborated these early suggestions [ref: 1].

A series of detailed analytical epidemiological studies of the British gas industry add further weight to the hypothesis that work in such coal gasification plants carries a risk for tumours of the lung, bladder and scrotum. There appeared to be a relationship between elevated relative risk of tumours and work in retort houses, particularly when the job had entailed exposure to fumes emanating from the retorts [ref: 1].

**B. Other relevant data**

No data were available to the Working Group.

**Overall evaluation**

Coal gasification is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 34 (1984)

**Reference**

1. IARC Monographs, 34, 65-99, 1984

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Last updated: 9 February 1998

# COAL-TAR PITCHES
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 174)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

A mortality analysis in the UK from 1946 showed a greatly increased risk for scrotal cancer among patent-fuel workers; furthermore, a large number of case reports describe the development of skin (including the scrotum) cancer in workers exposed to coal-tars or coal-tar pitch [ref: 1]. Several epidemiological studies have shown excesses of lung and bladder cancer among workers exposed to pitch fumes in aluminium production plants [ref: 2]. A slight excess of lung cancer was found among furnace and maintenance workers exposed to coal-tar pitch fumes in a calcium carbide production plant [ref: 3]. A cohort study of US roofers indicated an increased risk for cancer of the lung and suggested increased risks for cancers of the oral cavity, larynx, oesophagus, stomach, skin and bladder and for leukaemia. Some support for excess risks of lung, laryngeal and oral-cavity cancer is provided by other studies of roofers. One study showed a small excess of bladder cancer in tar distillers and in patent-fuel workers. An elevated risk of cancer of the renal pelvis was seen in workers exposed to 'petroleum or tar or pitch' [ref: 1]. One study of millwrights and welders exposed to coal-tars and coal-tar pitches in a stamping plant showed significant excesses of leukaemia and of cancers of the lung and digestive organs [ref: 4].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Application of coal-tar pitches and extracts of coal-tar pitches to the skin of mice produced malignant skin tumours. Extracts of coal-tar pitches had both initiating and promoting activities in mouse skin [ref: 1,5,6].

**C. Other relevant data**

No data were available on the genetic and related effects of coal-tar pitches in humans.

Extracts of coal-tar pitches and 'coal-tar' paints (formulated with coal-tar pitches) were mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. Extracts of emissions from a roofing-tar pot (coal-tar pitch-based tar) enhanced viral transformation in Syrian hamster embryo cells but did not cause DNA strand breaks. The same material induced sister chromatid exchanges and mutation in cultured rodent cells, both in the presence and absence of an exogenous metabolic system, and was mutagenic to *S. typhimurium* in the presence of an exogenous metabolic system [ref: 7].

**Overall evaluation**

Coal-tar pitches are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 35 (1985)

**References**

1. IARC Monographs, 35, 83-159, 1985

2. IARC Monographs, 34, 37-64, 1984

3. Kjuus, H., Andersen, A. & Langard, S. (1986) Incidence of cancer among workers producing calcium carbide. Br. J. ind. Med., 43, 237-242

4. Silverstein, M., Maizlish, N., Park, R. & Mirer, F. (1985) Mortality among workers exposed to coal tar pitch volatiles and welding emissions: an exercise in epidemiologic triage. Am. J. publ. Health, 75, 1283-1287

5. Robinson, M., Bull, R.J., Munch, J. & Meier, J. (1984) Comparative carcinogenic and mutagenic activity of coal tar and petroleum asphalt paints used in potable water supply systems. J. appl. Toxicol., 4, 49-56

6. Niemeier, R.W., Thayer, P.S., Menzies, K.T., von Thuna, P., Moss, C.E. & Burg, J. (1987) A comparison of the skin carcinogenicity of condensed roofing asphalt and coal tar pitch fumes. In: Proceedings of the International Symposium on Polynuclear Aromatic Hydrocarbons, Columbus, OH, Battelle (in press)

7. IARC Monographs, Suppl. 6, 186, 1987

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Last updated: 9 February 1998

# COAL-TARS
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 175)

**Coal-tars**
**CAS No.**: 8007-45-2
**Chem. Abstr. Name**: Coal-tars

**Coal-tars [high-temperature]**
**CAS No.**: 65996-89-6
**Chem. Abstr. Name**: Tar, coal, high-temp.

**Coal-tars [low-temperature]**
**CAS No.:** 65996-90-9
**Chem. Abstr. Name**: Tar, coal, low-temp.

**A. Evidence for carcinogenicity to humans** (*sufficient*)

There have been a number of case reports of skin cancer in patients who used tar ointments for a variety of skin diseases [ref: 1,2]. A mortality analysis in the UK from 1946 showed a greatly increased scrotal cancer risk for patent-fuel workers. Furthermore, a large number of case reports describe the development of skin (including the scrotum) cancer in workers exposed to coal-tar or coal-tar pitches [ref: 1]. Several epidemiological studies have shown an excess of lung cancer among workers exposed to coal-tar fumes in coal gasification and coke production [ref: 3,4]. One study showed a small excess of bladder cancer in tar distillers and in patent-fuel workers. An elevated risk of cancer of the renal pelvis was seen in workers exposed to 'petroleum or tar or pitch' [ref: 1. One study of millwrights and welders exposed to coal-tars and coal-tar pitches in a stamping plant showed significant excesses of leukaemia and of cancers of the lung and digestive organs [ref: 5].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Coal-tars from blast furnaces, coke ovens and coal gasification plants, as well as pharmaceutical coal-tars, were tested for carcinogenicity by skin application in mice, producing skin tumours. Pharmaceutical coal-tars and tars from coal gasification plants also produced skin tumours when applied to the ears of rabbits. Pharmaceutical coal-tars applied to the skin of rats produced lung tumours but not skin tumours. Inhalation of tar from coke ovens produced benign and malignant lung tumours in mice and rats and skin tumours in mice [ref: 1,3,4].

**C. Other relevant data**

An increased frequency of chromosomal aberrations was observed in peripheral lymphocytes of coal-tar workers, both smokers and nonsmokers. Extracts of urine from patients undergoing combined treatment with coal-tar preparations and ultraviolet light were mutagenic to *Salmonella typhimurium* [ref: 6].

Coal-tar induced transformation of Syrian hamster embryo cells. Samples of therapeutic coal-tar, extracts of coal-tar shampoos, an industrial coal-tar and vapours emitted from a coal-tar sample at 37 °C were mutagenic to *S. typhimurium* in the presence of an exogenous metabolic system [ref: 6].

**Overall evaluation**

Coal-tars are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 35 (1985)

**References**


1. IARC Monographs, 35, 83-159, 1985

2. Stern, R.S., Scotto, J. & Fears, T.R. (1985) Psoriasis and susceptibility to nonmelanoma skin cancer. J. Am. Acad. Dermatol., 12, 67-73

3. IARC Monographs, 34, 65-99, 1984

4. IARC Monographs, 34, 101-131, 1984

5. Silverstein, M., Maizlish, N., Park, R. & Mirer, R. (1985) Mortality among workers exposed to coal tar pitch volatiles and welding emissions: an exercise in epidemiologic triage. Am. J. publ. Health, 75, 1283-1287

6. IARC Monographs, Suppl. 6, 186, 1987


**Synonyms for Coal-tars**

- Carbo-cort
- Crude coal tar
- Estar
- Lavatar
- Pix carbonis
- Polytar bath
- Supertah
- Syntar
- Zetar

**Synonym for Coal-tars [high-temperature]**

- Tar decanter sludge

**Synonym for Coal-tars [low-temperature]**

- Coal oil

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Last updated: 9 February 1998

# COKE PRODUCTION
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 176)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

In the first half of the century, case reports of tumours of the skin (including the scrotum), bladder and respiratory tract, in association with employment in industries involving the destructive distillation of coal, suggested a link between that industry and human cancer. Despite their methodological shortcomings, descriptive epidemiological studies based on death certificates corroborated these early suggestions [ref: 1].

Later studies carried out in Japan, Sweden, the UK and the USA identified the lung as the site at which the excess cancer rates occurred most commonly among workers in coke production. All but two of the pertinent analytical epidemiological cohort studies provided evidence that work in coke production carries a significantly elevated risk of lung cancer. The two studies showing no lung cancer excess suffered from serious methodological limitations. The risk was evident in comparison with both the general population and non-coke production workers, and the extent of the increased relative risk estimates varied from three to seven fold. In those studies in which the relevant information was available, differences in smoking habits were shown not to have severely confounded the risk estimates [ref: 1].

Excess risk of kidney cancer has been repeatedly associated with work in coke plants. In one study in the USA, a seven-fold increase in risk was seen for workers employed for five years or more at coke ovens. In single studies, excess risks were reported for cancers of the large intestine and pancreas [ref: 1].

The largest study was conducted on a cohort of some 59 000 steel workers in the Pittsburgh area (USA) [ref: 1]. The study has recently been extended up to 1975 and the dose-response analysis of exposure to coal-tar pitch volatiles and lung cancer reviewed. Coke-oven workers (both white and nonwhite) exhibited a large, statistically significant increase in lung cancer mortality that was strongly associated with duration of exposure to coke-oven fumes and intensity of exposure, as documented by comparing topside- with side-oven experience. Significantly elevated mortality from prostatic and kidney cancer was also noted, but without clear evidence of an exposure-response relationship. Non-oven workers had no excess of lung cancer but a significantly increased mortality from cancer of the large intestine and pancreas. Cumulative exposure indices of exposure to coal-tar pitch volatiles were calculated and increasing lung cancer risk with increasing estimated exposure was found [ref: 2,3]. A possible causative agent is coal-tar fumes.

**Overall evaluation**

Coke production is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 34 (1984)

**B. Other relevant data**

An increase in the incidence of sister chromatid exchanges was observed in cultured peripheral blood lymphocytes from 12 nonsmoking coke-oven workers in a steel plant, when they were compared to a group of age-matched controls. Urine samples from nonsmoking coke-plant workers were mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. In a second study of coke-plant workers, the mutagenic activity in *S. typhimurium* of extracts of urine

samples collected after work was not statistically different from that of samples taken before work. Antigenicity against benzo[*a*]pyrene diol epoxide-DNA adducts has been demonstrated in peripheral blood lymphocytes of coke-oven workers [ref: 4].

**References**

1. IARC Monographs, 34, 101-131, 1984

2. Redmond, C.K. (1983) Cancer mortality among coke oven workers. Environ. Health Perspect., 52, 67-73

3. Rockette, H.E. & Redmond, C.K. (1985) Selection, follow-up and analysis in the coke oven study. Natl Cancer Inst. Monogr., 67, 89-94

4. IARC Monographs, Suppl. 6, 187, 1987

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Last updated: 9 February 1998

# CREOSOTES
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 177)

**CAS No.:** 8001-58-9
**Chem. Abstr. Name:** Creosote oil/wash oil

**A. Evidence for carcinogenicity to humans** (*limited*)

In a number of case reports, the development of skin cancer in workers exposed to creosote is described. One study involved a review of 3753 cases of cutaneous epithelioma from 1920 to 1945 and showed that 35 cases (12 of which were of the scrotum) had had exposure to creosote. Most cases occurred in workers handling creosotes or creosoted wood during timber treatment. A mortality analysis of workers in many occupations indicated an increased risk of scrotal cancer for creosote-exposed brickmakers [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Creosotes, creosote oils and anthracene oils were tested for carcinogenicity in mice by skin application, producing skin tumours, including carcinomas. One of the creosotes also produced lung tumours in mice after skin application [ref: 1].

**C. Other relevant data**

No occupationally related increase in mutagenicity was detected in the urine of creosote workers, but urine from rats administered creosote was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system [ref: 2].

Creosote enhanced transformation of Syrian hamster embryo cells initiated with benzo[*a*]pyrene in a two-stage transformation assay, and creosote and a coal-tar/creosote mixture gave positive results in the mouse lymphoma L5178Y system. Creosote, vapour emitted from creosote at 37 °C and a coal-tar/creosote mixture were mutagenic to *S. typhimurium* in the presence of an exogenous metabolic system [ref: 2].

**Overall evaluation**

Creosotes are *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 35 (1985)

**References**

1. IARC Monographs, 35, 83-159, 1985

2. IARC Monographs, Suppl. 6, 188, 1987

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# CYCLAMATES
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 178)

**Calcium cyclamate**
**CAS No.**: 139-06-0
**Chem. Abstr. Name**: Cyclohexylsulfamic acid, calcium salt

**Cyclamic acid**
**CAS No.**: 100-88-9
**Chem. Abstr. Name**: Cyclohexylsulfamic acid

**Cyclohexylamine**
**CAS No.**: 108-91-8
**Chem. Abstr. Name**: Cyclohexanamine

**Sodium cyclamate**
**CAS No.**: 139-05-9
**Chem. Abstr. Name**: Cyclohexylsulfamic acid, monosodium

**A. Evidence for carcinogenicity to humans** (*inadequate*)

The evidence that the risk of cancer is increased among users of artificial sweeteners is inconsistent [ref: 1]. Since the positive report of Howe *et al.* [ref: 2], reports have become available on six case-control studies and on one population study of bladder cancer.

The largest was a population-based study in ten areas of the USA, with 3010 bladder cases and 5783 controls. The relative risk for bladder cancer associated with use of artificial sweeteners was 1.0 (95% confidence interval, 0.9-1.1) among men and 1.1 (0.9-1.3) among women. Significant trends of increasing risk with increasing average daily consumption were found in certain subgroups examined *a priori* on the basis of the results of animal experiments; these subgroups were female nonsmokers and male heavy smokers [ref: 3]. Subsequent, independent re-analysis of the same data by a different statistical technique (multiple logistic regression) confirmed the original findings overall but cast doubt on the significance of the findings in the two subgroups because of inconsistent dose-response trends, especially among the male heavy smokers [ref: 4]. In response, the original investigators noted that the inconsistency derived from the development of risk scores which, in their opinion, were not correctly derived, as two relevant variables had been omitted [ref: 5]. In a subsequent report on data from one of the areas participating in this study, the use of hospital and population controls was compared. A higher proportion of hospital controls was found to have used artificial sweeteners than population controls [ref: 6]. This had been postulated earlier [ref: 2] as a possible reason for the negative findings of a hospital-based case-control study [ref: 7]. Bias resulting from use of prevalent rather than incident cases [ref: 8] has been suggested as a possible reason for the negative findings of another hospital based case-control study [ref: 9].

Two other case-control studies have also shown increased risks among subgroups. In one, conducted simultaneously in Japan, the UK and the USA, the relative risks among women in the US component of the study associated with 'any' use of diet drinks and of sugar substitutes were 1.6 and 1.5, respectively, and 2.6 and 2.1, respectively, for nonsmokers [ref: 10]. In the other two areas, however, a history of use of sugar substitutes, primarily saccharin, was not associated with an elevated bladder cancer risk [ref: 11]. In the other study, conducted in West Yorkshire, UK, although elevated risks were found for saccharin takers who were nonsmokers, the risks associated with cyclamate use were not examined [ref: 12].

Two studies in Denmark [ref: 13,14], one in the USA [ref: 15] and a further case-control study in Canada [ref: 16], however, gave negative results. In one of the Danish studies, incidence of bladder

cancer at ages 20-34 among people born 1941-1945 (when use of saccharin was high in Denmark) was compared with that among those born 1931-1940. The risk for men was 1.0 (0.7-1.6) and that for women, 0.3 (0.1-1.0) [ref: 13]. The other two studies were population-based case-control studies of bladder cancer. In Denmark, the relative risk for people of the two sexes combined was 0.78 (0.58-1.05) [ref: 14]. In a study in the USA of bladder cancer in women aged 20-49, the odds ratio for regular use of artificially sweetened beverages, table-top sweetener or both was 1.1 (0.7-1.7) [ref: 15]. In Canada, the odds ratio for use of cyclamate was 1.09 (0.60-1.97) in males and 0.92 (0.63-1.36) in females. In neither study were the increased risks seen in subgroups in other studies replicated.

In the USA, in a study of 1862 patients hospitalized for cancer and of 10 874 control patients, a greater proportion of artificial sweetener users was among women found only with cancer of the stomach. Little information was available on urinary-tract cancer. No overall association was found between artificial sweetener use and cancer [ref: 17].

**B. Evidence for carcinogenicity to animals** (*limited*)

Sodium cyclamate was tested for carcinogenicity both alone and in combination with other chemicals in different animal species and by several routes of administration. Following its oral administration to two strains of mice, an increased incidence of lymphosarcomas was observed in female mice of one strain; a few bladder tumours were seen in rats exposed orally. Several other experiments in mice, rats, hamsters and monkeys were inadequate for evaluation. A 10:1 mixture of sodium cyclamate:sodium saccharin was given to mice in one multigeneration experiment and to rats in two single-generation experiments: transitional-cell carcinomas were induced in the bladders of male rats of one strain given the highest dose [ref: 1]. In a similar two-generation experiment in rats, no treatment-related tumour was observed [ref: 18]. Instillation of low doses of *N*-methyl-*N*-nitrosourea into the bladder of rats fed sodium cyclamate for long periods resulted in a dose-related induction of transitional-cell neoplasms of the bladder. After subcutaneous injection of rats with sodium cyclamate, no tumour was observed at the site of injection, the only site for which tumour incidence was reported. A significant increase in the incidence of bladder carcinomas was observed in mice given bladder implants of pellets containing sodium cyclamate [ref: 1]. Transplacental application of cyclamate to rats did not produce an increase in tumour incidence at any site [ref: 19].

Calcium cyclamate did not alter tumour incidence when tested by oral administration in a two-generation experiment in rats but produced local tumours in another experiment following its subcutaneous injection [ref: 1].

Cyclohexylamine was tested by oral administration at several dose levels in different strains of mice and rats, and in one multigeneration study in mice. No tumour related to treatment was observed [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of calcium cyclamate, dicyclohexylamine or cyclohexylamine in humans. In a single study, eight persons ingesting sodium cyclamate (70 mg/kg per day) did not exhibit chromosomal aberrations in their lymphocytes [ref: 20].

Calcium cyclamate induced chromosomal aberrations in bone-marrow cells of gerbils, but not in bone-marrow cells or spermatogonia of rats treated *in vivo*. It did not induce dominant lethal mutations in rats or mice or micronuclei or sperm abnormalities in mice treated *in vivo*. It induced chromosomal aberrations in human lymphocytes but not in rat kangaroo cells in culture. It did not induce aneuploidy in *Drosophila*, but contradictory results were reported in assays for sex-linked recessive lethal mutations and heritable translocations. Calcium cyclamate was not mutagenic to bacteria [ref: 20].

Sodium cyclamate did not induce dominant lethal mutations or chromosomal aberrations in spermatogonia or spermatocytes of mice treated *in vivo*. It induced sister chromatid exchanges and chromosomal aberrations in cultured human lymphocytes and chromosomal aberrations in cultured Chinese hamster cells. It did not induce aneuploidy or sex-linked recessive lethal mutations in *Drosophila* or chromosomal aberrations in plants [ref: 20].

Cyclohexylamine did not induce dominant lethal mutations in one study in rats, but contradictory results were obtained in mice. It gave weakly positive results in the mouse spot test. Cyclohexylamine induced chromosomal aberrations in lymphocytes but not in bone-marrow cells of hamsters and lambs or in spermatogonia of hamsters and mice treated *in vivo*. In treated rats, chromosomal aberrations were induced in spermatogonia but not in leucocytes, and contradictory results were obtained for bone-marrow cells. Cyclohexylamine induced sister chromatid exchanges in cultured human lymphocytes, but, again, conflicting results were obtained concerning the induction of chromosomal aberrations. Cyclohexylamine enhanced virus-induced transformation of Syrian hamster embryo cells and induced chromosomal aberrations in cultured rat kangaroo cells. It did not induce somatic or sex-linked recessive lethal mutations, aneuploidy or heritable translocations in *Drosophila* and was not mutagenic and did not induce prophage in bacteria. In host-mediated assays, it did not induce mutation in bacteria or chromosomal aberrations in human leucocytes [ref: 20].

Dicyclohexylamine induced chromosomal aberrations in cultured human lymphocytes. It was not mutagenic to bacteria [ref: 20].

**Overall evaluation**

Cyclamates are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 73 (1999)

**Also see previous evaluation**: Vol. 22 (1980)

**References**

1. IARC Monographs, 22, 55-109, 171-185, 1980

2. Howe, G.R., Burch, J.D., Miller, A.B., Cook, G.M., Estève, J., Morrison, B., Gordon, P., Chambers, L.W., Fodor, G. & Winsor, G.M. (1980) Tobacco use, occupation, coffee, various nutrients and bladder cancer. J. natl Cancer Inst., 64, 701-713

3. Hoover, R.M. & Strasser, P.H. (1980) Artificial sweeteners and human bladder cancer. Preliminary results. Lancet, i, 837-840

4. Walker, A.M., Dreyer, N.A., Friedlander, E., Loughlin, J., Rothman, K.J. & Kohn, H.I. (1982) An independent analysis of the National Cancer Institute study on non-nutritive sweeteners and bladder cancer. Am. J. publ. Health, 72, 376-381

5. Hoover, R. & Hartge, P. (1982) Non-nutritive sweeteners and bladder cancer. Am. J. publ. Health, 72, 382-383

6. Silverman, D.T., Hoover, R.N. & Swanson, G.M. (1983) Artificial sweeteners and lower urinary tract cancer: hospital vs. population controls. Am. J. Epidemiol., 117, 326-334

7. Wynder, E.L. & Stellman, S.D. (1980) Artificial sweetener use and bladder cancer: a case-control study. Science, 207, 1214-1216

8. Goldsmith, D.F. (1982) Calculation of potential bias in the odds ratio illustrated by a study of saccharin use and bladder cancer. Environ. Res., 27, 298-306

9. Kessler I.I. & Clark, J.P. (1978) Saccharin, cyclamate, and human bladder cancer. No evidence of

an association. J. Am. med. Assoc., 240, 349-355

10. Morrison, A.S. & Buring, J.E. (1980) Artificial sweeteners and cancer of the lower urinary tract. New Engl. J. Med., 302, 537-541

11. Morrison, A.S., Verhoek, W.G., Leck, I., Aoki, K., Ohno, Y. & Obata, K. (1982) Artificial sweeteners and bladder cancer in Manchester, UK, and Nagoya, Japan. Br. J. Cancer, 45, 332-336

12. Cartwright, R.A., Adib, R., Glashan, R. & Gray, B.K. (1981) The epidemiology of bladder cancer in West Yorkshire. A preliminary report on non-occupational aetiologies. Carcinogenesis, 2, 343-347

13. Jensen, O.M. & Kamby, C. (1982) Intra-uterine exposure to saccharine and risk of bladder cancer in man. Int. J. Cancer, 29, 507-509

14. Møller-Jensen, O., Knudsen, J.B., Sørensen, B.L. & Clemmesen, J. (1983) Artificial sweeteners and absence of bladder cancer risk in Copenhagen. Int. J. Cancer, 32, 577-582

15. Piper, J.M., Matanoski, G.M. & Tonascia, J. (1986) Bladder cancer in young women. Am. J. Epidemiol., 123, 1033-1042

16. Risch, H.A., Burch, J.D., Miller, A.B., Hill, G.B., Steele, R. & Howe, G.R. (1987) Dietary factors and the incidence of cancer of the urinary bladder. Am. J. Epidemiol. (in press)

17. Morrison, A.S. (1979) Use of artificial sweeteners by cancer patients. J. natl Cancer Inst., 62, 1397-1399

18. Schmähl, D. & Habs, M. (1984) Investigations on the carcinogenicity of the artificial sweeteners sodium cyclamate and sodium saccharin in rats in a two-generation experiment. Arzneimittel.-Forsch., 34, 604-606

19. Schmähl, D. & Habs, M. (1980) Absence of carcinogenic response to cyclamate and saccharin in Sprague-Dawley rats after transplacental application. Arzneimittel.-Forsch., 30, 1905-1906

20. IARC Monographs, Suppl. 6, 188-195, 240-241, 1987

**Synonyms for Calcium cyclamate**

- Calcium cyclohexane sulphamate
- Calcium cyclohexylsulphamate
- Cyclamate calcium
- Cyclohexanesulphamic acid, calcium salt
- Cyclohexylsulphamic acid, calcium salt
- Cyclan
- Cylan
- Dietil
- Sucaryl calcium

**Synonyms for Cyclamic acid**

- Cyclamate
- Cyclohexanesulphamic acid
- Cyclohexylamidosulphuric acid
- Cyclohexylaminesulphonic acid
- Cyclohexylsulphamic acid
- *N*-Cyclohexylsulphamic acid
- Hexamic acid
- Sucaryl

- Sucaryl acid

**Synonyms for Cyclohexylamine**

- Aminocyclohexane
- Aminohexahydrobenzene
- CHA
- Hexahydroaniline
- Hexahydrobenzenamine

**Synonyms for Sodium cyclamate salt**

- Assugrin feinsuss
- Assugrin vollsuss [also contains saccharin]
- Asugryn
- Cyclamate sodium
- Cyclohexanesulphamic acid, monosodium salt
- Cyclohexylsulphamate sodium
- Cyclohexylsulphamic acid, monosodium salt
- Dulzor-etas
- Hachi-sugar
- Izbiosuc
- Natreen [also contains saccharin]
- Sodium cyclohexanesulphamate
- Sodium cyclohexyl amidosulfate
- Sodium cyclohexylsulphamate
- Sodium cyclohexylsulphamidate
- Sodium *N*-cyclohexylsulphamate
- Sodium sucaryl
- Sucaryl sodium
- Succaril [also contains saccharin]
- Sucrosa
- Sucrun 7
- Suessette
- Suestamin
- Sugarin
- Sugaron

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Last updated: 30 September 1999

# CYCLOPHOSPHAMIDE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 182)

**Cyclophosphamide**
**CAS No.:** 6055-19-2
**Chem. Abstr. Name**: 2*H*-1,3,2-Oxazaphosphorin-2-amine, *N*,*N*-bis(2-chloroethyl)-tetrahydro-, 2-oxide monohydrate

**Cyclophosphamide [anhydrous form]**
**CAS No.:** 50-18-0

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Many cases of cancer have been reported following therapy with cyclophosphamide [ref: 1].

Excess frequencies of bladder cancer following therapy with cyclophosphamide for nonmalignant diseases have been clearly demonstrated in two epidemiological studies [ref: 1,2]. Three recent studies confirmed that cyclophosphamide is also a leukaemogen. Among 602 patients treated predominantly with cyclophosphamide for non-Hodgkin's lymphoma in Denmark, nine cases of acute nonlymphocytic leukaemia (ANLL) or preleukaemia were observed, compared to 0.12 expected on the basis of incidence rates in the general population [ref: 3]. In the USA, three cases of ANLL or preleukaemia were observed among 333 women treated only with cyclophosphamide for ovarian cancer; 1.2 were expected [ref: 4]. In the German Democratic Republic, a case-control study was carried out of leukaemia arising as a second primary malignancy following breast or ovarian cancer. Relative risks of 1.5, 3.3 and 7.3 were estimated in association with cumulative doses of < 10 g, 10-29 g and > 30 g of cyclophosphamide, respectively [ref: 5].

Cyclophosphamide is a far less potent leukaemogen than 1,4-butanediol dimethanesulphonate (myleran) when used following surgery for lung cancer [ref: 6]. Similarly, melphalan produces a much higher incidence of leukaemia than cyclophosphamide when used in the therapy of multiple myeloma [ref: 7] and ovarian cancer [ref: 4]

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Cyclophosphamide has been tested for carcinogenicity by oral administration and by intravenous and intraperitoneal injection in rats and by subcutaneous and intraperitoneal injection in mice. It produced benign and malignant tumours at various sites, including the bladder, in rats after its oral or intravenous administration, and benign and malignant tumours at the site of injection and at distant sites in mice following its subcutaneous injection. There was some evidence of its carcinogenicity to mice and rats following intraperitoneal injection [ref: 1]. A study in which cyclophosphamide was given intraperitoneally to rats in combination with methotrexate and 5-fluorouracil resulted in induction of tumours in the nervous system, haematopoietic and lymphatic tissues, the urinary bladder and adrenal glands; however, because of lack of matched controls, it could not be concluded whether tumour inducation was due to a combined effect of the three chemicals or of any one of them [ref: 8].

**C. Other relevant data**

Cyclophosphamide is metabolized to an alkylating intermediate. Increased incidences of chromosomal aberrations and sister chromatid exchanges were observed in peripheral blood lymphocytes and, in one study, in bone-marrow cells of patients treated with cyclophosphamide for a variety of malignant and nonmalignant diseases [ref: 9].

Cyclophosphamide has been tested extensively for genetic effects in a wide variety of tests *in vivo* and *in vitro*, giving consistently positive results. It bound to DNA in kidney, lung and liver of mice and induced dominant lethal mutations, chromosomal aberrations, micronuclei, sister chromatid exchanges, mutation and DNA damage in rodents treated *in vivo*. In human cells *in vitro*, it induced chromosomal aberrations, sister chromatid exchanges and DNA damage. In rodent cells *in vitro*, it induced transformation, chromosomal aberrations, sister chromatid exchanges, mutation and unscheduled DNA synthesis. In *Drosophila*, it induced aneuploidy, heritable translocations and somatic and sex-linked recessive lethal mutations. In fungi, it induced aneuploidy, mutation, recombination, gene conversion and DNA damage. In host-mediated assays, it induced chromosomal aberrations and sister chromatid exchanges in human lymphoid cells, mutation and sister chromatid exchanges in Chinese hamster cells, gene conversion in yeast, and mutation in bacteria. It was active in body-fluid assays of urine from humans and rodents exposed *in vivo*, and in one study using plasma serum rats [ref: 9].

**Overall evaluation**

Cyclophosphamide is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 9 (1975); Vol. 26 (1981)

**References**


1. IARC Monographs, 26, 165-202, 1981

2. Kinlen, L.J. (1985) Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. Am. J. Med., 78 (Suppl. 1A), 44-49

3. Pedersen-Bjergaard, J., Ersbøll, J., Sørensen, H.M., Keiding, N., Larsen, S.O., Philip, P., Larsen, M.S., Schultz, H. & Nissen, N.I. (1985) Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. Ann. int. Med., 103, 195-200

4. Greene, M.H., Harris, E.L., Gershenson, D.M., Malkasian, G.D., Jr, Melton, L.J., III, Dembo, A.J., Bennett, J.M., Moloney, W.C. & Boice, J.D., Jr (1986) Melphalan may be a more potent leukemogen than cyclophosphamide. Ann. int. Med., 105, 360-367

5. Haas, J.F., Kittelmann, B., Mehnert, W.H., Staneczek, W., Mohner, M., Kaldor, J.M. & Day, N.E. (1987) Risk of leukaemia in ovarian tumour and breast cancer patients following treatment by cyclophosphamide. Br. J. Cancer, 55, 213-218

6. Stott, H., Fox, W., Girling, D.J., Stephens, R.J. & Galton, D.A.G. (1977) Acute leukaemia after busulphan. Br. med. J., ii, 1513-1517

7. Cuzick, J., Erskine, S., Edelman, D. & Galton, D.A.G. (1987) A comparison of the incidence of myelodysplastic syndrome and acute myeloid leukaemia following melphalan and cyclophosphamide treatment for myelomatosis. A report to the Medical Research Council's Working Party on leukaemia in adults. Br. J. Cancer, 55, 523-529

8. Habs, M., Schmahl, D. & Lin, P.Z. (1981) Carcinogenic activity in rats of combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil. Int. J. Cancer, 28, 91-96

9. IARC Monographs, Suppl. 6, 196-205, 1987

**Synonyms**

- Asta B 518
- B 518
- B 518-Asta
- 2-[Bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxaza-phosphorine 2-oxide monohydrate
- 2-[Bis(β-chloroethyl)amino]-1-oxa-3-aza-2-phosphacyclohexan-2-oxide monohydrate
- 1-Bis(2-chloroethyl)amino-1-oxo-2-aza-5-oxaphosphoridin monohydrate
- *N*,*N*-Bis(2-chloroethyl)-*N*'-(3-hydroxypropyl)phosphorodiamidic acid intramolecular ester monohydrate
- Bis(2-chloroethyl)phosphamide cyclic propanolamide ester monohydrate
- Bis(2-chloroethyl)phosphoramide cyclic propanolamide ester monohydrate
- *N*,*N*-Bis(2-chloroethyl)-*N*',*O*-propylenephosphoric acid ester diamide monohydrate
- *N*,*N*-Bis(β-chloroethyl)-*N*',*O*-propylenephosphoric acid ester diamide monohydrate
- *N*,*N*-Bis(β-chloroethyl)-*N*',*O*-trimethylenephosphoric acid ester diamide monohydrate
- Ciclofosfamide
- Clafen
- Claphene
- CP monohydrate
- Cyclophosphamid monohydrate
- 2-[Di(2-chloroethyl)amino]-1-oxa-3-aza-2-phosphacyclohexane 2-oxide monohydrate
- Cyclophospham
- Cyclophosphan
- Cyclophosphane
- Cytophosphan
- Cytoxan
- Endoxan
- Endoxana
- Endoxan-ASTA
- Enduxan
- Genoxal
- Mitoxan
- NSC 26271
- Procytox
- Sendoxan
- Syklofosfamid
- Zytoxan

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Last updated: 9 February 1998

# DACARBAZINE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 184)

**CAS No.:** 4342-03-4
**Chem. Abstr. Name**: 1*H*-Imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazenyl)-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of dacarbazine as a single agent was available to the Working Group. Occasional case reports of exposure to dacarbazine, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1].

In a large systematic follow-up of patients with Hogdkin's disease treated with an intensive chemotherapeutic combination including dacarbazine (plus adriamycin, vinblastine and bleomycin) but no alkylating agent, preliminary evidence suggested no excess of acute nonlymphocytic leukaemia in the first decade after therapy [ref: 2].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Following its oral or intraperitoneal administration to rats, dacarbazine produced tumours at various sites, including mammary gland, thymus, spleen and brain, in as little as 18 weeks after initial exposure [ref: 1]. After its intraperitoneal administration to rats at the end of pregnancy, dacarbazine produced tumours, the majority of which were malignant neurinomas, in offspring [ref: 3]. Dacarbazine produced tumours at various sites, including lung, haematopoietic tissue and uterus, after intraperitoneal administration to mice [ref: 1].

**C. Other relevant data**

Dacarbazine did not induce sister chromatid exchanges in lymphocytes of treated patients in one study. It gave weakly positive results for induction of sister chromatid exchanges in Chinese hamster cells *in vitro* and was mutagenic to cultured rodent cells and to bacteria [ref: 4].

**Overall evaluation**

Dacarbazine is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 203-212, 1981

2. Valagussa, P., Santoro, A., Bellani, F.F., Franchi, F., Banfi, A. & Bonadonna, G. (1982) Absence of treatment-induced second neoplasms after ABVD in Hodgkin's disease. Blood, 59, 488-494

3. Zeller, W.J. (1980) Prenatal carcinogenic action of 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide (DTIC) in the offspring of BD IX rats (Ger.). Arch. Geschwulstforsch., 50, 306-308

4. IARC Monographs, Suppl. 6, 208-209, 1987

**Synonyms**

- Deticene
- DIC
- 5-(3,3-Dimethyl-1-triazeno)imidazole-4-carboxamide
- 5-(3,3-Dimethyltriazeno)imidazole-4-carboxamide
- 4-(Dimethyltriazeno)imidazole-5-carboxamide
- 5-(Dimethyltriazeno)imidazole-4-carboxamide
- Dimethyl(triazeno)imidazolecarboxamide
- 5-(3,3-Dimethyl-1-triazenyl)-1H-imidazole-4-carboxamide
- DTIC
- DTIC-Dome
- NSC 45388

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Last updated: 2 March 1998

# DAPSONE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 185)

**CAS No.**: 80-08-0
**Chem. Abstr. Name**: Benzenamine, 4,4'-sulfonylbis-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Cases of cancer have been reported in patients treated with dapsone for dermatitis herpetiformis [ref: 1] and leprosy [ref: 2]. Several follow-up studies have been undertaken of patients with leprosy, some of whom were treated with dapsone [ref: 1,3-6]. Increased mortality from cancer, restricted to males (standardized mortality ratio [SMR], 1.5; 95% confidence interval, 1.1-1.9), has been observed only in the most recent of them. The excess was most evident for cancers of the oral cavity and bladder and for lymphoma in males (SMRs, 4.5, 4.0 and 3.0, respectively) and for dapsone users. Possible confounding effects of tobacco and alcohol intake could not be addressed, but there was no substantial increase in mortality from lung cancer [ref: 6].

**B. Evidence for carcinogenicity to animals** (*limited*)

Dapsone has been tested by oral administration in mice and rats, by intraperitoneal administration in mice and by prenatal and lifetime oral exposure in mice and rats. In three different studies in rats, high doses of dapsone induced mesenchymal tumours of the spleen in males (and of the peritoneum in two studies). An increased incidence of tumours of the thyroid was found in rats of each sex in one study and in males in a further study. The experiment in mice involving intraperitoneal administration of dapsone could not be evaluated. The other two experiments in mice did not provide evidence of carcinogenicity [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of dapsone in humans. It was not mutagenic to bacteria [ref: 7].

**Overall evaluation**

Dapsone is *not classifiable as to its carcinogenicity to humans (Group 3).*

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 24 (1980)

**References**

1. IARC Monographs, 24, 59-76, 1980

2. Troy, J.L., Grossman, M.E. & Walther, R.R. (1980) Squamous-cell carcinoma arising in a leprous neurotrophic ulcer. Report of a case. J. Dermatol. Surg. Oncol., 6, 659-661

3. Oleinick, A. (1968) Survival among leprosy patients with special consideration of cancer as a cause of death. Int. J. Lepr., 36, 318-327

4. Kolonel, L.N. & Hirohata, T. (1977) Leprosy and cancer: a retrospective cohort study in Hawaii. J. natl Cancer Inst., 58, 1577-1581

5. Tokudome, S., Kono, S., Ikeda, M., Kuratsune, M. & Kumamaru, S. (1981) Cancer and other causes of death among leprosy patients. J. natl Cancer Inst., 67, 285-289

6. Brinton, L.A., Hoover, R., Jacobson, R.R. & Fraumeni, J.F., Jr (1984) Cancer mortality among patients with Hansen's disease. J. natl Cancer Inst., 72, 109-114

7. IARC Monographs, Suppl. 6, 210-211, 1987

**Synonyms**

- Avlosulfon
- Avlosulphone
- Bis(4-aminophenyl)sulfone
- Bis(*p*-aminophenyl)sulfone
- Bis(*p*-aminophenyl)sulphone
- Bis-(4-aminophenyl)sulphone
- Croysulfone
- Croysulphone
- DADPS
- Dapson
- Dapsonum
- DDS
- DDS [pharmaceutical]
- DDS [VAN]
- 4,4'-Diaminodiphenyl sulfone
- 4,4'-Diaminodiphenyl sulphone
- Di(4-aminophenyl)sulfone
- Di(4-aminophenyl)sulphone
- Di(*p*-aminophenyl)sulfone
- Di(*p*-aminophenyl)sulphone
- Diamino-4,4'-diphenyl sulfone
- *p*,*p*-Diaminodiphenyl sulfone
- *p*,*p*-Diaminodiphenyl sulphone
- Diamino-4,4'-diphenyl sulphone
- Diaphenylsulfon
- Diaphenylsulfone
- Diaphenylsulphon
- Diaphenylsulphone
- Diphenasone
- Diphone
- Disulone
- Dubronax
- Dumitone
- Eporal
- F1358
- Maloprim
- Metabolite C
- Novophone
- Sulfona
- Sulfona-Mae
- Sulfone UCB
- 1,1'-Sulfonylbis(4-aminobenzene)
- 4,4'-Sulfonylbisaniline
- *p*,*p*-Sulfonyldianiline
- *p*,*p*-Sulphonyldianiline
- Sulphadione
- Sulphon-mere
- 1,1'-Sulphonylbis(4-aminobenzene)
- 4,4'-Sulfonylbisbenzamine

- *p*,*p*-Sulphonylbisbenzamine
- *p*,*p*-Sulfonylbisbenzamine
- *p*,*p*-Sulfonylbisbenzenamine
- 4,4'-Sulfonyldianiline
- 4,4'-Sulphonylbisbenzamine
- 4,4'-Sulphonylbisbenzenamine
- *p*,*p*-Sulphonylbisbenzenamine
- 4,4'-Sulphonyldianiline
- Sulphonyldianiline
- Tarimyl
- Udolac

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Last updated: 9 March 1998

# *ortho*-DICHLOROBENZENE (Group 3) and *para*-DICHLOROBENZENE (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.192)

***ortho*-Dichlorobenzene**
**CAS No.**: 95-50-1
**Chem. Abstr. Name**: Benzene, 1,2-dichloro-

***para*-Dichlorobenzene**
**CAS No.**: 106-46-7
**Chem. Abstr. name**: Benzene, 1,4-dichloro-

**A. Evidence for carcinogenicity to humans** (*inadequate* for *ortho*- and *para*-dichlorobenzene)

One report of a series of five cases has suggested an association between leukaemia and exposure to dichlorobenzenes [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate* for *ortho*-dichlorobenzene; *sufficient* for *para*-dichlorobenzene)

*ortho*-Dichlorobenzene was tested in mice and rats by gastric intubation; no evidence of carcinogenicity was observed [ref: 2]. A study by inhalation in several species was considered inadequate [ref: 1].

*para*-Dichlorobenzene was tested in mice and rats by gastric intubation; it caused renal tubular-cell adenocarcinomas in male rats and hepatocellular carcinomas in male and female mice [ref: 3]. It was also tested in mice and rats by inhalation; no increase in the incidence of tumours was noted, but the duration of exposure was limited [ref: 4].

**C. Other relevant data**

No data were available on the genetic and related effects of *ortho*- or *para*-dichlorobenzene in humans. *ortho*-Dichlorobenzene was not mutagenic to fungi or bacteria. *para*-Dichlorobenzene was mutagenic to fungi but not to bacteria [ref: 5].

**Overall evaluation**

*para*-Dichlorobenzene is *possibly carcinogenic to humans (Group 2B)*.

*ortho*-Dichlorobenzene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 73 (1999)

**Also see previous evaluations**: Vol. 7 (1974); Vol. 29 (1982)

**References**

1. IARC Monographs, 29, 213-238, 1982

2. National Toxicology Programme (1985) Toxicology and Carcinogenesis Studies of 1,2-Dichlorobenzene (*o*-Dichlorobenzene) (CAS No. 95-50-1) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies) (NTP TR 255; NIH Publ. No. 86-2511), Research Triangle Park, NC

3. National Toxicology Program (1987) Toxicology and Carcinogenesis Studies of 1,4-Dichlorobenzene (CAS No. 106-46-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies) (NTP TR No. 319; NIH Publ. No. 86-2575), Research Triangle Park, NC

4. Loeser, E. & Litchfield, M.H. (1983) Review of recent toxicology studies on *p*-dichlorobenzene. Food chem. Toxicol., 21, 825-832

5. IARC Monographs, Suppl. 6, 222-225, 1987

**Synonyms for *ortho*-Dichlorobenzene**

- Chloroben
- Chloroden
- Cloroben
- DCB
- 1,2-Dichlorobenzene
- *o*-Dichlorobenzene
- Dilatin DB
- Dizene
- Dowtherm E
- ODB
- ODCB
- Termitkil

**Synonyms for *para*-Dichlorobenzene**

- *para*-Chlorophenyl chloride
- Di-chloricide
- 1,4-Dichlorobenzene
- *p*-Dichlorobenzene
- Di-cloricide
- Evola
- Paracide
- Paradi
- Paradow
- Paramoth
- Parazene
- PDB
- PDCB
- Persia-perazol
- Santochlor

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Last updated: 30 September 1999

# 3,3'-DICHLOROBENZIDINE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 193)

**3,3'-Dichlorobenzidine**
**CAS No.**: 91-94-1
**Chem. Abstr. Name**: (1,1'-Biphenyl)-4,4'-diamine, 3,3'-dichloro-

**3,3'-Dichlorobenzidine Dihydrochloride**
**CAS No.**: 612-83-9
**Chem. Abstr. Name**: (1,1'-Biphenyl)-4,4'-diamine, 3,3'-dichloro-, dihydrochloride

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Three retrospective epidemiological studies of workers exposed to 3,3'-dichlorobenzidine gave no evidence of carcinogenicity, but the studies were of insufficient quality or statistical power to permit confident exclusion of this possibility. Because 3,3'-dichlorobenzidine and benzidine may be made in the same plant, 3,3'-dichlorobenzidine may have contributed to the incidence of bladder cancer attributed to benzidine [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

3,3'-Dichlorobenzidine was tested for carcinogenicity in mice, rats, hamsters and dogs by oral administration, in rats by subcutaneous administration and in mice by transplacental exposure. Following its oral administration, it produced liver-cell tumours in mice, hepatocellular carcinomas in dogs, mammary and Zymbal-gland tumours in rats and carcinomas of the urinary bladder in hamsters and dogs. Increased incidences of leukaemias were observed in rats following oral administration and in mice following transplacental exposure [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of 3,3'-dichlorobenzidine in humans. It has been reported to induce unscheduled DNA synthesis in cultured human cells. It was mutagenic to bacteria [ref: 2].

**Overall evaluation**

3,3'-Dichlorobenzidine is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 4 (1974) ; Vol. 29 (1982)

**References**

1. IARC Monographs, 29, 239-256, 1982

2. IARC Monographs, Suppl. 6, 226-227, 1987

**Synonyms for 3,3-Dichlorobenzidine**

- DCB
- 4,4'-Diamino-3,3'-dichlorobiphenyl
- 4,4'-Diamino-3,3'-dichlorodiphenyl
- Dichlorobenzidine
- *ortho,ortho'*-Dichlorobenzidine
- Dichlorobenzidine base
- 3,3'-Dichlorobenzidine base
- 3,3'-Dichlorobiphenyl-4,4'-diamine
- 3,3'-Dichloro-4,4'-biphenyldiamine
- 3,3'-Dichloro-4,4'-diaminobiphenyl
- 3,3'-Dichloro-4,4'-diamino(1,1-biphenyl)
- Curithane C126

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Last updated: 2 March 1998

# DIELDRIN
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 196)

**CAS No.**: 60-57-1

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Mean tissue levels of dieldrin were reported to be elevated in one necropsy study of 50 cancer patients compared to 42 control subjects [ref: 1]. Mean serum levels were not generally found to be elevated in cancer patients compared with controls in one study [ref: 2], but not in another [ref: 3]. Follow-up for four to 29 years (mean, 24 years) of 233 workers employed for four to 27 years (mean, 11 years) in the manufacture of aldrin, dieldrin and endrin revealed nine deaths from cancer with 12 expected (standardized mortality ratio [SMR], 75; 95% confidence interval, 25-125) [ref: 4,5]. In a similar study, 90% of 1155 men employed in the manufacture of aldrin, dieldrin and endrin were followed for 13 years or more. Mortality from all cancers was not increased (SMR, 82; 56-116), although there were apparent increases in mortality from cancers of the oesophagus, rectum and liver based on very small numbers [ref: 6].

**B. Evidence for carcinogenicity to animals** (*limited*)

Dieldrin has been tested by oral administration in mice, rats, trout, hamsters, dogs and monkeys. In mice, it produced benign and malignant liver neoplasms [ref: 1,7-10]; no carcinogenic effect was observed in feeding studies using several strains of rats [ref: 1,8,11], trout [ref: 12] and hamsters [ref: 13], the latter having been given relatively high doses. Feeding studies in dogs and monkeys were inadequate for evaluation [ref: 1]. Dietary administration to trout of dieldrin enhanced the incidence of liver tumours induced by dietary administration of aflatoxin $B_1$ [ref: 12].

**C. Other relevant data**

In one study, chromosomal aberrations were not found in peripheral blood lymphocytes of workers exposed to dieldrin [ref: 14].

Dieldrin did not induce dominant lethal mutations in mice or chromosomal aberrations in bone-marrow cells of Chinese hamsters treated *in vivo*. It induced unscheduled DNA synthesis in transformed human fibroblasts but not in rat hepatocytes; it did not induce single-strand breaks in Chinese hamster V79 cells. Dieldrin inhibited intercellular communication in human and rodent cell systems. It did not induce sex-linked recessive lethal mutations in *Drosophila*, was not mutagenic to bacteria and did not induce breakage of plasmid DNA [ref: 14].

**Overall evaluation**

Dieldrin is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 5 (1974)

**References**

1. IARC Monographs, 5, 125-156, 1974

2. Caldwell, G.G., Cannon, S.B., Pratt, C.B. & Arthur, R.D. (1981) Serum pesticide levels in patients with childhood colorectal carcinoma. Cancer, 48, 774-778

3. Davis, J.E., Barquet, A., Morgade, G. & Raffionelli, A. (1975) Epidemiologic studies of DDT and dieldrin residues and their relationship to human carcinogenesis. In: Proceedings of an International Symposition on Recent Advances in Assessing Health Effects of Environmental Pollution, Vol. 2 (EUR 5360), Luxembourg, Commission of the European Communities, pp. 695-702

4. van Raalte, H.G.S. (1977) Human experience with dieldrin in perspective. Ecotoxicol. environ. Saf., 1, 203-210

5. Ribbens, P.H. (1985) Mortality study of industrial workers exposed to aldrin, dieldrin and endrin. Int. Arch. occup. environ. Health, 56, 75-79

6. Ditraglia, D., Brown, D.P., Namekata, T. & Iverson, N. (1981) Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand. J. Work Environ. Health, 7 (Suppl. 4), 140-146

7. Tennekes, H.A., Wright, A.S., Dix, K.M. & Koeman, J.H. (1981) Effects of dieldrin, diet, and bedding on enzyme function and tumor incidence in livers of male CF-1 mice. Cancer Res., 41, 3615-3620

8. National Cancer Institute (1978) Bioassays of Aldrin and Dieldrin for Possible Carcinogenicity (Tech. Rep. Ser. No. 21; DHEW Publ. No. (NIH) 78-821), Bethesda, MD, Carcinogenesis Testing Program, Division of Cancer Cause and Prevention

9. Ruebner, B.H., Gershwin, M.E., Hsieh, L. & Dunn, P. (1980) Ultrastructure of spontaneous neoplasms induced by diethylnitrosamine and dieldrin in the $C_3H$ mouse. J. environ. Pathol. Toxicol., 4, 237-254

10. Meierhenry, E.F., Ruebner, B.H., Gershwin, M.E., Hsieh, L.S. & French, S.W. (1983) Dieldrin-induced Mallory bodies in hepatic tumors of mice of different strains. Hepatology, 3, 90-95

11. National Cancer Institute (1978) Bioassay of Dieldrin for Possible Carcinogenicity (Tech. Rep. Ser. No. 22; DHEW Publ. No. (NIH) 78-822), Bethesda, MD, Carcinogenesis Testing Program, Division of Cancer Cause and Prevention

12. Hendricks, J.D., Putnam, T.P. & Sinnhuber, R.O. (1979) Effect of dietary dieldrin on aflatoxin $B_1$ carcinogenesis in rainbow trout (*Salmo gairdneri*). J. environ. Pathol. Toxicol., 2, 719-728

13. Cabral, J.R.P., Hall, R.K., Bronczyk, S.A. & Shubik, P. (1979) A carcinogenicity study of the pesticide dieldrin in hamsters. Cancer Lett., 6, 241-246

14. IARC Monographs, Suppl. 6, 242-244, 1987

**Synonyms**

- ENT 16,225
- HEOD
- 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4,5,8-dimethano-naphthalene(endo-exo isomer)
- 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-exo-1,4:5,8-dimethano-
  naphthalene
- 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-exo-5,8-dimethano-

naphthalene
- 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo-exo-5,8-dimethano-
naphthalene
- 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,exo-5,8-dimethano-
naphthalene
- 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-exo-1,4-endo-5,8-dimethano-
naphthalene
- 1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-exo-5,8-endo-dimethano-
naphthalene

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Last updated: 9 March 1998

# DIETHYLSTILBOESTROL
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 273)

**Diethylstilboestrol**
**CAS No.**: 56-53-1
**Chem. Abstr. Name**: (E)-4,4'-(1,2-Diethyl-1,2-ethenediyl)bisphenol

**Diethylstilboestrol dipropionate**
**CAS No.**:130-80-3
**Chem. Abstr. Name**: (E)-4,4'-(1,2-Diethyl-1,2-ethenediyl)bisphenol dipropionate

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Diethylstilboestrol (DES) causes clear-cell adenocarcinoma of the vagina and cervix in women exposed in utero. There is sufficient evidence that administration of oestrogens for the control of symptoms of the climacteric is causally related to an increased incidence of endometrial carcinoma; DES is no different from other oestrogens in this respect [ref: 1].

There is also clear evidence that administration of DES in large doses during pregnancy increases the subsequent risk of breast cancer and that DES increases the risk of testicular cancer in males exposed *in utero*.

In four follow-up studies [ref: 2-5] of exposed and nonexposed groups of women, the possible effects of DES exposure during pregnancy on subsequent breast cancer risk have been evaluated. All have shown an increased risk in exposed women; two were randomized trials [ref: 2,3]. In one [ref: 2], there were 32 (4.6%) breast cancers among 693 women exposed to an average total dose of 12 g DES, and 21 (3.1%) breast cancers among 668 control (placebo) women. In the other [ref: 3], there were four (5.0%) breast cancers among 80 women exposed to an average total dose DES of 16 g (plus ethisterone, average total dose, 14 g), compared to none of 76 controls; all 156 women were diabetic. In two studies, an exposed group and a 'matched' unexposed group were followed-up [ref: 4,5]. One [ref: 4] found 118 (4.4%) breast cancer cases in 2680 women exposed to a mean DES dose of 5 g, and 80 (3.1%) among 2566 control women. The other [ref: 5] similarly showed 38 (2.5%) breast cancer cases among 1531 women exposed to a mean DES dose of 2 g, and 24 (1.7%) cases among the 1404 control women. The overall relative risk from these four studies is 1.5 ($p$ = 0.001).

A further group of 408 DES-exposed women (median dose, 1.5 g) was followed up and the eight breast cancer cases found were contrasted to the 8.1 cases expected on the basis of local breast cancer incidence rates [ref: 6]. If this study is considered together with the four studies described above, the overall relative risk is 1.4 ($p$ = 0.0016).

In all five papers [ref: 2-6], the possibility is discussed that there may be a long (15-20 years) 'latent' period before the first 'DES-induced' breast cancer would be seen. Clear evidence was found in a study [ref: 4] in which there was no difference in the breast cancer rates of exposed and unexposed women until 22 years after exposure, but an increasing difference thereafter. Similarly, in another study [ref: 3], there was no case in the exposed group in the first 18 years after exposure. In a further study [ref: 5], the relative risk was 1.3 before age 50 and 1.7 thereafter, and in another [ref: 6], three cases were reported with 5.1 expected before age 50 and five cases *versus* 3.0 expected thereafter. In contrast, however, a randomized study [ref: 2] showed 11 exposed cases and five nonexposed cases during the first 15 years of follow-up, compared to 21 exposed cases and 16 nonexposed cases thereafter. Further data are required to settle this issue.

The four follow-up studies [ref: 2-5] of exposed and nonexposed women also included information on other possibly 'hormone-related' cancers. The occurrence of endometrial cancer was not

increased in any study. The study [ref: 2] of 693 women exposed to DES and 668 controls showed increases in the occurrence of cancer of the ovary (4 exposed, 1 nonexposed), cancer of the cervix (7 exposed, 3 non-exposed) and cancer of the colon-rectum (2 exposed, 1 nonexposed); there was also a risk for cancer at these sites in the study of 1531 women exposed to DES and 1404 controls [ref: 5] (6 exposed, 2 nonexposed; 9 exposed, 6 nonexposed; 11 exposed, 7 nonexposed for the three sites, respectively). A third study [ref: 4] showed, in contrast, no elevation of rates for cancer at any other site, and there were seven deaths from cervical cancer in the control group and none in the exposed group, suggesting that matching in the control group was 'inadequate'; the authors could not identify the matching problem, and, in particular, they found that the two groups were well matched on educational level. The data are too few to draw any firm conclusions.

A greater frequency of abnormalities of the reproductive tract has been found in males exposed prenatally to DES in comparison with nonexposed controls, although the data are few. Cryptorchidism, a major risk factor for testicular cancer, is one of the associated lesions [ref: 1]. Cancer of the testis has been investigated in five case-control studies of fetal exposure to DES [ref: 7-11]. One [ref: 7] showed that 5.1% (4/78) of cases and 1% of controls had been exposed to hormones (in all likelihood DES) for bleeding; the second [ref: 8] similarly found that 5.8% (11/190) *versus* 2.3% (7/304) had had such exposure; the third [ref: 9] found 1.9% (2/108) *versus* 0 (0/108) exposed to DES; the fourth [ref: 10] found 1.0% (2/202) *versus* 1.0% (2/206) exposed to DES; and the fifth [ref: 11] found 1.9% (4/211) *versus* 0.9% (2/214) exposed to DES. The combined relative risk is 2.5 ($p$ = 0.014).

A number of unusual tumours have been reported in women exposed to DES *in utero*: a fatal adenocarcinoma of the endometrium at age 26 [ref: 12]; a pituitary adenoma at age 18 [ref: 13]; an invasive squamous-cell carcinoma of the cervix at age 21 [ref: 14]; an invasive adenosquamous-cell carcinoma of the cervix at age 27 [ref: 15]; and an ovarian teratoma at age 12 [ref: 16].

There has been no further report to add to the six cases of primary breast cancer in males with prostatic cancer treated with DES [ref: 1]. A case has been reported of a Leydig-cell tumour developing in such a man treated with DES at 1 mg per day for 2.5 years [ref 17]. There has been a second case report of hepatic angiosarcoma in a man treated over a long period with DES for prostatic cancer [ref: 1,18], and a second case report of a hepatoma in a prostatic cancer patient treated with DES at 3 mg per day for 4.5 years (to diagnosis of hepatoma) [ref: 1,19]. Three renal carcinomas have been reported after exposure to DES for prostatic cancer [ref: 20,21].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

DES has been tested in mice, rats, hamsters, frogs and squirrel monkeys, producing tumours principally in oestrogen-responsive tissues [ref: 1]. Female newborn mice injected with DES developed epidermoid carcinomas and granular-cell myoblastomas of the cervix and squamous carcinomas of the vagina [ref: 22]. Mice treated prenatally with DES developed adenocarcinomas of the uterus, cervix and vagina, epidermoid carcinomas of the uterine cervix and vagina and ovarian and mammary tumours [ref: 23-28]. Female mice fed diets containing DES developed cervical and endometrial adenocarcinomas, mammary adenocarcinomas, osteosarcomas and mesotheliomas [ref: 29-33]. Mice treated subcutaneously with DES had a slightly increased incidence of lymphomas and subcutaneous fibrosarcomas [ref: 34,35]. Prenatal exposure to DES potentiated mammary tumorigenesis in rats given 7,12-dimethylbenz[a]anthracene at about 50 days of age [ref: 36]. Rats given DES by subcutaneous pellet developed mammary and pituitary tumours. When these animals wee also treated with X-rays or neutrons, they developed a higher incidence of mammary tumours [ref: 37-39]. In other studies (subcutaneous, transplacental, oral), rats treated with DES developed mammary, hepatic and pituitary tumours [ref: 40-44]. When hamsters were treated prenatally with DES, females developed endometrial adenocarcinoma, squamous-cell papillomas of the cervix and vagina, and a mixed Mullerian tumour of the cervix (myosarcoma); in males, a leiomysarcoma of the seminal vesicles and a Cowper's gland adenoma were found [ref: 45]. Male hamsters castrated as adults and given DES subcutaneously developed renal tumours [ref: 46,47].

**C. Other relevant data**

No data were available on the genetic and related effects of DES in humans.

DES induced chromosomal aberrations in bone-marrow cells of mice treated *in vivo*, but data on

induction of sister chromatid exchanges and micronuclei were equivocal; it induced sister chromatid exchanges in one study in rats. Unusual nucleotides were found in kidney DNA following chronic treatment of hamsters with DES. Aneuploidy was induced in human cells *in vitro*, but data on induction of sister chromatid exchanges. chromosomal aberrations and mutation were inconclusive; it induced DNA strand breaks, but not unscheduled DNA synthesis, except in a single study. Tests for transformation in rat and Syrian hamster embryo cells gave positive results, while results for mouse cells were negative. Aneuploidy and DNA strand breaks were induced in rodent cells *in vitro*, but results for chromosomal aberrations and sister chromatid exchanges were equivocal; DES did not induce mutation or unscheduled DNA synthesis, except in a single study in Syrian hamster embryo cells. It did not inhibit intercellular communication of Chinese hamster V79 cells. It induced aneuploidy in fungi, but, in most studies, it did not induce mutation, recombination or gene conversion. It did not induce mutation in a variety of bacterial and insect systems, but it was mutagenic in plants. DNA damage was not induced in fungi or bacteria. DES induced single-strand breaks in bacteriophage DNA in the presence of a horseradish peroxidase activation system [ref: 48].

**Overall evaluation**

Diethylstilboestrol is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

**References**


1. IARC Monographs, 21, 131-134, 173-231, 1979

2. Bibbo, M., Haenszel, W.M., Wied, G.L., Hubby, M. & Herbst, A.L. (1978) A twenty-five-year follow-up of women exposed to diethylstilbestrol during pregnancy. New Engl. J. Med., 298, 763-767

3. Beral, V. & Colwell, L. (1980) Randomised trial of high doses of stilboestrol and ethisterone in pregnancy: Long-term follow-up of mothers. Br. med. J., 281, 1098-1101

4. Greenberg, E.R., Barnes, A.B., Resseguie, L., Barrett, J.A., Burnside, S., Lanza, L.L., Neff, R.K., Stevens, M., Young, R.H. & Colton, T. (1984) Breast cancer in mothers given diethylstilbestrol in pregnancy. New Engl. J. Med., 311, 1393-1398

5. Hadjimichael, O.C., Meigs, J.W., Falcier, F.W., Thompson, W.D. & Flannery, J.T. (1984) Cancer risk among women exposed to exogenous estrogens during pregnancy. J. natl Cancer Inst., 73, 831-834

6. Brian, D.D., Tilley, B.C., Labarthe, D.R., O'Fallon, W.M., Noller, K.L. & Kurland, L.T. (1980) Breast cancer in DES-exposed mothers. Absence of association. Mayo Clin. Proc., 55, 89-93

7. Henderson, B.E., Benton, B., Jing, J., Yu, M.C. & Pike, M.C. (1979) Risk factors for cancer of the testis in young men. Int. J. Cancer, 23, 598-602

8. Schottenfeld, D., Warshauer, M.E., Sherlock, S., Zauber, A.G., Leder, M. & Payne, R. (1980) The epidemiology of testicular cancer in young adults. Am. J. Epidemiol., 112, 232-246

9. Depue, R.H., Pike, M.C. & Henderson, B.E. (1983) Estrogen exposure during gestation and risk of testicular cancer. J. natl Cancer Inst., 71, 1151-1155

10. Brown, L.M., Pottern, L.M. & Hoover, R.N. (1986) Prenatal and perinatal risk factors for testicular cancer. Cancer Res., 46, 4812-4816

11. Moss, A.R., Osmond, D., Bacchetti, P., Torti, F.M. & Gurgin, V. (1986) Hormonal risk factors in testicular cancer. A case-control study. Am. J. Epidemiol., 124, 39-52

12. Barter, J.F., Austin, J.M., Jr & Shingleton, H.M. (1986) Endometrial adenocarcinoma after in utero diethylstilbestrol exposure. Obstet. Gynecol., 67 (Suppl.), 84S-85S

13. Cunningham, J.R., Gidwani, G.P., Gupta, M.S., Duchesneau, P.M. & Schumacher, O.P. (1982) Prolactin-secreting pituitary adenoma: occurrence following prenatal exposure to diethylstilbestrol. Cleveland Clin. Q., 49, 249-254

14. Lamb, E.J. (1977) Invasive squamous cell carcinoma of the cervix in a diethylstilbestrol-exposed offspring. Am. J. Obstet. Gynecol., 129, 924-925

15. Vandrie, D.M., Puri, S., Upton, R.T. & Demeester, L.J. (1983) Adenosquamous carcinoma of the cervix in a woman exposed to diethylstilbestrol *in utero*. Obstet. Gynecol., 61 (Suppl.), 84S-87S

16. Lazarus, K.H. (1984) Maternal diethylstilboestrol and ovarian malignancy in offspring. Lancet, i, 53

17. Deshmukh, A.S. & Hartung, W.H. (1983) Leydig cell tumor in patient on estrogen therapy. Urology, 21, 538-539

18. Ham, J.M., Pirola, R.C. & Crouch, R.L. (1980) Hemangioendothelial sarcoma of the liver associated with long-term estrogen therapy in a man. Dig. Dis. Sci., 25, 879-883

19. Brooks, J.J. (1982) Hepatoma associated with diethylstilbestrol therapy for prostatic carcinoma. J. Urol., 128, 1044-1045

20. Bellet, R.E. & Squitieri, A.P. (1974) Estrogen-induced hypernephroma. J. Urol., 112, 160-161

21. Nissenkorn, I., Servadio, C. & Avidor, I. (1979) Oestrogen-induced renal carcinoma. Br. J. Urol., 51, 6-9

22. Dunn, T.B. (1979) Cancer and other lesions in mice receiving estrogens. Recent Results Cancer Res., 66, 175-192

23. McLachlan, J.A. (1979) Transplacental effects of diethylstilbestrol in mice. Natl Cancer Inst. Monogr., 51, 67-72

24. McLachlan, J.A., Newbold, R.R. & Bullock, B.C. (1980) Long-term effects on the female mouse genital tract associated with prenatal exposure to diethylstilbestrol. Cancer Res., 40, 3988-3999

25. Lamb, J.C., IV, Newbold, R.R. & McLachlan, J.A. (1981) Visualization by light and scanning electron microscopy of reproductive tract lesions in female mice treated transplacentally with diethylstilbestrol. Cancer Res., 41, 4057-4062

26. Newbold, R.R. & MacLachlan, J.A. (1982) Vaginal adenosis and adenocarcinoma in mice exposed prenatally or neonatally to diethylstilbestrol. Cancer Res., 42, 2003-2011

27. Walker, B.E. (1983) Uterine tumors in old female mice exposed prenatally to diethylstilbestrol. J. natl Cancer Inst., 70, 477-484

28. Nagasawa, H., Mori, T. & Nakajima, Y. (1980) Long-term effects of progesterone or diethylstilbestrol with or without estrogen after maturity on mammary tumorigenesis in mice. Eur. J. Cancer, 16, 1583-1589

29. Highman, B., Greenman, D.L., Norvell, M.J., Farmer, J. & Shellenberger, T.E. (1980) Neoplastic and preneoplastic lesions induced in female C3H mice by diets containing diethylstilbestrol or 17β-estradiol. J. environ. Pathol. Toxicol., 4, 81-95

30. Highman, B., Roth, S.I. & Greenman, D.L. (1981) Osseous changes and oesteosarcomas in mice continuously fed diets containing diethylstilbestrol or 17β-estradiol. J. natl Cancer Inst., 67, 653-662

31. Greenman, D.L., Highman, B., Kodell, R.L., Morgan, K.T. & and Norvell, M. (1984) Neoplastic and nonneoplastic responses to chronic feeding of diethylstilbestrol in C3H mice. J. Toxicol. environ. Health, 14, 551-567

32. Greenman, D.L., Kodell, R.L., Highman, B., Schieferstein, G.J. & Norvell, M. (1984) Influence of strain and age on the induction of mammary tumours by diethylstilboestrol in C3H mice. Food chem. Toxicol., 22, 871-874

33. Greenman, D.L., Highman, B., Chen, J.J., Schieferstein, G.J. & Norvell, M.J. (1986) Influence of age on induction of mammary tumors by diethylstilbestrol in C3H/HeN mice with low murine mammary tumor virus titer. J. natl Cancer Inst., 77, 891-898

34. Boján, F., Rédai, I. & Gomba, S. (1979) Induction of lymphomas by urethane in combination with diethylstilboestrol in CFLP mice. Experientia, 35, 378-379

35. Ways, S. (1982) Local induction of fibrosarcomas by diethylstilbestrol. Int. Res. Commun. System med. Sci., 10, 796-797

36. Boylan, E.S. & Calhoon, R.E. (1979) Mammary tumorigenesis in the rat following prenatal exposure to diethylstilbestrol and postnatal treatment with 7,12-dimethylbenz(a)anthracene. J. Toxicol. environ. Health, 5, 1059-1071

37. Holtzman, S., Stone, J.P. & Shellabarger, C.J. (1979) Synergism of diethylstilbestrol and radiation in mammary carcinogenesis in female F344 rats. J. natl Cancer Inst., 63, 1071-1074

38. Holtzman, S., Stone, J.P. & Shellabarger, C.J. (1981) Synergism of estrogens and X-rays in mammary carcinogenesis in female ACI rats. J. natl Cancer Inst., 67, 455-459

39. Shellabarger, C.J., Chmelevsky, D., Kellerer, A.M., Stone, J.P. & Holtzman, S. (1982) Induction of mammary neoplasms in the ACI rat by 430-keV neutrons, X-rays, and diethylstilbestrol. J. natl Cancer Inst., 69, 1135-1146

40. Sumi, C., Yokoro, K. & Matsushima, R. (1983) Induction of hepatic tumors by diethylstilbestrol alone or in synergism with *N*-nitrosobutylurea in castrated male WF rats. J. natl Cancer Inst., 70, 937-942

41. Phelps, C. & Hymer, W.C. (1983) Characterization of estrogen-induced adenohypophyseal tumors in the Fischer 344 rat. Neuroendocrinology, 37, 23-31

42. Rothschild, T.C., Calhoon, R.E. & Boylan, E.S. (1985) Transplacental carcinogenicity of diethylstilbestrol (DES) in female ACI rats (Abstract No. 770). Proc. Am. Assoc. Cancer Res., 26, 195

43. Inoh, A., Kamiya, K., Fujii, Y. & Yokoro, K. (1985) Protective effects of progesterone and tamoxifen in estrogen-induced mammary carcinogenesis in ovariectomized W/FU rats. Jpn. J. Cancer Res. (Gann), 76, 699-704

44. Wanless, I.R. & Medline, A. (1982) Role of estrogens as promoters of hepatic neoplasia. Lab. Invest., 46, 313-320

45. Rustia, M. (1979) Role of hormone imbalance in transplacental carcinogenesis induced in Syrian golden hamsters by sex hormones. Natl Cancer Inst. Monogr., 51, 77-87

46. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

47. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

48. IARC Monographs, Suppl. 6, 250-256, 1987

**Synonyms for Diethylstilboestrol**

- Acnestrol
- Antigestil
- Bio-des
- 3,4-Bis(*para*-hydroxyphenyl)-3-hexene
- Bufon
- Comestrol
- Cyren
- Cyren A
- Dawe's destrol
- DEB
- DES
- Desma
- Destrol
- DiBestrol '2' Premix
- Dicorvin
- DiEstryl
- α,α'-Diethylstilbenediol
- (E)-α,α'-Diethyl-4,4'-stilbenediol
- *trans*-α,α'-Diethyl-4,4'-stilbenediol
- *trans*-Diethylstilbesterol
- Diethylstilbestrol
- *trans*-Diethylstilbestrol
- *trans*-Diethylstilboestrol
- 4,4'-Dihydroxydiethylstilbene
- 4,4'-Dihydroxy-α,β-diethylstilbene
- Distilbene
- Domestrol
- Estilbin 'MCO'
- Estrobene
- Estromenin
- Estrosyn
- [Follidiene]
- Fonatol
- Grafestrol
- Gynopharm
- Hi-Bestrol
- Idroestril
- Iscovesco
- Menostilbeen
- Microest
- Milestrol
- Neo-Oestranol I
- Oekolp
- Oestrogenine
- Oestrol Vetag
- Oestromenin
- Oestromensyl
- Oestromon

- Pabestrol
- Palestrol
- Percutatrine oestrogenique Iscovesco
- Rumestrol 1
- Rumestrol 2
- Sedestran
- Serral
- Sexocretin
- Sibol
- Sintestrol
- Stibilium
- Stilbestrol
- Stilbetin
- Stilboefral
- Stilboestrol
- Stilboestroform
- Stilbofollin
- Stilbol
- Stilkap
- Stil-Rol
- Synestrin
- Synthoestrin
- Synthofolin
- Syntofolin
- Tampovagan stilboestrol
- Tylosterone
- Vagestrol

**Synonyms for Diethylstilboestrol dipropionate**

- Clinestrol
- Cyren B
- Dibestil
- α,α,'-Diethyl-4,4'-stilbenediol dipropionate
- (E)-α,α'-Diethyl-4,4'-stilbenediol dipropionate
- α,α'-Diethyl-4,4'-stilbenediol trans-dipropionate
- α,α'-Diethyl-4,4'-stilbenediol dipropionyl ester
- Diethylstilbene dipropionate
- Diethylstilbesterol dipropionate
- Diethylstilbestrol dipropionate
- Diethylstilbestrol propionate
- Diethylstilboestrol dipropionate
- Diethylstilboestrol propionate
- Dihydroxydiethylstilbene dipropionate
- *para*,*para*'-Dipropionoxy-*trans*-α,β-diethylstilbene
- Estilben
- Estilbin
- Estrobene DF
- Estrobene DP
- Estrogenin
- Estrostilben
- Euvestin
- Gynolett
- Horfemine
- Neo-Oestranol II
- Neo-Oestronol II
- New-Oestranol 11
- Oestrogynaedron
- Orestol
- Pabestrol D
- Sinciclan
- Stilbestrol dipropionate
- Stilbestrol propionate
- Stilbestronate

- Stilboestrol dipropionate
- Stilboestrol DP
- Stilbofax
- Stilronate
- Synoestron
- Syntestrin
- Syntestrine
- Willestrol

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Last updated: 9 February 1998

# 3,3'-DIMETHOXYBENZIDINE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 198)

**CAS No.:** 119-90-4

**A. Evidence for carcinogenicity to humans** (*inadequate*)

3,3'-Dimethoxybenzidine (together with 3,3'-dichlorobenzidine and *ortho*-toluidine) has been prepared in the same plants as benzidine and may therefore have contributed to the bladder cancer risk associated with benzidine [ref: 1]. No case is on record in the USSR of an occupational urinary bladder neoplasm produced solely by this compound [ref: 2].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Following its oral administration, 3,3'-dimethoxybenzidine produced tumours in rats at various sites, including the bladder, intestine, skin and Zymbal gland; it produced forestomach papillomas in hamsters [ref: 3].

**C. Other relevant data**

3,3'-Dimethoxybenzidine has been found in the urine of workers exposed to it [ref: 3].

No data were available on the genetic and related effects of 3,3'-dimethoxybenzidine in humans. It induced sister chromatid exchanges in Chinese hamster cells *in vitro* and unscheduled DNA synthesis in human cells and rat hepatocytes *in vitro*. It was mutagenic to bacteria [ref: 4].

**Overall evaluation**

3,3'-Dimethoxybenzidine is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**

1. Clayson, D.B. (1976) Occupational bladder cancer. Prev. Med., 5, 228-244

2. Genin, V.A. (1974) Hygienic assessment of dianisidine-sulphate production from standpoint of carcinogenous hazard for workers (Russ.). Gig. Tr. prof. Zabol., 6, 18-22

3. IARC Monographs, 4, 41-47, 1974

4. IARC Monographs, Suppl. 6, 262-263, 1987

**Synonyms**

- Bianisidine

- 4,4'-Diamino-3,3'-dimethoxybiphenyl
- Di-para-amino-di-meta-methoxydiphenyl
- Dianisidine
- ortho-Dianisidine
- 3,3'-Dimethoxy-4,4'-diaminobiphenyl

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Last updated: 2 March 1998

# ERIONITE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 203)

**CAS No.:** 66733-21-9

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Descriptive studies have demonstrated very high mortality from malignant mesothelioma, mainly of the pleura, in three Turkish villages where there was contamination from erionite and where exposure had occurred from birth [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Erionite has been tested in mice by intraperitoneal injection and in rats by inhalation, intrapleural and intraperitoneal administration, producing high incidences of mesotheliomas [ref: 1,2].

**C. Other relevant data**

Erionite fibres were identified in lung tissue samples in cases of pleural mesothelioma; ferruginous bodies were found in a much higher proportion of inhabitants in contaminated villages in Turkey than in those of two control villages [ref: 1].

No data were available on the genetic and related effects of erionite in humans. It induced unscheduled DNA synthesis in human cells *in vitro* and transformation and unscheduled DNA synthesis in mouse C3H 10T1/2 cells [ref: 3].

**Overall evaluation**

Erionite is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 42 (1987)

**References**

1. IARC Monographs, 42, 225-239 1987

2. Pott, F. (1987) The fibre as a carcinogenic agent (Ger.). Zbl. Bakt. Hyg. B, 184, 1-23

3. IARC Monographs, Suppl. 6, 291-292, 1987

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Last updated: 9 February 1998

# ETHYLENE THIOUREA
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 207)

**CAS No.:** 96-45-7

**A. Evidence for carcinogenicity to humans** (*inadequate*)

In one incidence study, 1929 workers were identified as having worked at some time with ethylene thiourea in one of several rubber manufacturing companies and in one firm producing ethylene thiourea. No case of thyroid cancer was reported in this group to the regional cancer registry between 1957 and 1971, although less than one case would have been expected [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

In three studies, ethylene thiourea produced high incidences of follicular carcinomas of the thyroid in rats after its oral administration; animals of each sex were affected, although male rats had a higher incidence. Lower doses produced thyroid follicular hyperplasia [ref: 2-6]. In mice, oral administration of ethylene thiourea produced liver tumours; the thyroids of these animals were not examined [ref: 2]. In dosed rats, either shortened survival due to thyroid tumours or altered body weights may have obscured a potential carcinogenic effect on the liver due to administration of ethylene thiourea. A feeding study in hamsters showed no effect [ref: 6].

**C. Other relevant data**

No data were available on the genetic and related effects of ethylene thiourea in humans.

Ethylene thiourea did not induce dominant lethal mutations, micronuclei or sister chromatid exchanges in mice or chromosomal aberrations in rats treated *in vivo*. It did not induce unscheduled DNA synthesis in human fibroblasts *in vitro* or chromosomal aberrations, sister chromatid exchanges, mutation or unscheduled DNA synthesis in rodent cells *in vitro*. Ethylene thiourea did not induce sex-linked recessive lethal mutations in *Drosophila*, but it induced aneuploidy and mutation in yeast. Studies on gene conversion and DNA damage in yeast and on mutation in bacteria have given conflicting results [ref: 7].

**Overall evaluation**

Ethylene thiourea is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001)

**Also see previous evaluation**: Vol. 7 (1974)

**References**

1. Smith, D. (1976) Ethylene thiourea - a study of possible teratogenicity and thyroid carcinogenicity. J. Soc. occup. Med., 26, 92-94

2. IARC Monographs, 7, 45-52, 1974

3. Graham, S.L., Hansen, W.H., Davis, K.J. & Perry, C.H. (1973) Effects of one-year administration of ethylenethiourea upon the thyroid of the rat. J. agric. Food Chem., 21, 324-329

4. Graham, S.L., Davis, K.J., Hansen, W.H. & Graham, C.H. (1975) Effects of prolonged ethylene thiourea ingestion on the thyroid of the rat. Food Cosmet. Toxicol., 13, 493-499

5. Weisburger, E.K., Ulland, B.M., Nam, J.-M., Gart, J.J. & Weisburger, J.H. (1981) Carcinogenicity tests of certain environmental and industrial chemicals. J. natl Cancer Inst., 67, 75-88

6. Gak, J.-C., Graillot, C. & Truhaut, R. (1976) Difference in sensitivity of the hamster and of the rat with regard to the effects of the long-term administration of ethylene thiourea (Fr.). Eur. J. Toxicol., 9, 303-312

7. IARC Monographs, Suppl. 6, 304-307, 1987

**Synonyms**

- 4,5-Dihydroimidazole-2(3*H*)-thione
- *N*,*N*'-Ethylenethiourea
- 1,3-Ethylene-2-thiourea
- ETU
- 2-Imidazolidinethione
- 2-Imidazoline-2-thiol
- 2-Mercaptoimidazoline
- NA-22
- NA-22-D
- Pennac CRA
- Sodium-22 neoprene accelerator
- 2-Thiol-dihydroglyoxaline
- Warecure C

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Last updated: 2 March 1998

# FLUORIDES (INORGANIC, USED IN DRINKING-WATER)
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 208)

**Sodium fluoride**
**CAS No.**: 7681-49-4

**Fluosilicic acid**
**CAS No.**: 16961-83-4
**Chem. Abstr. Name**: Silicate (2-), hexafluoro-, dihydrogen

**Sodium silicofluoride**
**CAS No.**: 16893-85-9
**Chem. Abstr. Name**: Silicate (2-), hexafluoro-, disodium

**Fluorspar**
**CAS No.**: 14542-23-5
**Chem. Abstr. Name**: Fluorite [$CaF_2$]

**Stannous fluoride**
**CAS No.**: 7783-47-3
**Chem. Abstr. Name**: Tin fluoride [$SnF_2$]

**Sodium monofluorophosphate**
**CAS No.**: 10163-15-2
**Chem. Abstr. Name**: Phosphorofluoridic acid, disodium salt

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Only studies on water fluoridation and cancer were reviewed. Comparisons have been made of mortality from cancers at all sites and from particular types of cancer between areas with high concentrations of inorganic fluoride in drinking-water (either occurring naturally or as a consequence of fluoridation) and areas with low concentrations, or before and after fluoridation; the areas or groups of areas most frequently studied are Australia, Canada, China, England and Wales, New Zealand, Norway and the USA [ref: 1-6]. When possible, confounding of fluoride concentration with relevant variables such as age, sex, race and ethnic composition of the populations was taken into account. Fluoridation of drinking-water was introduced in the USA in 1950 [ref: 1], and thus the studies in the USA encompass periods of observation of 20 years or more. Studies of areas with different levels of naturally fluoridation cover longer periods of exposure [ref: 1,6]. The studies have shown no consistent tendency for people living in areas with high concentrations of fluoride in the water to have higher cancer rates than those living in areas with low concentrations or for cancer mortality rates to increase following fluoridation.

In several studies, trends in cancer incidence or mortality in naturally or artificially fluoridated areas and in areas with low natural fluoride content and no artificially fluoridated water were evaluated according to individual cancer sites or groups of sites [ref: 1,3,4,6]. Since a large number of comparisons were made, some would be expected by chance alone to show differences. However, no consistent difference has been seen, and there have been as many significant negative associations between fluoridated water supplies and cancer incidence or mortality as there have been positive associations.

Many studies, therefore, cover the range of doses of fluorides in drinking-water to which humans are exposed, and these are mutually consistent in not showing a positive association between exposure to fluoride and overall cancer rates or rates of different cancers. The Working Group noted

that the studies involved were of the ecological or correlation type. The Group was therefore unable to classify the evidence for inorganic fluorides used in drinking-water as 'suggesting lack of carcinogenicity'.

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Sodium fluoride was tested in three experiments in three different strains of mice by oral administration. The available data are insufficient to allow an evaluation to be made [ref: 1].

**C. Other relevant data**

Epidemiological studies have shown no association between the presence of fluorides in drinking-water and the incidence of Down's syndrome [ref: 7].

Sodium fluoride did not induce DNA strand breaks in testicular cells of rats treated *in vivo* and did not cause chromosomal aberrations in bone-marrow or testicular cells or sister chromatid exchanges in bone-marrow cells of mice treated *in vivo*. It was reported to induce unscheduled DNA synthesis in cultured human cells, and conflicting results were obtained on the induction of chromosomal aberrations; it did not induce sister chromatid exchanges. It induced transformation of Syrian hamster embryo cells *in vitro*. At high doses and low cell survival, sodium fluoride induced dose-related increases in mutations in cultured mouse lymphoma cells. It did not induce aneuploidy in *Drosophila*. It induced chromosomal aberrations in plants. It did not induce gene conversion in yeast and was not mutagenic to bacteria [ref: 7].

Stannous fluoride, sodium monofluorophosphate and sodium silicofluoride did not induce sex-linked recessive lethal mutation in *Drosophila*, and sodium monoflourophosphate did not induce dominant lethal mutations in *Drosophila* [ref: 7].

**Overall evaluation**

Fluorides (inorganic, used in drinking-water) *are not classifiable as to their carcinogenicity to humans*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 27 (1982)

**References**

1. IARC Monographs, 27, 237-303, 1982

2. Wang, B. (1981) The relationship between malignancy and fluorine content in the drinking water in Xilinkuolemeng, Nei Menggu (Chin.). Zhonghua Zhongliu Zazhi, 3, 19-21

3. Neuberger, J.S. (1982) Fluoridation and cancer: an epidemiologic appraisal. J. Kansas med. Soc., 83, 134-139

4. Chilvers, C. (1982) Cancer mortality by site and fluoridation of water supplies. J. Epidemiol. Commun. Health, 36, 237-242

5. Chilvers, C. (1983) Cancer mortality and fluoridation of water supplies in 35 US cities. Int. J. Epidemiol., 12, 397-404

6. Chilvers, C. & Conway, D. (1985) Cancer mortality in England in relation to levels of naturally occurring fluoride in water supplies. J. Epidemiol. Commun. Health, 39, 44-47

7. IARC Monographs, Suppl. 6, 312-315, 1987

**Synonyms for Sodium fluoride**

- Antibulit
- Cavi-Trol
- Credo
- Disodium difluoride
- F1-Tabs
- FDA 0101
- Flozenges
- Fluor-O-Kote
- Fluoral
- Fluorident
- Fluorigard
- Fluorineed
- Fluorinse
- Fluoritab
- Fluorocid
- Fluorol
- Flura
- Flura-Drops
- Flura-Gel
- Flura-Loz
- Flurcare
- Flursol
- Fungol B
- Gel II
- Gelution
- Gleem
- Iradicav
- Kari-rinse
- Karidium
- Karigel
- Lea-cov
- Lemoflur
- Luride
- Luride lozi-tabs
- Na frinse
- Nafeen
- NaFpak
- Natrium fluoride
- Nufluor
- Ossalin
- Ossin
- Pediaflor
- Pedident
- Pennwhite
- Pergantene
- Phos-flur
- Point two
- Predent
- Rafluor
- Rescue squad
- So-flo
- Sodium fluoride cyclic dimer
- Sodium hydrofluoride
- Sodium monofluoride
- Stay-flo
- Studafluor
- Super-dent
- T-Fluoride
- Thera-flur

- Thera-flur-N
- Trisodium trifluoride
- Villiaumite
- Zymafluor

**Synonyms for Fluosilicic acid**

- Dihydrogen hexafluorosilicate (2-)
- Dihydrogen hexafluorosilicate
- FKS
- Fluorosilicic acid
- Hexafluorosilicic acid
- Hexafluosilicic acid
- Hydrofluorosilicic acid
- Hydrogen hexafluorosilicate
- Hydrosilicofluoric acid
- Sand acid
- Silicofluoric acid
- Silicon hexafluoride dihydride

**Synonyms for Sodium silicofluoride**

- Disodium hexafluorosilicate (2-)
- Disodium hexafluorosilicate
- Disodium silicofluoride
- Prodan
- Salufer
- Silicon sodium fluoride
- Sodium fluorosilicate
- Sodium fluosilicate
- Sodium hexafluorosilicate
- Sodium hexafluosilicate
- Sodium silicon fluoride

**Synonyms for Fluorspar**

- Acid-spar
- Calcium difluoride
- Calcium fluoride
- Irtran 3
- Liparite
- Met-spar

**Synonyms for Stannous fluoride**

- Aim
- Cap-Tin Mouthrinse
- Crest
- Fluoristan
- Gel-Kam
- Iradicar $SnF_2$
- Iradicar Stannous Fluoride
- King's Gel-Tin
- Stancare
- Stanide
- Tin bifluoride
- Tin difluoride
- Tin fluoride

**Synonyms for Sodium monofluorophosphate**

- Aquafresh
- Colgate with MFP fluoride
- Disodium phosphorofluoridate
- Disodium fluorophosphate
- Disodium monofluorophosphate
- Macleans Fluoride
- MFP
- Sodium fluorophosphate
- Sodium phosphorofluoridate

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Last updated: 9 March 1998

# 5-FLUOROURACIL
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 210)

**CAS No.**: 51-21-8
**Chem. Abstr. Name**: 2,4(1*H*,3*H*)-Pyrimidinedione, 5-fluoro-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of 5-fluorouracil as a single agent was available to the Working Group. Occasional case reports of exposure to 5-fluorouracil, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1].

No increased risk of second malignancies was found among 276 patients with colorectal cancer randomized to low-dose (20 mg/kg bw) 5-fluoro-2'-deoxyuridine adjuvant therapy, followed for 1774 person-years (14 second noncolorectal cancers observed, 15 expected) [ref: 2].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

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 [ref: 1]. It was reported that ingestion of 5-fluorouracil prevented or delayed the appearance of spontaneous mammary and pituitary tumours in old female rats; no histopathological evaluation was made of the tumours that developed [ref: 3]. A study in which 5-fluorouracil was given intraperitoneally to rats in combination with methotrexate and cyclophosphamide results in induction of tumours in the nervous system, haematopoietic and lymphatic tissue, the urinary bladder and the adrenal glands; however, because of the lack of matched controls, it could not be concluded whether tumour induction was due to a combined effect of the three chemicals or of any one of them [ref: 4].

**C. Other relevant data**

Neither chromosomal aberrations (in two patients) nor sister chromatid exchanges (in three patients) were induced following administration of 5-fluorouracil [ref: 5].

5-Fluorouracil induced micronuclei and aneuploidy but not specific locus mutations in mice treated *in vivo*. It induced aneuploidy, chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*, but caused genetic crossing-over in fungi. Studies on mutation in bacteria were inconclusive [ref: 5].

**Overall evaluation**

5-Fluorouracil is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 217-235, 1981

2. Boice, J.D., Greene, M.H., Keehn, R.J., Higgins, G.A. & Fraumeni, J.F., Jr (1980) Late effects of low-dose adjuvant chemotherapy in colorectal cancer. J. natl Cancer Inst., 64, 501-511

3. Ferguson, T. (1980) Prevention and delay of spontaneous mammary and pituitary tumors by long- and short-term ingestion of 5-fluorouracil in Wistar-Furth rats. Oncology, 37, 353-356

4. Habs, M., Schmähl, D. & Lin, P.Z. (1981) Carcinogenic activity in rats of combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil. Int. J. Cancer, 28, 91-96

5. IARC Monographs, Suppl. 6, 316-318, 1987

**Synonyms**

- Adrucil
- 2,4-Dioxo-5-fluoropyrimidine
- Efudex
- Efudix
- Fluoroplex
- 5-Fluoropyrimidin-2,4-diol
- 5-Fluoro-2,4-(1*H*,3*H*)-pyrimidinedione
- 5-Fluoro-2,4-pyrimidinedione
- 5-Fluoropyrimidine-2,4-(1*H*,3*H*)-dione
- 5-Fluoropyrimidine-2,4-dione
- Fluorouracil
- 5-Fluracil
- Fluracilum
- Fluoro uracil
- Fluoro-uracile
- Fluracil
- Fluril
- FU
- 5-FU
- NSC 19893
- Phthoruracil
- Ro-2-9757

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Last updated: 9 March 1998

# FURNITURE AND CABINET-MAKING
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 380)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Employment in the furniture-making industry has been associated with nasal adenocarcinoma; an increased risk for other nasal cancers has also been suggested [ref: 1]. Subsequent case reports [ref: 2-11] and epidemiological studies [ref: 12-18] have clearly corroborated an increased risk of nasal adenocarcinoma among workers in the furniture and cabinet-making industry.

A study was made of the incidence of and mortality from cancer in 5371 men employed in the Buckinghamshire, UK, furniture industry and followed for an average of 19 years since commencing work. The incidence of nasal adenocarcinoma was about 100 times that expected from the local population. For cancer of the bronchus, the standard registration ratio was 82 (95% confidence interval, 61-107), based on 53 cases, and the standardized mortality ratio (SMR) (corrected for the Oxford region) was 79 (59-105). However, a significant trend of increasing SMR with increasing dustiness of work was found. A trend of increasing SMR for bronchial cancer with increasing duration of work (not significant) was also found. A sample of the workforce alive in 1969 contained a lower percentage of current smokers than the general population, and there were slightly fewer smokers among the men in the dustiest jobs than in the less dusty jobs [ref: 12]. However, an update of the same study at the end of 1982 found no significant increase in mortality nor any trend towards increasing mortality with increased dustiness of work for cancer at any site apart from the nasal cavity [ref: 16].

A Swedish pilot case-control study found an odds ratio of 4.1 (1.6-10.6) for respiratory cancer other than nasal cancer in relation to wood work. This ratio was based on six exposed cases, four of which were in furniture workers (odds ratio, 6.0) [ref: 19]. In another Swedish study, 8141 furniture workers were followed for 19 years. Nasal adenocarcinoma was 63.4 times more common than expected, but no increased risk was found for laryngeal cancer, lung cancer or sinonasal cancer other than adenocarcinoma [ref: 17].

A cohort study of the Danish carpenters' and cabinet-makers' union [ref: 20] gives SMRs for lung cancer of 96 (68-114) in men aged 20-64 and 110 (92-127) in men aged 65-84.

Mortality from multiple myeloma among furniture workers was investigated in a US case-control study of 301 male cases and 858 controls who had died from other causes. Employment in the furniture industry was associated with a nonsignificant excess risk (odds ratio, 1.3) of multiple myeloma. The risk was somewhat higher for those who had died before age 65 (odds ratio, 1.7) and for those born before 1905 (odds ratio, 1.5), and was significantly elevated for those born before 1905 and who died before age 65 (odds ratio, 5.4; based on five cases; $p < 0.05$) [ref: 21].

A proportionate mortality study showed an elevated risk for death from all cancer (proportionate mortality ratio [PMR], 112; $p < 0.01$), stomach cancer (PMR, 128; $p < 0.01$) and non-Hodgkin's lymphoma (PMR, 139; $p < 0.05$) among woodworkers (including carpenters, cabinet-makers and furniture workers, lumber graders and scalers, sawyers in sawmills and woodworkers not classified elsewhere). In this mixed category, there was no death from sinonasal cancer [ref: 22].

Epidemiological data reported here and previously [ref: 1] thus provide sufficient evidence that nasal adenocarcinomas have been caused by employment in the furniture-making industry. The excess risk occurs (mainly) among those exposed to wood dust.

According to Acheson *et al.* [ref: 13], the fact that woodworking machinists (who saw timber) and cabinet- and chain makers (who shape, finish, sand and assemble furniture) experience similar risks makes it unlikely that the tumours are due to a chemical agent applied to the wood at a particular

stage of the process, but that they are more probably due to a substance in wood itself. Beech and oak, especially, have been incriminated, but the possibility that other hardwoods are carcinogenic cannot be ruled out. The carcinogenic substances in hardwood are, however, unknown.

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Among hamsters exposed by inhalation to fine particles of beech wood dust, one animal out of 22 had a nasal tumour. In these limited studies, inhalation of wood dust did not increase the incidence of nasal or respiratory-tract tumours induced by *N*-nitrosodimethylamine [ref: 23,24].

**C. Other relevant data**

A fraction of a methanol extract of beech-wood dust was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system [ref: 25].

**Overall evaluation**

Furniture and cabinet-making are *carcinogenic to humans (Group 1)*.

*For definition of the italicized terms, see Preamble Evaluation.*

***Also see previous evaluation**: Vol. 25 (1981)*

***References***


*1. IARC Monographs, 25, 99-138, 1981*

*2. Duclos, J.-C., Dubreuil, C., Contassot, J.C., Guinchard, R. & Arnould, G. (1979) Nasal ethmoid adenocarcinomas in woodworkers. Clinical and forensic aspects (Fr.). Arch. Mal. prof., 40, 909-917*

*3. Cecchi, F., Buiatti, E., Kriebel, D., Nastasi, L. & Santucci, M. (1980) Adenocarcinoma of the nose and paranasal sinuses in shoemakers and woodworkers in the province of Florence, Italy (1963-77). Br. J. ind. Med., 37, 222-225*

*4. Merler, E., Carnevale, F., D' Andrea, F., Macaccaro, G., Pisa, R., Capitanio, A., Cavazzani, M., Gentile, A. & Fantoni, G. (1981) Neoplasm of the nasal cavities and the paranasal sinuses and occupational exposure to wood dust (Ital.). Med. Lav., 72, 87-95*

*5. Marandas, P., Schwaab, G. & Cachin, Y. (1980) Wood workers and ethmoid tumours (Fr.). Ouest méd. 33, 1149-1153*

*6. Cabal, C. & Teyssier, J.-M. (1981) Ethmoid tumours in wood workers (Fr.). Arch. Mal. prof., 42, 303-305*

*7. Duclos, J.C., Dubreuil, C., Guinchard, R. & Arnould, G. (1981) Ethmoid nasal adenocarcinomas in wood workers (Fr.). Arch. Mal. prof., 42, 292-294*

*8. Marandas, P., Schwaab, G., Lecointre, F., Pene, F. & Vandenbrouck, C. (1981) Ethmoid tumours. Role of wood work and clinical aspects (Fr.). Arch. Mal. prof., 42, 294-300*

*9. Klintenberg, C., Olofsson, J., Hellquist, H. & Sökjer, H. (1984) Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. Cancer, 54, 482-488*

*10. von Thürauf, J. & Hartung, M. (1984) Adenocarcinoma of the nose and paranasal sinuses in*

*people employed in the wood industry in the Federal Republic of Germany (Ger.). Zbl. Arbeitsmed., 34, 8-15*

*11. Wolf, J., Hartung, M., Schaller, K.H., Kochem, W. & Valentin, H. (1986) Occurrence of adenocarcinoma of the nasal and paranasal sinuses in woodworkers (Ger.) Arbeitsmed. Sozialmed. Präventivmed., 7, 3-22*

*12. Rang, E.H. & Acheson, E.D. (1981) Cancer in furniture workers. Int. J. Epidemiol., 10, 253-261*

*13. Acheson, E.D., Winter, P.D., Hadfield, E. & Macbeth, R.G. (1982) Is nasal adenocarcinoma in the Buckinghamshire furniture industry declining? Nature, 299, 263-265*

*14. Battista, G., Cavallucci, F., Comba, P., Quercia, A., Vindigni, C. & Sartorelli, E. (1983) A case-referent study on nasal cancer and exposure to wood dust in the province of Sienna, Italy. Scand. J. Work Environ. Health, 9, 25-29*

*15. Hernberg, S., Westerholm, P., Schultz-Larsen, K., Degerth, R., Kuosma, E., Englund, A., Engzell, U., Sand Hansen, H. & Mutanen, P. (1983) Nasal and sinonasal cancer. Connection with occupational exposures in Denmark, Finland and Sweden. Scand. J. Work Environ. Health, 9, 315-326*

*16. Acheson, E.D., Pippard, E.C. & Winter, P.D. (1984) Mortality of English furniture makers. Scand. J. Work Environ. Health, 10, 211-217*

*17. Gerhardsson, M.R., Norell, S.E., Kiviranta, H.J. & Ahlbom, A. (1985) Respiratory cancers in furniture workers. Br. J. ind. Med., 42, 403-405*

*18. Malker, H.S.R., McLaughlin, J.K., Blot, W.J., Weiner, J.A., Malker, B.K., Ericsson, J.L.E. & Stone, B.J. (1986) Nasal cancer and occupation in Sweden, 1961-1979. Am. J. ind. Med., 9, 477-485*

*19. Esping, B. & Axelson, O. (1980) A pilot study on respiratory and digestive tract cancer among woodworkers. Scand. J. Work Environ. Health, 6, 201-205*

*20. Olsen, J. & Sabroe, S. (1979) A follow-up study of non-retired and retired members of the Danish Carpenter/Cabinet Makers' Trade Union. Int. J. Epidemiol., 8, 375-382*

*21. Tollerud, D.J., Brinton, L.A., Stone, B.J., Tobacman, J.K. & Blattner, W.A. (1985) Mortality from multiple myeloma among North Carolina furniture workers. J. natl Cancer Inst., 74, 799-801*

*22. Gallagher, R.P., Threlfall, W.J., Band, P.R. & Spinelli, J.J. (1987) Cancer mortality experience of woodworkers, loggers, fishermen, farmers, and miners in British Columbia. Natl Cancer Inst. Monogr., 69, 163-167*

*23. Wilhelmsson, B., Lundh, B., Drettner, B. & Stenkvist, B. (1985) Effects of wood dust exposure and diethylnitrosamine. A pilot study in Syrian golden hamsters. Acta otolaryngol., 99, 160-171*

*24. Drettner, B., Wilhelmsson, B. & Lundh, B. (1985) Experimental studies on carcinogenesis in the nasal mucosa. Acta otolaryngol., 99, 205-207*

*25. IARC Monographs, Suppl. 6, 573, 1987*

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*Last updated: 9 February 1998*

# GRISEOFULVIN
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:**: (1987) (p. 391)

**CAS No.**: 126-07-8
**Chem. Abstr. Name**: 2-S-*trans*)-7-Chloro-2',4,6-trimethoxy-6'-methylspiro[benzofuran-2(3*H*),1'-(2)-cyclohexene]-3,4'-dione

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Griseofulvin induced liver tumours following its oral administration to adult mice [ref: 1-3] or its subcutaneous administration to infant male mice [ref: 1]. When given orally to rats and hamsters, it produced a significant increase in the incidence of thyroid tumours in rats but had no carcinogenic effect in hamsters [ref: 2].

**Overall evaluation**

Griseofulvin is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001)

**Also see previous evaluation**: Vol. 10 (1976)

**References**

1. IARC Monographs, 10, 153-161, 1976

2. Rustia, M. & Shubik, P. (1978) Thyroid tumours in rats and hepatomas in mice after griseofulvin treatment. Br. J. Cancer, 38, 237-249

3. Chlumská, A.A. & Janousek, V. (1981) Hepatomas after long-term administration of griseofulvin (Czech.). Cesk. Patol., 17, 83-87

**Synonyms**

- Amudane
- Biogrisin-FP
- 7-Chloro-4,6-dimethoxycoumaran-3-one-2-spiro-1'-(2'-methoxy-6'-methylcyclohex-2'-en-4'-one)
- 7-Chloro-2',4,6-trimethoxy-6'β-methylspiro[benzofuran-2(3*H*),1'-(2)-cyclohexene]-3,4'-dione
- 7-Chloro-2',4,6-trimethoxy-6'-methyl-(2S-trans)-spiro[benzofuran-2*H*(3*H*),1'-(2)-cyclohexene]-
  3,4'-dione
- Curling factor
- Delmofulvina
- Fulcin
- Fulcine
- Fulvicin
- Fulvina

- Fungivin
- Fulvistatin
- Greosin
- Gricin
- Grifulvin
- Grisactin
- Griscofulvin
- Grisefuline
- Griseo
- (+)-Griseofulvin
- Grisetin
- Grisofulvin
- Grisovin
- Grysio
- Guservin
- Lamoryl
- Likuden
- Neo-Fulcin
- NSC 34533
- Poncyl
- Spirofulvin
- Sporostatin

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Last Updated: 2 March 1998

# GYROMITRIN
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 391)

**CAS No.**: 16568-02-8

**Chem. Abstr. Name**: Hydrazinecarboxaldehyde, ethylidenemethyl-

**Evidence for carcinogenicity to animals** (*limited*)

In one study, gyromitrin was administered by intragastric intubation to mice, producing increased incidences of tumours of the forestomach, clitoral gland and lung in females and of tumours of the preputial gland in males [ref: 1].

**Reference**

1. IARC Monographs, 31, 163-170, 1983

**Overall evaluation**

Gyromitrin is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 31 (1983)

**Synonyms**

- Formic acid, ethylidenemethylhydrazide
- Acetaldehyde-*N*-formyl-*N*-methylhydrazone
- Acetaldehyde-*N*-methyl-*N*-formylhydrazone
- Acetaldehyde methylformylhydrazone
- Ethylidene gyromitrin
- Acetaldehyde formylmethylhydrazone

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Last updated: 9 March 1998

# HAEMATITE AND FERRIC OXIDE:

## FERRIC OXIDE
## (Group 3)

## HAEMATITE
## (Group 3)

## UNDERGROUND HAEMATITE MINING WITH EXPOSURE TO RADON
## (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 216)

**Ferric oxide**
**CAS No.**: 1309-37-1

**Haematite**
**CAS No.**: 1317-60-8

**A. Evidence for carcinogenicity to humans** (*inadequate* for haematite and ferric oxide; *sufficient* for underground haematite mining with exposure to radon)

Underground haematite miners have a higher incidence of lung cancer in the presence of exposure to radon daughters (although other agents might also contribute to the risk) than surface haematite miners [ref: 1-11]. Haematite mining with low-grade exposure to radon daughters and silica dust was not associated with excess lung cancer in a relatively large cohort [ref: 12]. The importance of exposure to radon daughters in the occurrence of lung cancer in haematite miners is also suggested by the time trend of lung cancer rates in a mining population [ref: 4]. One mining population with an increased lung cancer risk but with current low exposure to radon daughters might have had higher exposures in the past due to poorer ventilation [ref: 13,14].

Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer [ref: 1,15], but the influence of factors in the workplace other than ferric oxide, i.e., soot, silica and asbestos in foundry work, cannot be discounted. In other studies of metal and chemical workers exposed to ferric oxide, the incidence of lung cancer has generally not been increased [ref: 1,16].

**B. Evidence for carcinogenicity to animals** (*inadequate* for haematite; *evidence suggesting lack of carcinogenicity* for ferric oxide)

No conclusive carcinogenic effect was observed in mice, hamsters or guinea-pigs given ferric oxide intratracheally or by inhalation [ref: 1]. Repeated intratracheal instillation to hamsters of benzo[*a*]pyrene bound to fine ferric oxide dust particles induced squamous-cell and anaplastic carcinomas [ref: 17]. There was no increase in tumour yield in hamsters administered a constant dose of benzo[*a*]pyrene and increasing amounts of ferric oxide intratracheally, indicating that, beyond a certain ratio of benzo[*a*]pyrene to ferric oxide, the latter does not affect tumour yield [ref: 18]. Administration of ferric oxide particles alone occasionally induced interstitial fibrosis, indicating that ferrous oxide particles act as cofactors in this system, mainly as carriers [ref: 19]. In one study, intrapleural inoculation of the respirable fraction of iron ore mine dust to female BALB/c mice resulted in an increased incidence of lung adenomas; in a second study, an increased incidence of lymphoma/leukaemia was observed in female C57BL/6J mice exposed chronically to the same dust. In neither study was the number of animals specified, nor whether the mice were killed serially or died; in the second study, the type of exposure was not specified [ref: 20]. In several studies in hamsters, ferric oxide was not carcinogenic when given alone but enhanced lung and nasal-cavity

carcinogenesis induced by *N*-nitrosodiethylamine and *N*-nitrosodimethylamine, respectively [ref: 21-23].

### C. Other relevant data

No data were available on the genetic and related effects of ferric oxide in humans. It did not induce transformation of Syrian hamster embryo cells [ref: 24].

### Overall evaluation

Ferric oxide is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Haematite is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Underground haematite mining with exposure to radon is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 1 (1972)

### References


1. IARC Monographs, 1, 29-39, 1972

2. Damber, L. & Larsson, L.-G. (1985) Underground mining, smoking, and lung cancer: a case-control study in the iron ore municipalities in northern Sweden. J. natl Cancer Inst., 74, 1207-1213

3. Edling, C. (1982) Lung cancer and smoking in a group of iron ore miners. Am. J. ind. Med., 3, 191-199

4. Edling, C. & Axelson, O. (1983) Quantitative aspects of radon daughter exposure and lung cancer in underground miners. Br. J. ind. Med., 40, 182-187

5. Icsó, J. & Szöllösová, M. (1984) The incidence of lung cancer in the miners of iron-ore mines (Czech). Pracov. Lék., 36, 294-298

6. Jorgensen, H.S. (1973) A study of mortality from lung cancer among miners in Kiruna 1950-1970. Work Environ. Health, 10, 126-133

7. Jorgensen, H.S. (1984) Lung cancer among underground workers in the iron ore mine of Kiruna based on thirty years of observation. Ann. Acad. Med., 13 (Suppl.), 371-377

8. Larsson, L.-G. & Damber, L. (1982) Interaction between underground mining and smoking in the causation of lung cancer: a study of nonuranium miners in northern Sweden. Cancer Detect. Prev., 5, 385-389

9. Radford, E.P. (1981) Radon daughters in the induction of lung cancer in underground miners. In: Peto, R. & Schneiderman, M., eds, Quantification of Occupational Exposure (Banbury Report 9), Cold Spring Harbor, NY, CSH Press, pp. 151-163

10. Radford, E.P. & St Clair Renard, K.G. (1984) Lung cancer in Swedish iron miners exposed to low doses of radon daughters. New Engl. J. Med., 310, 1485-1494

11. St Clair Renard, K.G. (1974) Respiratory cancer mortality in an iron ore mine in northern Sweden. Ambio, 3, 67-69

12. Lawler, A.B., Mandel, J.S., Schuman, L.M. & Lubin, J.H. (1985) A retrospective cohort mortality study of iron ore (hematite) miners in Minnesota. J. occup. Med., 27, 507-517

13. Anthoine, D., Braun, P., Cervoni, P., Schwartz, P. & Lamy, P. (1979) Should the lung cancer of iron miners in the Lorraine be considered an occupational disease? 270 new cases observed from 1964-1978 (Fr.). Rev. fr. Mal. respir., 7, 63-65

14. Pham, Q.T., Gaertner, M., Mur, J.M., Braun, P., Gabiano, M. & Sadoul, P. (1983) Incidence of lung cancer among iron miners. Eur. J. respir. Dis., 64, 534-540

15. Tola, S., Koskela, R.-S., Hernberg, S. & Järvinen, E. (1979) Lung cancer mortality among iron foundry workers. J. occup. Med., 21, 753-760

16. Axelson, O. & Sjöberg, A. (1979) Cancer incidence and exposure to iron oxide dust. J. occup. Med., 21, 419-422

17. Saffiotti, U. (1969) Experimental respiratory tract carcinogenesis. Prog. exp. Tumor Res., 11, 302-333

18. Sellakumar, A.R., Montesano, R., Saffiotti, U. & Kaufman, D.G. (1973) Hamster respiratory carcinogenesis induced by benzo[*a*]pyrene and different dose levels of ferric oxide. J. natl Cancer Inst., 50, 507-510

19. Stenback, F., Rowland, J. & Sellakumar, A. (1976) Carcinogenicity of benzo[*a*]pyrene and dusts in the hamster lung instilled intratracheally with titanium oxide, aluminium oxide, carbon and ferric oxide. Oncology, 33, 29-34

20. Keast, D., Tam, N., Sheppard, N. & Papadimitriou, J.M. (1985) The role of tobacco smoke, iron ore mine dusts, viruses, and chemicals in experimental cancer. Arch. environ. Health, 40, 296-300

21. Stenbäck, F., Ferrero, A., Montesano, R. & Shubik, P. (1973) Synergistic effect of ferric oxide on dimethylnitrosamine carcinogenesis in the Syrian golden hamster. Z. Krebsforsch., 79, 31-38

22. Nettesheim, P., Creasia, D.A. & Mitchell, T.J. (1975) Carcinogenic and cocarcinogenic effects of inhaled synthetic smog and ferric oxide particles. J. natl Cancer Inst., 55, 159-169

23. Feron, V.J., Emmelot, P. & Vossenaar, T. (1972) Lower respiratory tract tumours in Syrian golden hamsters after intratracheal instillations of diethylnitrosamine alone and with ferric oxide. Eur. J. Cancer, 8, 445-449

24. IARC Monographs, Suppl. 6, 310-311, 1987

**Synonyms for Ferric oxide**

- Food Yellow 11
- Iron oxide
- Sesquioxide of iron
- Solvent Yellow 6

**Synonyms for Haematite**

- Blood stone

- Iron ore
- Red iron ore

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Last updated: 9 February 1998

# HEXACHLOROBENZENE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 219)

**CAS No.**: 118-74-1

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No report of a direct association between hexachlorobenzene and human cancer is available. Hepatocellular carcinoma has been associated with porphyria [ref: 1-5]. However, although abnormal porphyrin metabolism persisted at least 20 years after an epidemic of porphyria cutanea tarda in Turkey, caused by consumption of grain treated with hexachlorobenzene [ref: 6], no excess cancer occurrence has been reported in this population 25 years after the accident [ref: 7].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

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 each sex; in hamsters of each sex, it produced hepatomas, liver haemangioendotheliomas and thyroid adenomas. An experiment involving intraperitoneal administration in mice was considered to be inadequate [ref: 6]. In a study in rats fed hexachlorobenzene in the diet, hepatomas, hepatocellular carcinomas, bile-duct adenomas and renal-cell adenomas were observed [ref: 8]. In a two-generation feeding study in rats with lower dose levels, increased incidences of parathyroid adenomas and adrenal phaeochromocytomas were observed in animals of each sex and liver neoplastic nodules in females of the $F_1$ generation [ref: 9]. After 90 weeks' feeding of hexachlorobenzene to rats, 100% of surviving females and only 16% of males had developed liver tumours [ref: 10].

**C. Other relevant data**

No data were available on the genetic and related effects of hexachlorobenzene in humans. It did not induce dominant lethal mutations in rats treated *in vivo*. It did not induce chromosomal aberrations in cultured Chinese hamster cells or mutation in bacteria [ref: 11].

**Overall evaluation**

Hexachlorobenzene is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001)

**Also see previous evaluation**: Vol. 20 (1979)

**References**

1. Kordac, V. (1972) Frequency of occurrence of hepatocellular carcinoma in patients with porphyria cutanea tarda in long-term follow-up. Neoplasma, 19, 135-139

2. Solis, J.A., Betancor, P., Campos, R., Enriquez de Salamanca, R., Rojo, P., Marin, I. & Schüller, A. (1982) Association of porphyria cutanea tarda and primary liver cancer: report of ten cases. J. Dermatol., 9, 131-137

3. Lithner, F. & Wetterberg, L. (1984) Hepatocellular carcinoma in patients with acute intermittent porphyria. Acta med. scand., 215, 271-274

4. Hardell, L., Bengtsson, N.O., Jonsson, U., Eriksson, S. & Larsson, L.G. (1984) Aetiological aspects on primary liver cancer with special regard to alcohol, organic solvents, and acute intermittent porphyria - an epidemiological investigation. Br. J. Cancer, 50, 389-397

5. Axelson, O. (1986) A review of porphyria and cancer and the missing link with human exposure to hexachlorobenzene. In: Morris, C.R. & Cabral, J.R.P., eds, Hexachlorobenzene: Proceedings of An International Symposium (IARC Scientific Publications No. 77), Lyon, International Agency for Research on Cancer, pp. 585-589

6. IARC Monographs, 20, 155-178, 1979

7. Peters, H.A., Gocmen, A., Cripps, D.J., Bryan, G.T. & Dogramaci, I. (1982) Epidemiology of hexachlorobenzene-induced porphyria in Turkey. Clinical and laboratory follow-up after 25 years. Arch. Neurol., 39, 744-749

8. Ertürk, E., Lambrecht, R.W., Peters, H.A., Cripps, D.J., Gocmen, A., Morris, C.R. & Bryan, G.T. (1986) Oncogenicity of hexachlorobenzene. In: Morris, C.R. & Cabral, J.R.P., eds, Hexachlorobenzene: Proceedings of an International Symposium (IARC Scientific Publications No. 77), Lyon, International Agency for Research on Cancer, pp. 417-423

9. Arnold, D.L., Moodie, C.A., Charbonneau, S.M., Grice, H.C., McGuire, P.F., Bryce, F.R., Collins, C.T., Zawidzka, Z.Z., Krewski, D.R., Nera, E.A. & Munro, I.C. (1985) Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. Food chem. Toxicol., 23, 779-793

10. Smith, A.G., Francis, J.E., Dinsdale, D., Manson, M.M. & Cabral, J.R.P. (1985) Hepatocarcinogenicity of hexachlorobenzene in rats and the sex difference in hepatic iron status and development of porphyria. Carcinogenesis, 6, 631-636

11. IARC Monographs, Suppl. 6, 331-332, 1987

**Synonyms**

- Amatin
- Anticarie
- Bunt-cure
- Bunt-no-more
- Co-op hexa
- Granox NM
- HCB
- Julin's carbon chloride
- No Bunt
- No Bunt 40
- No Bunt 80
- No Bunt liquid
- Pentachlorophenyl chloride
- Perchlorobenzene
- Sanocide
- Snieciotox

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Last updated: 2 March 1998

# HEXACHLOROCYCLOHEXANES
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 220)

**Hexachlorocyclohexane [mixed isomers]**
**CAS No.**: 608-73-1
**Chem. Abstr. Name**: 1,2,3,4,5,6-Hexachlorocyclohexane

**Hexachlorocyclohexane [α-isomer]**
**CAS No.**: 319-84-6
**Chem. Abstr. Name**: 1α,2α,3β,4α,5β,6α-Hexachlorocyclohexane

**Hexachlorocyclohexane [β-isomer]**
**CAS No.**: 319-85-7
**Chem. Abstr. Name**: 1α,2β,3α,4β,5α,6β-Hexachlorocyclohexane

**Lindane**
**CAS No.**: 58-89-9
**Chem. Abstr. Name**: 1α,2α,3β,4α,5α,6β-Hexachlorocyclohexane

**Hexachlorocyclohexane [δ-isomer]**
**CAS No.**: 319-86-8
**Chem. Abstr. Name**: 1α,2α,3α,4β,5α,6β-Hexachlorocyclohexane

**Hexachlorocyclohexane [ε-isomer]**
**CAS No.**: 6108-10-7
**Chem. Abstr. Name**: 1α,2α,3α,4β,5β,6β-Hexachlorocyclohexane

**Hexachlorocyclohexane [ζ-isomer]**
**CAS No.**: 6108-11-8
**Chem. Abstr. Name**: 1α,2α,3α,4α,5α,6α-Hexachlorocyclohexane

**Hexachlorocyclohexane [η-isomer]**
**CAS No.**: 6108-12-9
**Chem. Abstr. Name**: 1α,2α,3α,4α,5β,6β-Hexachlorocyclohexane

**Hexachlorocyclohexane [θ-isomer]**
**CAS No.**: 6108-13-0
**Chem. Abstr. Name**: 1α,2α,3α,4α,5α,6β-

**A. Evidence for carcinogenicity to humans** (*inadequate* for hexachlorocyclohexanes)

Four cases of leukaemia were reported in men exposed to γ-hexachlorocyclohexane (lindane) with or without other chemicals [ref: 1,2]. Cases of aplastic anaemia have also been associated with exposure to this compound [ref: 1]. Mean tissue levels of hexachlorocyclohexanes were reported to be elevated in two of three studies of autopsy patients; in one of these, in four liver cancer patients, the level of the β-isomer was abnormally high [ref: 3-5]. Mean serum levels of β-hexachlorocyclohexane were not appreciably higher in four cancer patients than in three controls [ref: 6]. Exposure to γ-hexachlorocyclohexane was recorded in case-control studies of soft-tissue sarcomas and of lymphomas [ref: 7,8] but was insufficiently frequent for any conclusion to be drawn. An increase in lung cancer mortality was observed in agricultural workers who had used hexachlorocyclohexane (unspecified) and a variety of other pesticides and herbicides (standardized mortality ratio, 180 [95% confidence interval, 140-240]) [ref: 9].

**B. Evidence for carcinogenicity to animals** (*sufficient* for technical-grade and for the α isomer; *limited* for the β and for the γ isomers)

Technical-grade, α- and β-hexachlorocyclohexane and the γ isomer (lindane) produced liver tumours in mice when administered orally [ref: 1,10,11]; the technical grade also produced lymphoreticular neoplasms [ref: 10]. In two studies in rats, an increased incidence of liver tumours was observed with the α isomer [ref: 1,12], and in one study in rats a few thyroid tumours were observed with the γ isomer [ref: 1]; other studies in rats [ref: 11,13-15] were considered to be inadequate. Studies in hamsters [ref: 11] and dogs [ref: 16] were also inadequate. Technical-grade hexachlorocyclohexane and the γ isomer were tested inadequately by skin application in mice [ref: 1,10]. α-Hexachlorocyclohexane enhanced the incidence of liver neoplasms induced in rats by *N*-nitrosodiethylamine [ref: 12].

**C. Other relevant data**

In a single study, chromosomal aberrations were not found in workers involved in the production of γ-hexachlorocyclohexane (lindane) [ref: 17].

Technical-grade hexachlorocyclohexane, but not γ- hexachlorocyclohexane, induced dominant lethal mutations in mice; chromosomal aberrations were not found in bone-marrow cells of mice exposed to technical-grade or γ-hexachlorocyclohexane *in vivo*. γ-Hexachlorocyclohexane did not induce unscheduled DNA synthesis in human cells *in vitro* and did not induce micronuclei or chromosomal aberrations in cultured rodent cells; it induced DNA strand breaks but not unscheduled DNA synthesis. It inhibited intercellular communication in Chinese hamster V79 cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*. α- Hexachlorocyclohexane was not mutagenic to yeast, but the gamma isomer induced gene conversion. Neither γ- nor β-hexachlorocyclohexane was mutagenic to bacteria, and α- and β-hexachlorocyclohexane did not cause DNA damage in bacteria [ref: 17].

**Overall evaluation**

Hexacyclohexanes are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 5 (1974); Vol. 20 (1979)

**References**

1. IARC Monographs, 20, 195-239, 1979

2. Sidi, Y., Kiltchevsky, E., Shaklai, M. & Pinkhas, J. (1983) Acute myeloblastic leukemia and insecticide. N.Y. State J. Med., 83, 161

3. Hoffman, W.S., Adler, H., Fishbein, W.I. & Bauer, F.C. (1967) Relation of pesticide concentrations in fat to pathological changes in tissues. Arch. environ. Health, 15, 758-765

4. Radomski, J.L., Deichmann, W.B., Clizer, E.E. & Rey, A. (1968) Pesticide concentrations in the liver, brain and adipose tissue of terminal hospital patients. Food Cosmet. Toxicol., 6, 209-220

5. Kasai, A., Asanuma, S. & Nakamura, S. (1972) Studies on organochlorine pesticide residues in human organs. Part III (Jpn.). Nippon Noson Igakkai Zasshi, 21, 296-297

6. Caldwell, G.G., Cannon, S.B., Pratt, C.B. & Arthur, R.D. (1981) Serum pesticide levels in patients with childhood colorectal carcinoma. Cancer, 48, 774-778

7. Eriksson, M., Hardell, L., Berg, N.O., Möller, T. & Axelson, O. (1981) Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. Br. J. ind. Med., 38, 27-33

8. Hardell, L., Eriksson, M., Lenner, P. & Lundgren, E. (1981) Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br. J. Cancer, 43, 169-176

9. Barthel, E. (1981) Increased risk of lung cancer in pesticide-exposed male agricultural workers. J. Toxicol. environ. Health, 8, 1027-1040

10. Kashyap, S.K., Nigam, S.K., Gupta, R.C., Karnik, A.B. & Chatterjee, S.K. (1979) Carcinogenicity of hexachlorocyclohexane (BHC) in pure inbred Swiss mice. J. environ. Sci. Health, B14, 305-318

11. Munir, K.M., Soman, C.S. & Bhide, S.V. (1983) Hexachlorocyclohexane-induced tumorigenicity in mice under different experimental conditions. Tumori, 69, 383-386

12. Schulte-Hermann, R. & Parzefall, W. (1981) Failure to discriminate initiation from promotion of liver tumors in a long-term study with the phenobarbital-type inducer α-hexachlorocyclohexane and the role of sustained stimulation of hepatic growth and monooxygenases. Cancer Res., 41, 4140-4146

13. Angsubhakorn, S., Bhamarapravati, N., Romruen, K., Sahaphong, S. & Thamavit, W. (1977) Alpha benzene hexachloride inhibition of aflatoxin $B_1$-induced hepatocellular carcinoma. A preliminary report. Experientia, 34, 1069-1970

14. Hiasa, Y., Ohshima, M., Ohmori, T. & Murata, Y. (1978) Effect of α-benzene hexachloride on 2-fluorenylacetamide carcinogenesis in rats. Gann, 69, 423-426

15. Angsubhakorn, S., Bhamarapravati, N., Romruen, K., Sahaphong, S., Thamavit, W. & Miyamoto, M. (1981) Further study of alpha benzene hexachloride inhibition of aflatoxin $B_1$ hepatocarcinogenesis in rats. Br. J. Cancer, 43, 881-883

16. Rivett, K.F., Chesterman, H., Kellett, D.N., Newman, A.J. & Worden, A.N. (1978) Effects of feeding lindane to dogs for periods of up to 2 years. Toxicology, 9, 273-289

17. IARC Monographs, Suppl. 6, 333-335, 1987

**Synonyms for Hexachlorocyclohexane [mixed isomers]**

- Benzahex
- Benzex
- BHC
- Dol
- Dolmix
- FBHC
- HCCH
- Hexachlor
- Hexachloran
- Hexafor
- Hexyclan
- Kotol
- Soprocide

**Synonyms for Hexachlorocyclohexane [α-isomer]**

- α-Benzene hexachloride

- α-BHC
- α-HCH
- α-Hexachloran
- α-Hexachlorane
- α-Hexachlorcyclohexane
- α-1,2,3,4,5,6-Hexachlorcyclohexane
- α-Hexachlorocyclohexane
- α-1,2,3,4,5,6-Hexachlorocyclohexane
- α-Lindane

**Synonyms for Hexachlorocyclohexane [β-isomer]**

- β-Benzene hexachloride
- β-BHC
- β-HCH
- β-Hexachlorobenzene
- β-Hexachlorocyclohexane
- β-1,2,3,4,5,6-Hexachlorocyclohexane
- β-Lindane

**Synonyms for Lindane**

- Aalindan
- Aficide
- Agrocide
- Agrocide III
- Agrocide WP
- Ameisenmittel Merck
- Ameisentod
- Aparasin
- Aphtiria
- Aplidal
- Arbitex
- BBH
- Ben-Hex
- Bentox 10
- γ-Benzene hexachloride
- Bexol
- γ-BHC
- 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
- HCH
- γ-HCH
- Heclotox
- Hexa
- Hexachloran

- Hexachloran-gamma
- Hexachlorane
- Hexachlorane-gamma
- γ-Hexachlorobenzene
- γ-Hexachlorocyclohexane
- γ-1,2,3,4,5,6-Hexachlorocyclohexane
- Hexatox
- Hexaverm
- Hexicide
- Hexyclan
- HGI
- Hortex
- Isotox
- Jacutin
- Kokotine
- Kwell
- Lendine
- Lentox
- Lidenal
- Lindafor
- Lindagam
- γ-Lindane
- Lindatox
- Lindosep
- Lintox
- Lorexane
- Milbol 49
- Mszycol
- Neo-scabicidol
- Nexen FB
- Nexit
- Nexit-stark
- Nexol-E
- Nicochloran
- Novigam
- Omnitox
- Ovadziak
- Owadziak
- Pedraczak
- Pflanzol
- Quellada
- Sang-gamma
- Silvanol
- Spritz-Rapidin
- Sprehpflanzol
- Streunex
- TAP 85
- Tri-6
- Viton

**Synonyms for Hexachlorocyclohexane [δ-isomer]**

- δ-Benzene hexachloride
- δ-BHC
- δ-HCH
- δ-Hexachlorocyclohexane
- δ-1,2,3,4,5,6-Hexachlorocyclohexane
- δ-Lindane

**Synonyms for Hexachlorocyclohexane [ε-isomer]**

- ε-Benzene hexachloride
- ε-BHC

- ε-HCH
- ε-Hexachlorocyclohexane
- ε-1,2,3,4,5,6-Hexachlorocyclohexane
- ε-Lindane

**Synonyms for Hexachlorocyclohexane [ζ-isomer]**

- ζ-Hexachlorocyclohexane
- ζ-Lindane

**Synonyms for Hexachlorocyclohexane [η-isomer]**

- η-Hexachlorocyclohexane
- η-Lindane

**Synonym for Hexachlorocyclohexane [θ-isomer]**

- θ-Hexachlorocyclohexane
- θ-Lindane

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Last updated: 2 March 1998

# HYDRALAZINE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 222)

**Hydralazine**
**CAS No.**: 86-54-4
**Chem. Abstr. Name**: 1(2*H*)-Phthalazinone hydrazone

**Hydralazine hydrochloride**
**CAS No.**: 304-20-1
**Chem. Abstr. Name**: 1(2*H*)-Phthalazinone hydrazone, monohydrochloride

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Two studies suggest an association between exposure to hydralazine and cancer. One was confined to patients with and without signs of toxicity due to hydralazine, and potential confounding factors were not controlled for. The other involved a small number of subjects exposed to hydralazine, but the possibility of selection bias could not be excluded [ref: 1]. However, a study of 3988 participants in a hypertensive detection and follow-up programme suggested no increased risk for cancer at all sites from use of hydralazine. A logistic regression estimate of cancer risk after controlling for age, sex, race, smoking behaviour and concomitant drug therapy was 0.89 (95% confidence interval, 0.45-1.8). It was noted that this estimate of no excess risk was restricted to a hypertensive population over 40 years of age, exposed to hydralazine for various periods (none longer than five years) [ref: 2]. Another study involving women with breast cancer also showed no increased risk with use of hydralazine (relative risk, 0.9; 0.5-1.7) [ref: 3].

**B. Evidence for carcinogenicity to animals** (*limited*)

Hydralazine hydrochloride was tested in one experiment in mice by oral administration. A significant increase in the incidence of lung tumours was reported [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of hydralazine in humans.

In a single limited study, hydralazine did not induce DNA damage in animals treated *in vivo*. It induced sister chromatid exchanges in human lymphocytes *in vitro*, whereas assays for chromosomal aberrations in rodent cells *in vitro* were inconclusive. Hydralazine induced unscheduled DNA synthesis in rat and rabbit hepatocytes *in vitro* and induced mutation and DNA damage in bacteria [ref: 4].

**Overall evaluation**

Hydralazine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 24 (1980)

**References**

1. IARC Monographs, 24, 85-100, 1980

2. Rogers, A.S. (1984) Hydralazine: an estimate of cancer risk in a hypertensive program (Abstract). Diss. Abstr. int., 44, 2123

3. Kaufman, D.W., Kelly, J.P., Rosenberg, L., Stolley, P.D., Schottenfeld, D. & Shapiro, S. (1987) Hydralazine and breast cancer. J. natl Cancer Inst., 78, 243-246

4. IARC Monographs, Suppl. 6, 338-340, 1987

**Synonyms for Hydralazine**

- Hydralazin
- Hydrallazine
- 1-Hydrazinophthalazine

**Synonyms for Hydralazine hydrochloride**

- Aiselazine
- Appresinum
- Aprelazine
- Apresazide
- Apresine
- Apresolin
- Apresoline
- Apresoline-esidrix
- Apresoline HCl
- Apresoline hydrochloride
- Apressin
- Apressoline
- Aprezolin
- Ba 5968
- C 5968
- Ciba 5968
- Dralzine
- Hidralazin
- Hipoftalin
- 1-Hydrazinophthalazine hydrochloride
- Hydralazine chloride
- Hydralazine HCl
- Hydrapress
- 1-Hydrazinophthalazine monohydrochloride
- Hyperazin
- Hyperazine
- Hypophthalin
- Hypos
- Ipolina
- Lopres
- Lopress
- Nor-press 25
- 1(2*H*)-Phthalazinone hydrazone hydrochloride
- Praparat 5968
- Rolazine
- Serpasil apresoline No. 2

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Last updated: 9 March 1998

# IRON AND STEEL FOUNDING
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 224)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Analytical cohort epidemiological studies of foundry workers conducted in a number of countries have typically noted risks of lung cancer elevated between 1.5 and 2.5 fold [ref: 1,2]. Proportionate mortality studies have also shown the proportion of deaths from lung cancer to be 1.5- to 1.8-fold greater than that in the general population. Associations between foundry work and lung cancer have similarly been observed in studies of mortality statistics [ref: 1].

In two studies in which site-specific cancer deaths among iron and steel foundry workers were compared with corresponding rates for the general population, significantly increased risks for cancer of the digestive system were observed; in one, the elevated risk was for cancers in the 'digestive system', in the other, it was for 'stomach cancer' [ref: 1].

Results of studies of a single cohort of steel foundry workers in the USA showed a significantly elevated risk of cancer of the genito-urinary system when compared with the entire steel worker population under study, the risk being significantly elevated also for some specific sites (prostate and kidney) [ref: 1].

Elevated lung cancer risks have also been reported in a grey-iron foundry [ref: 2], in steel foundries [ref: 3], in iron and steel foundries [ref: 2] and among persons living near steel foundries [ref: 4]. No consistent excess of lung cancer, however, was reported among foundrymen employed in a nickel-chromium alloy foundry [ref: 5]. Other cancer excesses reported have included leukaemia, stomach cancer and urogenital cancer [ref: 2]. Despite the absence of information to specify definitely the carcinogenic substances in the work environment (e.g., polynuclear aromatic hydrocarbons, silica, metal fumes, formaldehyde), the consistency of the excess in studies from around the world shows that certain exposures in iron and steel founding can cause lung cancer in humans. Most studies lacked information on smoking, but, when it was available, it did not appear that tobacco use could explain the lung cancer excess.

**B. Other relevant data**

Antigenicity against benzo[*a*]pyrene diol epoxide-DNA adducts has been demonstrated in peripheral lymphocytes of foundry workers [ref: 5].

**Overall evaluation**

Iron and steel founding *entails exposures that are carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 34 (1984)

**References**

1. IARC Monographs, 34, 133-190, 1984

2. IARC Monographs, 42, 39-143, 1987

3. Fletcher, A.C. & Ades, A. (1984) Lung cancer mortality in a cohort of English foundry workers. Scand. J. Work Environ. Health, 10, 7-16

4. Lloyd, O.L., Smith, G., Lloyd, M.M., Holland, Y. & Gailey, F. (1985) Raised mortality from lung cancer and high sex ratios of births associated with industrial pollution. Br. J. ind. med., 42, 475-480

5. Cornell, R.G. & Landris, J.R. (1984) Mortality patterns among nickel/chromium alloy foundry workers. In: Sunderman, F.W., Jr, ed., Nickel in the Human Environment (IARC Scientific Publications No. 53), Lyon, International Agency for Research on Cancer, pp. 87-93

5. IARC Monographs, Suppl. 6, 344, 1987

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# IRON DEXTRAN COMPLEX
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 226)

**CAS No.**: 9004-66-4

**A. Evidence for carcinogenicity to humans** (*inadequate*)

An early report was made of a woman who had developed an undifferentiated soft-tissue sarcoma following multiple injections of iron-dextran complex [ref: 1]. In a report on 196 cases of sarcoma of the buttock, four of 90 for whom records on drug use were still available had been given intramuscular injections of iron. In three of the cases, an interval of at least two years had elapsed [ref: 2]. A selective tendency to report receiving iron injections may have introduced bias. A review of reports during the period 1960-1977 indicated that nine malignancies had been described in five reports. Two were thought to have been foreign-body reactions to fat necrosis; one was a metastatic carcinoma at the site of an iron-dextran injection; and one was a reticulum-cell sarcoma with fractures of the pelvis possibly only coincidentally related to iron injections six years before. Several of the remainder were of different histological type [ref: 3]. Only one, a poorly differentiated spindle-cell fibrosarcoma, was believed likely to be related to iron-dextran injections given 14 years previously [ref: 4]. No further case report or epidemiological study is known to the Working Group. It seems probable that the considerable publicity given to the initial case report [ref: 1] and the tendency to give parenteral iron therapy intravenously may have considerably reduced human exposure to intramuscularly administered iron-dextran complex.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Iron-dextran complex has been tested in mice, rabbits and rats by repeated subcutaneous or intramuscular injections, producing local tumours at the injection site [ref: 1,5]. The Working Group noted that iron-dextran complex accumulates at the site of injection in rodents, in contrast to its rapid dispersal after injection in human beings.

**C. Other relevant data**

No adequate data were available to the Working Group.

**Overall evaluation**

Iron dextran complex is *possibly carcinogenic to humans (Group 2B)*.

**References**

1. IARC Monographs, 2, 161-178, 1973

2. Greenberg, G. (1976) Sarcoma after intramuscular iron injection. Br. med. J., ii, 1508-1509

3. Fielding, J. (1977) Does sarcoma occur in man after intramuscular iron? Scand. J. Haematol., Suppl. 32, 100-104

4. Robertson, A.G. & Dick, W.C. (1977) Intramuscular iron and local oncogenesis. Br. med. J., i, 946

5. Hruby, M. & Damková, E. (1985) Induction and transplantability of ferridextran tumours in inbred strains of Rattus norvegicus (Czech.). Sbornik Lék., 87, 114-120

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 2 (1973)

**Synonyms**

- Dextran iron complex
- Iron dextran injection
- Ironorm injection

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Last updated: 3 March 1998

# ISONICOTINIC ACID HYDRAZIDE (ISONIAZID)
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 227)

**CAS No.**: 54-85-3

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Several early studies showed no significant excess of cancer among patients treated with isoniazid [ref: 1]. A study of 3842 tuberculosis patients followed for 16-24 years showed slight excesses of deaths from malignant neoplasms of the bronchus, lung and pleura in 2041 patients treated with isoniazid during 1953-1957 and followed through to 1973 (relative risk, 1.6 [95% confidence interval, 1.2-2.1], but none in 655 treated for tuberculosis in 1950-1952 when isoniazid was not generally available (0.7 [0.1-1.5]). An excess of all malignant neoplasms was also seen in patients treated in 1953-1957 (1.4 [1.2-1.7]), but also in 145 patients not treated with isoniazid over the same period (1.8 [0.7-2.9]). Again, no excess was observed in those treated for tuberculosis in 1950-1952. No dose-response effect was seen either for total consumption or for maximum daily dose of isoniazid [ref: 2]. Additional studies of cancer incidence and mortality among patients treated with isoniazid have shown no excess of lung cancer, or of cancer as a whole, that could be attributed to treatment [ref: 3-6]. A cancer incidence study in patients with tuberculosis, involving heavy smokers, showed an excess of lung cancer among men exposed to isoniazid (3.4, based on 88 cases observed, 26.2 expected) but also among those not exposed (2.6, based on 18 cases observed, 7.0 expected). The difference between the two ratios was not statistically significant. The corresponding figures for women were 4.6, based on 14 cases exposed, and 0.5, based on one case not exposed [ref: 7]. In a preliminary analysis of one-year case records, 72 (4.9%) cancer patients had healed tuberculosis compared with 26 (2%) noncancer patients [ref: 8]. Four case-control studies concerning bladder and kidney cancers [ref: 9], bladder cancer [ref: 10,11] and cancer in children [ref: 12] have provided no conclusive evidence of a risk associated with isoniazid therapy. A single case of mesothelioma has been reported in a nine-year-old child whose mother was treated with isoniazid for a positive tuberculin skin test in the second and third trimesters of pregnancy [ref: 13].

**B. Evidence for carcinogenicity to animals** (*limited*)

Isoniazid produced lung tumours in mice after its oral, intraperitoneal or subcutaneous administration [ref: 1,8,13-16]. Studies in rats were considered inadequate for evaluation [ref: 1]. No tumour was produced in hamsters after given oral administration of isoniazid [ref: 1].

**C. Other relevant data**

In the one available study, isoniazid did not induce chromosomal aberrations in lymphocytes of treated patients [ref: 17].

Isoniazid did not induce dominant lethal mutations in mice, or chromosomal aberrations, sister chromatid exchanges or DNA damage in rodents treated *in vivo*. Results for chromosomal aberrations and sister chromatid exchanges in human cells *in vitro* were inconclusive; it did not induce unscheduled DNA synthesis. In cultured rodent cells, it induced chromosomal aberrations and sister chromatid exchanges, but not DNA damage. It did not induce transformation of Syrian hamster embryo cells. It did not induce gene conversion in yeast. Isoniazid was mutagenic to *Salmonella typhimurium* but not, in a single study, to *Escherichia coli* [ref: 17].

**Overall evaluation**

Isonicotinic acid hydrazide (Isoniazid) is *not classifiable as to its carcinogenicity to humans (Group*

*3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**


1. IARC Monographs, 4, 159-172, 1974

2. Stott, H., Peto, J., Stephens, R., Fox, W., Sutherland, I., Foster-Carter, A.F., Teare, H.D. & Fenning, J. (1976) An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. Tubercle, 57, 1-15

3. Glassroth, J.L., White, M.C. & Snider, D.E., Jr (1977) An assessment of the possible association of isoniazid with human cancer deaths. Am. Rev. respir. Dis., 116, 1065-1074

4. Howe, G.R., Lindsay, J., Coppock, E. & Miller, A.B. (1979) Isoniazid exposure in relation to cancer incidence and mortality in a cohort of tuberculosis patients. Int. J. Epidemiol., 8, 305-312

5. Boice, J.D. & Fraumeni, J.F., Jr (1980) Late effects following isoniazid therapy. Am. J. publ. Health, 70, 987-989

6. Costello, H.D. & Snider, D.E., Jr (1980) The incidence of cancer among participants in a controlled, randomized isoniazid preventive therapy trial. Am. J. Epidemiol., 111, 67-74

7. Clemmesen, J. & Hjalgrim-Jensen, S. (1979) Is isonicotinic acid hydrazide (INH) carcinogenic to man? A 24-year follow-up of 3371 tuberculosis cases. Ecotoxicol. environ. Saf., 3, 439-450

8. Bhide, S.V., Maru, G.B., Mate, N.B., Menon, M. & Gangadharan, P. (1981) Metabolic studies on the possible mode of action of isoniazid tumorigenicity. J. Cancer Res. clin. Oncol., 99, 153-166

9. Glassroth, J.L., Snider, D.E. & Comstock, G.W. (1977) Urinary tract cancer and isoniazid. Am. Rev. respir. Dis., 116, 331-333

10. Miller, C.T., Neutel, C.I., Nair, R.C., Marrett, L.D., Last, J.M. & Collins, W.E. (1978) Relative importance of risk factors in bladder carcinogenesis. J. chron. Dis., 31, 51-56

11. Kantor, A.F., Hartge, P., Hoover, R.N. & Fraumeni, J.F., Jr (1985) Tuberculosis chemotherapy and risk of bladder cancer. Int. J. Epidemiol., 14, 182-184

12. Sanders, B.M. & Draper, G.J. (1979) Childhood cancer and drugs in pregnancy. Br. med. J., i, 717-718

13. Tuman, K.J., Chilcote, R.R., Berkow, R.I. & Moohr, J.W. (1980) Mesothelioma in child with prenatal exposure to isoniazid. Lancet, ii, 362

14. Maru, G.B., Sawai, M.M. & Bhide, S.V. (1980) Prevention of isoniazid tumorigenicity by antitoxicants of isoniazid in Swiss mice. J. Cancer Res. clin. Oncol., 97, 145-151

15. Maru, G.B. & Bhide, S.V. (1982) Effect of antioxidants and antitoxicants of isoniazid on the formation of lung tumours in mice by isoniazid and hydrazine sulphate. Cancer Lett., 17, 75-80

16. Menon, M.M. & Bhide, S.V. (1983) Perinatal carcinogenicity of isoniazid (INH) in Swiss mice. J.

Cancer Res. clin. Oncol., 105, 258-261

17. IARC Monographs, Suppl. 6, 347-350, 1987

**Synonyms**

- Actobine
- Actotibine
- Aldoxal
- Andrazida
- Aneufos simple
- Anteben
- Antimicina
- Antituberkulosum trogalen
- Armazide
- Azuren
- Bacikoch
- Bacillin
- Banzid
- Basidracida
- Becazida
- Buco-hidracid
- Cedin
- Cemidon
- Chemiazid
- Chemidon
- Cin-vis
- Cotinazin
- Cotinizin
- Dardex
- Diazid
- Dif-azidrin
- Dinacrin
- Dioforin
- Ditubin
- Dracotil
- Ducun
- Ebidene
- Eralon
- Ertuban
- Eutizon
- Evalon
- Evigril
- Fimalene
- Fimazid
- FSR-3
- GINK
- Hain
- HIA
- Hidraciber
- Hidracida
- Hidrafasa
- Hidral-grey
- Hidralter
- Hidranic
- Hidranizil
- Hidra-Noxi
- Hidraquimia
- Hidrasegur
- Hidrasix
- Hidrasonil
- Hidrassal
- Hidrastol

- Hidratorax
- Hidrazida-I.N.
- Hidrazinol
- Hidrina
- Hidrulta
- Hidrun
- Hiperazida
- Hycozid
- Hydra
- Hydrazid polfa
- Hydrazide horus
- Hydrazide medial
- Hydrazide otsuka
- Hydrozin
- Hyzyd
- Idocobin
- Ido-Tebin
- Idrazil
- INA
- INAH
- Inazid
- INH
- Inhizid
- Inizid
- Iscotin
- Isidrina
- Ismazide
- Isobicina
- Isocid
- Isocidene
- Isocotin
- Iso-Dexter
- Isolyn
- Isomerina
- Isonazida
- Isonerit
- Isonex
- Isonhidrol
- Isoniazid
- Isoniazide
- Isoniazone
- Isonicazide
- Isonicid
- Isonico
- Isonicol
- Isonicotan
- Isonicotil
- Isonicotinoylhydrazine
- Isonicotinylhydrazine
- Isonide
- Isonidrin
- Isonikazid
- Isonilex
- Isonilyd
- Isonin
- Isonindon
- Isoniton
- Isonitrit
- Isonizan
- Isonizide
- Iso-pentabine
- Isopyrin astra
- Isotebe
- Isotebezid
- Isotinyl

- Isotubin
- Isoxine
- Isozid
- Isozide
- Isozin
- Isozyd
- Isonisin
- Kemia
- Kozidrina
- Kridansimple
- L 1945
- Laniazid
- Laniozid
- Lefos
- Leotubrin-wirkstoff
- Lesviazida
- Lubacida
- Marsilid
- Marvidrazida
- Mesegacida
- Micosan
- Milazide
- Mybasan
- Mycoseptina
- Neoplasina
- Neoteben
- Neoxin
- Neoxon
- Neumandin
- Nevin
- Niadrin
- Niazid
- Niazida
- Nicazid
- Nicazide
- Nicetal
- Nicizina
- Niconyl
- Nicosciorin
- Nicotibina
- Nicotibine
- Nicotisan
- Nicotubin
- Nicozid
- Nicozide
- Nicozin
- Nidaton
- Nidrazid
- Nieteban
- Nikozid
- Niplen
- Nitadon
- Nortibina
- Nydrazid
- Nyscozid
- Pacrazid
- Pelazid
- Percin
- Percitron
- Peritracida
- Phthisen
- Pycazide
- Pyreazid
- Pyricidin
- Pyridicin

- 4-Pyridinecarboxylic acid hydrazide
- Pyridine-4-carboxylic acid hydrazide
- Pyridine-γ-carboxylic acid hydrazide
- Pyrinal
- Pyrizidin
- Raumanon
- Rebilon
- Retozide
- Rimicid
- Rimifon
- Rimitsid
- Rinverfons
- Roberazyd
- Robisellin
- Roxifen miquel
- RU-EF-Tb
- Sanohidrazina
- Sauterazid
- Stanozide
- Sumifon
- Tb-Phlogin
- T.B. Razide
- TB-Vis
- Tebecid
- Tebecin
- Tebenic
- Tebesium-wirkstoff
- Tebetracin
- Tebexin
- Tebilon
- Tebos
- Teebaconin
- Tekazin
- Tibazide
- Tibemid
- Tibinid
- Tibinide
- Tibison
- Tibitan
- Tibivis
- Tibizide
- Tibusan
- Tisin
- Tisiodrazida
- Tizide
- Tizopan
- Tubazid
- Tubazide
- Tubeco
- Tubercid
- Tuberian
- Tuberon
- Tubezin
- Tubicon
- Tubilysin
- Tubomel
- Tubriz
- Tyvid
- Unicozyde
- Vazadrine
- Vederon
- Zidafimia
- Zideluy
- Zinadon
- Zonazide

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# LEAD AND LEAD COMPOUNDS:
# LEAD AND INORGANIC LEAD COMPOUNDS
# (Group 2B)
# ORGANOLEAD COMPOUNDS
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 230)

**Lead**
**CAS No.**: 7439-92-1

**Lead acetate**
**CAS No.**: 301-04-2
**Chem. Abstr. Name**: Acetic acid, lead (2+) salt

**Lead acetate trihydrate**
**CAS No.**: 6080-56-4
**Chem. Abstr. Name**: Acetic acid, lead (2+) salt, trihydrate

**Lead carbonate**
**CAS No.**: 598-63-0
**Chem. Abstr. Name**: Carbonic acid, lead (2+) salt (1:1)

**Lead chloride**
**Chem. Abstr. Name**: 7758-95-4
**Chem. Abstr Name**: Lead chloride [$PbCl_2$]

**Lead naphthenate**
**CAS No.**: 50825-29-1

**Lead nitrate**
**CAS No.**: 10099-74-8
**Chem. Abstr. Name**: Nitric acid, lead (2+) salt

**Lead oxide**
**CAS No.**: 1317-36-8
**Chem. Abstr. Name**: Lead oxide [Pb0]

**Lead phosphate**
**CAS No.**: 7446-27-7
**Chem. Abstr. Name**: Phosphoric acid, lead (2+) salt (2:3)

**Lead subacetate**
**CAS No.**: 1335-32-6
**Chem. Abstr. Name**: Lead, bis(acetato-*O*)tetrahydroxytri-

**Lead tetroxide**
**CAS No.**: 1314-41-6
**Chem. Abstr. Name**: Lead oxide [$Pb_3O_4$]

**Tetraethyllead**
**CAS No.**: 78-00-2
**Chem. Abstr. Name**: Plumbane, tetraethyl-

**Tetramethyllead**
**CAS No.**: 75-74-1
**Chem. Abstr. Name**: Plumbane, tetramethyl-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Three epidemiological studies of workers exposed to lead and lead compounds were reviewed previously [ref: 1]: one on smelters and battery workers in the USA, one on workers exposed to tetraethyllead in the USA, and one on copper smelters in the USA; data on the first of these populations have been updated [ref: 2]. A study on battery workers in the UK [ref: 3] is now available, and studies of a US lead smelter [ref: 4] and of a Swedish copper smelter [ref: 5] have also been reported. A statistically significant excess of cancers of the digestive system (21 observed, 12.6 expected) was found in the study of battery workers in the UK, spanning 1925-1976, although the excess was confined to the years 1963-1966 [ref: 3]. Significant excesses of stomach cancer (34 observed, 20.2 expected) and of respiratory cancers (116 observed, 93.5 expected) were seen in the study of US battery plant workers [ref: 2], although there was a downward trend in standardized mortality ratio by number of years of employment; in the lead production facilities, the excesses noted for stomach and respiratory cancers were not significant [ref: 2]. A nonsignificant excess of respiratory cancer (41 observed, 36.9 expected) was reported in one of the studies of smelters [ref: 4], with 28 observed and 25.7 expected in the group with high exposure to lead. Excesses were also noted in this study for kidney cancer (6 observed, 2.9 expected) and bladder cancer (6 observed, 4.2 expected) [ref: 4]. A small study of workers at a Swedish smelter [ref: 5] with long-term exposure to lead demonstrated a nonsignificant excess of lung cancers (8 observed, 5 expected). Two cases of kidney cancer in lead smelter workers have also been reported [ref: 6,7].

The excesses of respiratory cancer in these studies were relatively small, showed no clear-cut trend with length or degree of exposure, and could have been confounded by factors such as smoking or exposure to arsenic.

A study of workers manufacturing tetraethyllead revealed excesses of respiratory cancer (15 observed, 11.2 expected) and brain cancer (3 observed, 1.6 expected) [ref: 8].

**B. Evidence for carcinogenicity to animals** (*sufficient* for inorganic lead compounds; *inadequate* for organolead compounds)

Lead acetate and lead subacetate were tested for carcinogenicity by oral, subcutaneous and intraperitoneal administration in rats, lead phosphate was tested by subcutaneous and intraperitoneal administration in rats, and lead subacetate was tested by oral administration in mice. Renal tumours were produced in animals of each species by each route of administration. Rats given lead acetate or lead subacetate orally developed gliomas. Lead subacetate also produced an increased incidence of lung adenomas in mice after intraperitoneal administration [ref: 1]. Oral administration of lead dimethyldithiocarbamate (ledate) increased the incidence of reticulum-cell sarcomas in male mice of one strain [ref: 9] but was not carcinogenic to mice or rats in another experiment [ref: 10].

Synergistic effects were reported [ref: 1,11-14] in the kidneys of rats given lead acetate and *N*-nitroso-*N*-(hydroxyethyl)ethylamine, *N*-(4'-fluoro-4-biphenyl)acetamide or 2-(nitrosoethylamine)ethanol orally and in the lungs of hamsters given lead oxide with benzo[*a*]pyrene intratracheally. Lead subacetate given in the diet increased the incidences of liver and kidney tumours induced in rats by 2-acetylaminofluorene given in the diet [ref: 1].

The lead compounds tested for carcinogenicity in animals are almost all soluble salts that were selected on the basis of ease of administration. Metallic lead, lead oxide and lead tetraalkyls have not been tested adequately.

**C. Other relevant data**

Studies of chromosomal aberrations in people exposed to lead have given conflicting results: positive reports have been published concerning workers in lead-battery industries and lead smelters, but

other studies of workers under comparable conditions have given negative results. Increased incidences of sister chromatid exchanges have been reported in the peripheral blood lymphocytes of workers exposed to lead but not in those of children exposed to high levels of lead in the environment. An increased incidence of sperm abnormalities was seen in men exposed occupationally to lead [ref: 15].

Although a few studies in rodents treated with lead salts *in vivo* have shown small (but significant) increases in the frequency of chromosomal aberrations and micronuclei in bone-marrow cells, most studies showed no increase. Lead salts caused morphological sperm abnormalities in mice but not in rabbits. Sister chromatid exchanges and unscheduled DNA synthesis were not induced in cells of animals treated with lead salts *in vivo*. Lead salts did not induce chromosomal aberrations in human lymphocytes *in vitro*. Conflicting results have been obtained in assays for transformation in cultured rodent cells. Lead salts did not cause aneuploidy in *Drosophila*, mutation or gene conversion in yeast or mutation or DNA damage in bacteria [ref: 15].

Tetraethyl- and tetramethyllead did not induce mutation in bacteria [ref: 15].

**References**


1. IARC Monographs, 23, 39-141, 325-415, 1980

2. Cooper, W.C., Wong, O. & Kheifets, L. (1985) Mortality among employees of lead battery plants and lead producing plants, 1947-1980. Scand. J. Work Environ. Health, 11, 331-345

3. Malcolm, D. & Barnett, H.A.R. (1982) A mortality study of lead workers 1925-76. Br. J. ind. Med., 39, 404-410

4. Selevan, S.G., Landrigan, P.J., Stern, F.B. & Jones, J.H. (1985) Mortality of lead smelter workers. Am. J. Epidemiol., 122, 673-783

5. Gerhardsson, L., Lundström, N.-G., Nordberg, G. & Wall, S. (1986) Mortality and lead exposures: a retrospective cohort study of Swedish smelter workers. Br. J. ind. Med., 43, 707-712

6. Baker, E.L., Jr, Goyer, R.A., Fowler, B.A., Khettry, U., Bernard, D.B., Adler, S., White, R. de V., Babayan, R. & Feldman, R.G. (1980) Occupational lead exposure, nephropathy, and renal cancer. Am. J. ind. Med., 1, 139-148

7. Lilis, R. (1981) Long term occupational lead exposure, chronic nephropathy, and renal cancer: a case report. Am. J. ind. Med., 2, 293-297

8. Sweeney, M.H., Beaumont, J.J., Waxweiler, R.J. & Halperin, W.E. (1986) An investigation of mortality from cancer and other causes of death among workers employed at an East Texas chemical plant. Arch. environ. Health, 41, 23-28

9. IARC Monographs, 12, 131-135, 1976

10. National Cancer Institute (1979) Bioassay of Lead Dimethyldithiocarbamate for Possible Carcinogenicity (Tech. Rep. Ser. No. 151; DHEW Publ. No. (NIH) 79-1707), Washington DC, US Department of Health, Education and Welfare

11. Hinton, D.E., Lipsky, M.M., Heatfield, B.M. & Trump, B.F. (1979) Opposite effects of lead on chemical carcinogenesis in kidney and liver of rats. Bull. environ. Contam. Toxicol., 23, 464-469

12. Tanner, D.C. & Lipsky, M.M. (1984) Effect of lead acetate on *N*-(4'-fluoro-4-biphenyl)acetamide-induced renal carcinogenesis in the rat. Carcinogenesis, 5, 1109-1113

13. Shirai, T., Ohshima, M., Masuda, A., Tamano, S. & Ito, N. (1984) Promotion of 2-(ethylnitrosamine)ethanol-induced renal carcinogenesis in rats by nephrotoxic compounds: positive responses with folic acid, basic lead acetate, and *N*-(3,5-dichlorophenyl)succinimide but not with 2,3-dibromo-1-propanol phosphate. J. natl Cancer Inst., 72, 477-482

14. Hiasa, Y., Ohshima, M., Kitahori, Y., Fujita, T., Yuasa, T. & Miyashiro, A. (1983) Basic lead acetate: promoting effect on the development of renal tubular cell tumors in rats treated with *N*-ethyl-*N*-hydroxyethylnitrosamine. J. natl Cancer Inst., 70, 761-765

15. IARC Monographs, Suppl. 6, 351-354, 1987

**Overall evaluation**

Lead and inorganic lead compounds are *possibly carcinogenic to humans (Group 2B)*.

Organolead compounds are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 1 (1972); Vol. 2 (1973) ; Vol. 12 (1976) ; Vol. 23 (1980)

**Synonyms for Lead**

- KS-4
- Lead flake
- Lead S2
- Pigment Metal 4
- SO
- SI

**Synonyms for Lead acetate**

- Dibasic lead acetate
- Lead[II] acetate
- Lead (2+) acetate
- Lead diacetate
- Lead dibasic acetate
- Plumbous acetate
- Salt of Saturn
- Sugar of Lead

**Synonym for Lead acetate trihydrate**

- Lead diacetate trihydrate

**Synonyms for Lead carbonate**

- Dibasic lead carbonate
- Lead (2+) carbonate
- White lead

**Synonyms for Lead chloride**

- Lead[II] chloride
- Lead (2+) chloride

- Lead dichloride
- Plumbous chloride

**Synonyms for Lead nitrate**

- Lead dinitrate
- Lead[II] nitrate
- Lead (2+) nitrate

**Synonyms for Lead oxide**

- Lead monoxide
- Lead oxide yellow
- Lead[II] oxide
- Lead protoxide
- Plumbous oxide
- Litharge
- Litharge pure
- Litharge Yellow L-28
- Massicot
- Massicotite
- Pigment Yellow 46
- Yellow lead ocher

**Synonyms for Lead phosphate**

- Lead orthophosphate
- Lead phosphate (3:2)
- Lead (2+) phosphate
- Perlex Paste 500
- Perlex Paste 600A
- Trilead phosphate

**Synonyms for Lead subacetate**

- Basic lead acetate
- Bis(aceto)dihydroxytrilead
- Bis(acetato)tetrahydroxytrilead
- Lead acetate, basic
- Monobasic lead acetate
- Subacetate lead

**Synonyms for Lead tetroxide**

- Lead orthoplumbate
- Lead oxide, red
- Lead tetraoxide
- Orange lead
- Saturn red
- Pigment Red 105
- Plumboplumbic oxide
- Red lead
- Red lead oxide
- Trilead tetroxide
- Mineral Orange
- Minium
- Minium red
- Paris red

**Synonyms for Tetraethyllead**

- TEL
- Tetraethylplumbane

**Synonyms for Tetramethyllead**

- Tetramethylplumbane
- TML

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Last updated: 3 March 1998

# LEATHER GOODS MANUFACTURE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 235)

**Evidence for carcinogenicity to humans** (*inadequate*)

A few cases of leukaemia have been reported following exposure to benzene (a known human carcinogen [ref: 1]) during the manufacture of leather goods other than boots and shoes. The number of cases of nasal cancer reported is insufficient to make an association with employment in the manufacture of leather goods (other than boots and shoes) [ref: 2]. A positive association between bladder cancer and employment in the leather products industry is suggested by a number of studies. A case-control study in West Yorkshire, UK, showed a statistically nonsignificant risk of bladder cancer associated with employment in leather goods production (as well as tanning, and boot and shoe repairing) [ref: 3]. Indications of an association with dusty leather occupations (not only shoemaking) came from a similar study in London [ref: 4]. In two of three areas in which a collaborative study of environmental risk factors for bladder cancer was conducted, a significant association with employment in 'leather' was found. The term 'leather' comprised the manufacture of leather goods, the leather or tanning industry or shoemaking [ref: 5]. Leather goods manufacture was most probably included in the leather exposure found to be statistically significantly associated with bladder cancer in another study in the USA [ref: 6]. None of the studies provides sufficient grounds to evaluate the specific role of the production of leather goods in the established association of leather work and cancer risk to humans.

**Overall evaluation**

Leather goods manufacture entails exposures that are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 25 (1981)

**References**

1. IARC Monographs, 29, 93-148, 391-397, 1982

2. IARC Monographs, 25, 279-292, 1981

3. Cartwright, R.A. & Boyko, R.W. (1984) Kidney cancer among leather workers. Lancet, i, 850-851

4. Baxter, P.J. & McDowall, M.E. (1986) Occupation and cancer in London: an investigation into nasal and bladder cancer using the Cancer Atlas. Br. J. ind. Med., 43, 44-49

5. Morrison, A.S., Ahlbom, A., Verhoek, W.G., Aoki, K., Leck, I., Ohno, Y. & Obata, K. (1985) Occupation and bladder cancer in Boston, USA, Manchester, UK, and Nagoya, Japan. J. Epidemiol. Commun. Health, 39, 294-300

6. Marrett, L.D., Hartge, P. & Meigs, J.W. (1986) Bladder cancer and occupational exposure to leather. Br. J. ind. Med., 43, 96-100

Last updated: 9 March 1998

# LEATHER TANNING AND PROCESSING
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 236)

**Evidence for carcinogenicity to humans** (*inadequate*)

Early studies of cancer risks possibly associated with leather industries provide little information specifically related to workers in tanneries. There was no evidence to suggest an association between leather tanning and nasal cancer [ref: 1]. Following the observation of an increased risk of nasal cancer among boot and shoe manufacturers, possibly associated with exposure to dust from leather tanned by a particular process [ref: 2], a study was designed to examine the possible cancer risk carried by different methods of leather tanning. The mortality experience of two groups of men working in tanneries in 1939 was compared to that of the population of England and Wales, and for no cause of death was a statistically significant increase above expectation found. Among the 573 men employed in tanneries using a process with vegetable extracts, one death from nasal cancer was observed (0.21 expected); among 260 employees using a tanning process with chrome salts (tri- and hexavalent), one death from soft-tissue tumour (0.07 expected) was reported [ref: 3].

In a Swedish study, a slight increase in mortality from stomach cancer and a three-fold, significantly increased risk for cancer of the pancreas were found to be associated with the occupational titles 'tanners' and 'tannery workers' as recorded in the registry of deaths and burials of a parish where a tannery had been in operation from 1873 to 1960. Tannery work involved exposure to chromium and, probably, to chlorophenols; smoking was an unlikely explanation for the findings, but the contribution of various dietary habits could not be ruled out [ref: 4]. Suggestions of increased risks for intestinal cancer and lung cancer and for cancer of the tonsils were imputed by a mortality study of workers employed in a tannery plant using chromium salts and synthetic tannins [ref: 5]. An association between lung cancer and tanning was also suggested by a study of incident cases in the UK [ref: 6] and by a study of cancer deaths among shoe and leather workers in the USA, in which the estimated risk for tannery workers relative to a group of workers classified as nonexposed was 4.2, which was statistically significant. Chromium and arsenicals were mentioned as possibly contributing to the excess of lung cancer [ref: 7]. Significantly increased lung cancer mortality was also found among a group of fur tanners in the USA, who had probably been exposed to chrome (hexavalent) tanning agents [ref: 8].

In a study of bladder cancer and occupation, a relative risk of 1.5 was found for leather tanners , which is not statistically significant [ref: 1]. No significant excess of bladder cancer was found in another study in tanners in the UK [ref; 9]. In two of three areas in which a collaborative study of environmental risk factors for bladder cancer was conducted, a significant association with employment in 'leather' was found; the term 'leather' comprised the leather or tanning industry, the manufacture of leather goods or shoemaking [ref: 10].

In a cohort of 1629 leather tanners in Sweden, eight cases of kidney cancer were observed, while 3.4 would have been expected from regional rates [ref: 11]. The hypothesis of this association was not supported by another study [ref: 12].

**Overall evaluation**

Leather tanning and processing entail exposures that are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 25 (1981)

**References**


1. IARC Monographs, 25, 201-247, 1981

2. Acheson, E.D., Pippard, E.C. & Winter, P.D. (1982) Nasal cancer in the Northamptonshire boot and shoe industry: is it declining ? Br. J. Cancer, 46, 940-946

3. Pippard, E.C., Acheson, E.D. & Winter, P.D. (1985) Mortality of tanners. Br. J. ind. Med., 42, 285-287

4. Edling, C., Kling, H., Flodin, U. & Axelson, O. (1986) Cancer mortality among leather tanners. Br. J. ind. Med., 43, 494-496

5. Puntoni, R., Valerio, A., Cresta, E., Filiberti, R., Bonassi, S. & Vercelli, M. (1984) Mortality study in a tannery (Ital.). Med. Lav., 75, 471-477

6. Coggon, D., Pannett, B., Osmond, C. & Acheson, E.D. (1986) A survey of cancer and occupation in young and middle aged men. I. Cancers of the respiratory tract. Br. J. ind Med., 43, 332-338

7. Garabrant, D.H. & Wegman, D.H. (1984) Cancer mortality among shoe and leather workers in Massachusetts. Am. J.

8. Sweeney, M.H., Walrath, J. & Waxweiler, R.J. (1985) Mortality among retired fur workers. Dyers, dressers (tanners) and service workers. Scand. J. Work Environ. Health, 11, 257-264

9. Cartwright, R.A. & Boyko, R.W. (1984) Kidney cancer among leather workers. Lancet, i, 850-851

10. Morrison, A.S., Ahlbom, A., Verhoek, W.G., Aoki, K., Leck, I., Ohno, Y. & Obata, K. (1985) Occupation and bladder cancer in Boston, USA, Manchester, UK, and Nagoya, Japan. J. Epidemiol. commun. Health, 39, 294-300

11. Malker, H.R., Malker, B.K., McLaughlin, J.K. & Blot, W.J. (1984) Kidney cancer among leather workers. Lancet, i, 56

12. Acheson, E.D. & Pippard, E.C. (1984) Kidney cancer among leather workers. Lancet, i, 563


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Last updated: 11 March 1998

# LUMBER AND SAWMILL INDUSTRIES (INCLUDING LOGGING) (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 383)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Information on the occurrence of cancer in lumber and sawmill workers is limited. The available epidemiological data come primarily from surveys of statements of occupation on death certificates. Nasal tumours, malignant lymphomas and leukaemias and soft-tissue sarcomas have been linked with work in the lumber and sawmill industries, but the results are not consistent [ref: 1].

In a case-control study based on an analysis of occupational data in the hospital records of 121 men seen for nasal cancer in British Columbia, Canada, between 1939 and 1977, a relative risk of 2.5 (adjusted for smoking and ethnic origin) was found to be associated with exposure to wood. There was increased risk for most histological types of epithelial tumour, except for transitional tumours. Of the 28 wood workers with nasal cancer, 16 had worked in the forestry industry, seven had been carpenters, four had been construction workers and one had been a cabinet-maker [ref: 2].

In a case-control study based on 167 cases of nasal or sinonasal cancer and 167 controls from Denmark, Finland and Sweden, exposure mainly to softwood dust (pine and spruce, but also some birch) was associated with epidermoid and anaplastic carcinomas, but not with adenocarcinomas. There were 13 cases with exposure only to softwood *versus* four controls (odds ratio, 3.3; 95% confidence interval, 1.1-9.4). Of these, four cases (all with epidermoid carcinoma) and two controls had been sawmill workers. Only two of the four cases had had potential exposure to chlorophenols [ref: 3].

In a Norwegian study based on 70 cases of various forms of sinonasal cancer (4 cases observed, 0.4 expected in saw- and planingmill workers; 3 observed, 1.8 expected in forestry workers), three cases of non-Hodgkin's lymphoma were associated with employment in saw- and planingmill firms. The comparison was made beween the number of cases observed in different occupations and the expected number of cases according to the 1946 census data of workers in these occupations [ref: 4].

A case-control study of Hodgkin's disease [ref: 5], using death certificates from North Carolina, USA, counties with a 'significant proportion' of the population employed in the furniture industry and in lumbering, showed an excess risk only among occupational groups with exposure to wood or paper. Carpenters and lumberers had a relative risk of 4.2 for Hodgkin's disease (95% confidence interval, 1.4-12.5). In Oregon, USA, a case-control study on leukaemia (ICD-9 codes 204-208) [ref: 6] showed a three-fold increase in risk for patients who had worked for ten years or more in the sawmill industry ($p$ = 0.017), based on nine exposed cases.

In a proportionate mortality study of the causes of death of 375 union-affiliated Swedish lumberjacks who had died between 1968 and 1977, there were fewer deaths from cancer than expected (PMR, 88; 69-111). A marked deficiency of deaths from lung cancer (SMR, 33) and excesses of deaths from kidney cancer (SMR, 193; 92-407) and from cancers of the lymphatic and haematopoietic systems (SMR, 191; 105-349) were found. No information was given about the histology of these two groups of tumours. The mortality experience of Swedish males during that period was used as the standard for comparison [ref: 7].

A cohort study comparing the mortality experience of 10 322 men employed in the wood working industries with that of 406 798 non-wood workers showed no excess risk for all cancers combined. In the subcohort of lumber and sawmill workers, there was no statistically significantly increase in the incidence of cancer at any site. No case of nasal cancer was reported [ref: 8].

A nested case-control study [ref: 9], based on an average of 25 years' follow-up of 3805 men

working in the Finnish particle-board, plywood, sawmill or formaldehyde glue industries between 1944 and 1965, showed no clear connection between respiratory cancer incidence and most of the exposures studied, although some odds ratios were statistically significantly increased. For example, exposure to pesticides (in wood dust) and phenol was associated with elevated odds ratios, which became more marked among workers with more than ten years' exposure to pesticides. The raised odds ratios for exposure to phenol were partly explained by smoking and exposure to pesticides. Because of the mixed exposure, no single pesticide could be linked with respiratory cancer. Exposure to terpenes and other products of coniferous wood was also significantly associated with respiratory cancer when the duration of exposure exceeded five years. None of the odds ratios for exposure to wood dust and chlorophenols was statistically significant.

A proportionate mortality study showed an elevated risk for death from all cancers (proportionate mortality ratio [PMR], 112; $p < 0.01$), stomach cancer (PMR, 128; $p < 0.01$) and non-Hodgkin's lymphoma (PMR, 139; $p < 0.05$) among woodworkers (including carpenters, cabinet and furniture workers, lumber graders and scalers, sawyers in sawmills and woodworkers not classified elsewhere). In this mixed category, there was no death from sinonasal cancer [ref: 10].

The epidemiological data reported here and previously [ref: 1] are not sufficient to make a definite assessment of the carcinogenic risks of employment in the lumber and sawmill industries. It should also be noted that these two industries differ greatly with regard to exposures other than wood dust. Some studies suggest that the incidences of nasal cancers, lung cancer and Hodgkin's and non-Hodgkin's lymphoma may be increased. The patterns are not consistent, the results are based on few cases and, in some studies, work in furniture manufacture has not been excluded sufficiently well. The hypothesis of a link with Hodgkin's disease is not adequately supported. Soft-tissue sarcomas and histiocytic lymphomas have been reported following exposure to chlorophenols and phenoxyacetic acid herbicides, but the risk to sawmill and lumber workers was not quantified directly. Stomach cancer incidence was slightly elevated in these occupational groups in six mortality series; however, this might be related to nonoccupational factors.

**Overall evaluation**

Lumber and sawmill industries (including logging) entail exposures that are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 25 (1981)

**References**

1. IARC Monographs, 25, 49-97, 1981

2. Elwood, J.M. (1981) Wood exposure and smoking: association with cancer of the nasal cavity and paranasal sinuses in British Columbia. Can. med. Assoc. J., 15, 1573-1577

3. Hernberg, S., Westerholm, P., Schultz-Larsen, K., Degerth, R., Kuosma, E., Englund, A., Engzell, U., Sand Hansen, H. & Mutanen, P. (1983) Nasal and sinonasal cancer. Connection with occupational exposures in Denmark, Finland and Sweden. Scand. J. Work Environ. Health, 9, 315-326

4. Voss, R., Stenersen, T., Oppedal, B.R. & Boysen, M. (1985) Sinonasal cancer and exposure to softwood. Acta otolaryngol., 99, 172-178

5. Greene, M.H., Brinton, L.A., Fraumeni, J.F., Jr & D'Amico, R. (1978) Familial and sporadic Hodgkin's disease associated with occupational wood exposure. Lancet, ii, 626-627

6. Burkart, J.A. (1982) Leukemia in hospital patients with occupational exposure to the sawmill industry. West J. Med., 137, 440-441

7. Edling, C. & Granstam, S. (1980) Causes of death among lumberjacks - a pilot study. J. occup. Med., 22, 403-406

8. Stellman, S. & Garfinkel, L. (1984) Cancer mortality among woodworkers. Am. J. ind. Med., 5, 343-357

9. Kauppinen, T.P., Partanen, T.J., Nurminen, M.M., Nickels, J.I., Hernberg, S.G., Hakulinen, T.R., Pukkala, E.I. & Savonen, E.T. (1986) Respiratory cancers and chemical exposures in the wood industry: A nested case-control study. Br. J. ind. Med., 43, 84-90

10. Gallagher, R.P., Threlfall, W.J., Band, P.R. & Spinelli, J.J. (1987) Cancer mortality experience of woodworkers, loggers, fishermen, farmers, and miners in British Columbia. Natl Cancer Inst. Monogr., 69, 163-167

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# MEDROXYPROGESTERONE ACETATE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 289)

**CAS No.**: 71-58-9
**Chem. Abstr. Name**: (6α)-17-(Acetyloxy)-6-methylpregn-4-ene-3,20-dione

**A. Evidence for carcinogenicity to humans** (*inadequate*)

The results of one cross-sectional study of the development of breast nodules in women given medroxyprogesterone acetate was difficult to interpret because of methodological considerations [ref: 1]. Two small cohort studies in the USA showed relative risks (and 95% confidence limits) of breast cancer in women exposed to medroxyprogesterone acetate of 0.69 (0.3-1.4) [ref: 2] and 1.1 (0.5-2.4) [ref: 3], but both included only women with short-term exposure and limited duration of follow-up. A case-control study of 30 women with breast cancer and 179 controls [ref: 4] yielded a relative risk of 1.0 (no confidence limits given) for use of medroxyprogesterone acetate at some time. Preliminary analyses of a collaborative case-control study in Thailand, Kenya and Mexico sponsored by the World Health Organization [ref: 5], based on 427 cases (39 'ever' users) and 5951 controls (557 'ever' users), provided estimates of relative risk (and 95% confidence limits) for breast cancer of 1.0 (0.7-1.5) in women who 'ever' used medroxyprogesterone acetate, 1.1 (0.7-1.9) for users for 1-12 months, 1.2 (0.7-2.2) for users for 13-36 months and 0.8 (0.4-1.7) for users for 37 months or more.

Medroxyprogesterone acetate causes reversible changes in the endometrium, from proliferative to secretory or suppressed [ref: 4]. In one small cohort study, one case of uterine leiomyosarcoma was found, with 0.83 cancers of the uterine corpus expected, giving a relative risk of 1.2 [0.03-6.7] [ref: 2]. In the collaborative study [ref: 5], the estimated relative risk for endometrial cancer in 'ever' users of medroxyprogesterone acetate was 0.3 (0.04-2.4), based on 57 cases, only one of which was exposed, and 316 matched controls (30 exposed).

In the small cohort study [ref: 2], one ovarian cancer case occurred in a medroxyprogesterone acetate user, with 1.16 expected, giving a relative risk of 0.86 [0.02-4.6]. Preliminary analysis of data from the collaborative study [ref: 5], based on 105 cases (seven exposed) and 637 matched controls (74 exposed) yielded a relative risk for ovarian cancer of 0.7 (0.3-1.7) in 'ever' users of medroxyprogesterone acetate.

The results of two cohort studies of dysplasia and of carcinoma *in situ* of the uterine cervix in women given medroxyprogesterone acetate were conflicting and difficult to interpret because of methodological problems [ref: 1]. Preliminary results from the collaborative study [ref: 5], based on 920 cases of invasive cervical carcinoma (126 exposed to medroxyprogesterone acetate) and 5833 controls (545 exposed) yielded estimated relative risks of 1.2 (0.9-1.5) in 'ever' users, after controlling for parity, history of vaginal discharge, age at first sexual relationship, number of sexual partners, number of prior Pap smears and use of an intrauterine device and oral contraceptives. Relative risks in users for 1-12, 13-24, 25-60 and 61 months or more were estimated to be 1.4 (1.0-2.0), 1.2 (0.7-2.0), 0.6 (0.4-1.1) and 1.4 (0.9-2.2), respectively.

Preliminary analyses of data from the collaborative study [ref: 5] showed the relative risk for primary liver cancer (all histological types combined) in women who had ever used medroxyprogesterone acetate to be 1.0 (0.4-2.8), based on 57 cases (seven exposed) and 290 controls (34 exposed).

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Medroxyprogesterone acetate was tested by intramuscular injection in dogs and by subcutaneous implantation in mice. It induced adenocarcinomas of the mammary gland in one study in female

mice [ref: 6], and produced malignant mammary tumours in dogs [ref: 1]. After four years of intramuscular treatment of dogs with a human contraceptive dose, a dose-related increase in the incidence of mammary nodules was seen; the incidence of mammary-gland nodules at that time was comparable with that seen in dogs given progesterone at 25 times the canine luteal level [ref: 7]. Female dogs treated with medroxyprogesterone acetate for at least one year had a significant increase in the incidence of large and small mammary nodules as compared with control animals in one study [ref: 8], and a dose-related increase in the incidence of large mammary nodules was found in another after intramuscular administration [ref: 9].

**C. Other relevant data**

No data were available on the genetic and related effects of medroxyprogesterone acetate alone in humans. See, however, the summary of data for combined oral contraceptives. Medroxyprogesterone acetate induced sister chromatid exchanges in mouse cells *in vitro*.

**Overall evaluation**

Medroxyprogesterone acetate is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 6 (1974) ; Vol. 21 (1979)

**References**

1. IARC Monographs, 21, 417-429, 1979

2. Liang, A.P., Levenson, A.G., Layde, P.M., Shelton, J.D., Hatcher, R.A., Potts, M. & Michelson, M.J. (1983) Risk of breast, uterine corpus, and ovarian cancer in women receiving medroxyprogesterone injections. J. Am. med. Assoc., 249, 2909-2912

3. Danielson, D.A., Jick, H., Hunter, J.R., Stergachis, A. & Madsen, S. (1982) Nonestrogenic drugs and breast cancer. Am. J. Epidemiol., 116, 329-332

4. Greenspan, A.R., Hatcher, R.A., Moore, A., Rosenberg, M.J. & Ory, H.W. (1980) The association of depo-medroxyprogesterone acetate and breast cancer. Contraception, 21, 563-569

5. Special Programme of Research, Development and Research Training in Human Reproduction (1986) Depot-medroxyprogesterone acetate DMPA and cancer. Memorandum from a WHO meeting. WHO Bull., 64, 375-382

6. Lanari, C., Molinolo, A.A. & Pasqualini, C.D. (1986) Induction of mammary adenocarcinomas by medroxyprogesterone acetate in BALB/c female mice. Cancer Lett., 33, 215-223

7. Frank, D.W., Kirton, K.T., Murchison, T.E., Quinlan, W.J., Coleman, M.E., Gilbertson, T.J., Feenstra, E.S. & Kimball, F.A. (1979) Mammary tumors and serum hormones in the bitch treated with medroxyprogesterone acetate or progesterone for four years. Fertil. Steril., 31, 340-346

8. van Os, J.L., van Laar, P.H., Oldenkamp, E.P. & Verschoor, J.S.C. (1981) Oestrus control and the incidence of mammary nodules in bitches, a clinical study with two progestogens. Vet. Q., 3, 46-56

9. Concannon, P.W., Spraker, T.R., Casey, H.W. & Hansel, W. (1981) Gross and histopathologic effects of medroxyprogesterone acetate and progesterone on the mammary glands of adult beagle bitches. Fertil. Steril., 36, 373-387

10. IARC Monographs, Suppl. 6, 359-360, 1987

**Synonyms for Medroxyprogesterone acetate**

- 17α-Acetoxy-6α-methylprogesterone
- Amen
- Clinovir
- Depcorlutin
- Depo-clinovir
- Depomedroxyprogesterone acetate
- Depo-provera
- Deporone
- Farlutal
- Farlutin
- Gesinal
- Gestapuran
- Gestapuron
- 17-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate
- 17α-Hydroxy-6α-methylprogesterone acetate
- Luteocrin
- Lutopolar
- Lutoral
- MAP
- Metigestrona
- Metilgestene
- Metipregnone
- 6α-Methyl-17-acetoxyprogesterone
- 6α-Methyl-17α-hydroxyprogesterone acetate
- MPA
- Nogest
- Oragest
- Perlutex
- Prodasone
- Progestalfa
- Progevera
- Promone-E
- Provera
- Proverone
- Provest
- Repromix
- Sirprogen
- Sodelut G
- U 8839
- Veramix

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Last updated: 3 March 1998

# MELPHALAN
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 239)

**CAS No.**: 148-82-3
**Chem. Abstr. Name**: 4-[Bis(2-chloroethyl)amino]-L-phenylalanine

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Epidemiological studies of patients with ovarian carcinoma [ref: 1-3], multiple myeloma [ref: 4,5] or breast cancer [ref: 6] have consistently shown very large excesses of acute nonlymphocytic leukaemia in the decade following therapy with melphalan. The relative risk was consistently estimated to be in excess of 100, to increase with increasing dose, and to be roughly the same with and without radiotherapy [ref: 7].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Melphalan has been tested in mice and rats by intraperitoneal injection, producing lymphosarcomas and a dose-related increase in the incidence of lung tumours in mice and peritoneal sarcomas in rats [ref: 8].

**C. Other relevant data**

Melphalan is a bifunctional alkylating agent. Patients treated therapeutically with melphalan had increased frequencies of chromosomal aberrations and sister chromatid exchanges in their peripheral lymphocytes [ref: 9].

Melphalan induced chromosomal aberrations in bone-marrow cells of rats treated *in vivo*. The compound induced chromosomal aberrations, sister chromatid exchanges and DNA damage in human cells *in vitro*. It induced transformation of C3H 10T1/2 cells. In cultured rodent cells, it induced chromosomal aberrations, sister chromatid exchanges, mutation and DNA damage. It induced aneuploidy and sex-linked recessive lethal mutations in *Drosophila* and mutation in bacteria [ref: 9].

**Overall evaluation**

Melphalan is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 9 (1975)

**References**

1. Einhorn, N., Eklund, G., Franzén, S., Lambert, B., Lindsten, J., & Söderhall, S. (1982) Late side effects of chemotherapy in ovarian carcinoma. A cytogenetic, hematologic, and statistical study. Cancer, 49, 2234-2241

2. Reimer, R.R., Hoover, R., Fraumeni, J.F., Jr & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. New Engl. J. Med., 297, 177-181

3. Greene, M.H., Boice, J.D., Jr, Greer, B.E., Blessing, J.A. & Dembo, A.J. (1982) Acute nonlymphocytic leukemia after therapy with alkylating agents for ovarian cancer. A study of five randomized clinical trials. New Engl. J. Med., 307, 1416-1421

4. Law, I.P. & Blom, J. (1977) Second malignancies in patients with multiple myeloma. Oncology, 34, 20-24

5. Gonzalez, F., Trujillo, J.M. & Alexanian, R. (1977) Acute leukemia in multiple myeloma. Ann. intern. Med., 86, 440-443

6. Greene, M.H., Harris, E.L., Gershenson, D.M., Malkasian, G.D., Jr, Melton, L.J., III, Dembo, A.J., Bennett, J.M., Moloney, W.C. & Boice, J.D., Jr (1986) Melphalan may be a more potent leukemogen than cyclophosphamide. Ann. intern. Med., 105, 360-367

7. Fisher, B., Rockette, H., Fisher, E.R., Wickerham, D.L., Redmond, C. & Brown, A. (1985) Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiotherapy: the NSABP experience. J. clin. Oncol., 3, 1640-1658

8. IARC Monographs, 9, 167-180, 1975

9. IARC Monographs, Suppl. 6, 363-365, 1987

**Synonyms**

- Alkeran
- L-3-[*para*-[Bis(2-chloroethyl)amino]phenyl]alanine
- CB 3025
- *para*-Di(2-chloroethyl)amino-L-phenylalanine
- *para*-Di(2-chloroethyl)aminophenylalanine
- Melfalan
- NSC 88-6
- Phenylalanine mustard
- L-Phenylalanine mustard
- Phenylalanine nitrogen mustard
- Sarcolysin
- L-Sarcolysin
- Sarcolysine
- L-Sarcolysine
- L-Sarkolysin
- SK 15673

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Last updated: 9 February 1998

# 6-MERCAPTOPURINE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 240)

**CAS No.**: 50-44-2
**Chem. Abstr. Name**: 6*H*-Purine-6-thione,1,7-dihydro-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of 6-mercaptopurine as a single agent was available to the Working Group. Occasional case reports of exposure to 6-mercaptopurine, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

6-Mercaptopurine was tested by intraperitoneal administration and by skin painting (followed by croton oil) in mice and by intraperitoneal, subcutaneous and intravenous injection in rats. Limitations to the data in all the reports precluded evaluation of the possible carcinogenicity of this compound [ref: 1].

**C. Other relevant data**

6-Mercaptopurine induced chromosomal aberrations and sister chromatid exchanges in lymphocytes of treated patients in single studies [ref: 2].

In rodents treated *in vivo*, 6-mercaptopurine induced dominant lethal mutations, chromosomal aberrations and micronuclei, but not aneuploidy. The compound induced chromosomal aberrations in human lymphocytes *in vitro*. It induced mutation in cultured rodent cells and chromosomal aberrations and sister chromatid exchanges but not aneuploidy in Chinese hamster cells *in vitro*. It did not transform mouse C3H 10T1/2 cells. 6-Mercaptopurine was mutagenic to and caused DNA damage in bacteria [ref: 2].

**Overall evaluation**

6-Mercaptopurine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 249-266, 1981

2. IARC Monographs, Suppl. 6, 366-368, 1987

**Synonyms**

- IND 1226

- Ismipur
- Leukerin
- Leupurin
- Mercaleukin
- Mercapurin
- Mern
- 6-Mercaptopurin
- Mercaptopurine
- Mercapto-6-purine
- 6-Mercapto-1*H*-purine
- Mercaptopurinum
- 7-Mercapto-1,3,4,6-tetrazaindene
- 6-MP
- NSC 755
- Purine-6-thiol
- Purinethiol
- 6-Purinethiol
- 3*H*-Purine-6-thiol
- Purinethol
- Thiohypoxanthine
- 6-Thiopurine
- 6-Thioxopurine

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Last updated: 11 March 1998

# METHOTREXATE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 241)

**CAS No.**: 59-05-2
**Chem. Abstr. Name**: L-Glutamic acid, *N*-(4-[[(2,4-diamino-6-pteridinyl]methyl]-methylamino]benzoyl-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

The relationship between methotrexate treatment and subsequent malignancy has been investigated in one cohort of 457 patients (3522 person-years) treated for trophoblastic tumours (2 observed, 3.5 expected) [ref: 1] and in a cohort of 248 patients treated for psoriasis (10 observed, 22 expected) [ref: 2]. A case control study of treatment for psoriasis has also been performed, in which 26 cases of noncutaneous cancer (104 matched controls) and 80 cases of nonmelanoma skin cancer (297 matched controls) were studied; relative risks were 1.0 and 1.2, respectively [ref: 3]. In each comparison, no excess (significant or otherwise) or subsequent malignancy was observed.

**B. Evidence for carcinogenicity to animals** (*inadequate*)

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 showed a high incidence of lung carcinomas, but the study design did not include matched controls. No other study revealed a carcinogenic effect, but the significance of several was limited because of deficiencies in experimental design or reporting of data [ref: 4]. A study in which methotrexate was given intraperitoneally in combination with cyclophosphamide and 5-fluorouracil to rats resulted in induction of tumours in the nervous system, haematopoietic and lymphatic tissues, the urinary bladder and adrenal glands; however, because of lack of matched controls, it could not be concluded whether tumour induction was due to a combined effect of the three chemicals or to any one of them [ref: 5].

**C. Other relevant data**

In patients treated with methotrexate, chromosomal aberrations were observed in bone-marrow cells, and, in one of two studies, sister chromatid exchanges were induced in lymphocytes [ref: 6].

Methotrexate induced micronuclei in mice, but neither aneuploidy in mouse oocytes nor DNA strand breaks in granuloma cells of rats treated *in vivo*. It induced chromosomal aberrations in human and rodent cells in vitro and sister chromatid exchanges in rodent but not in human cells *in vitro*. It did not induce unscheduled DNA synthesis in human cells *in vitro*. It caused transformation of C3H 10T1/2 cells but not of Syrian hamster embryo cells and was mutagenic to mouse lymphoma cells but not to Chinese hamster cells *in vitro*. Methotrexate induced genetic crossing-over but not sex-linked recessive lethal mutations in *Drosophila*. It was not mutagenic to *Salmonella typhimurium* but gave conflicting results in *Escherichia coli* and was mutagenic to *Bacillus subtilis*. It did not induce DNA damage in bacteria [ref: 6].

**Overall evaluation**

Methotrexate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

## References


1. Rustin, G.J.S., Rustin, F., Dent, J., Booth, M., Salt, S. & Bagshawe, K.D. (1983) No increase in second tumors after cytotoxic chemotheraphy for gestational trophoblastic tumors. New Engl. J. Med., 308, 473-476

2. Nyfors, A. & Jensen, H. (1983) Frequency of malignant neoplasms in 248 long-term methotrexate-treated psoriatics. A preliminary study. Dermatologica, 167, 260-261

3. Stern, R.S., Zierler, S. & Parrish, J.A. (1982) Methotrexate used for psoriasis and the risk of noncutaneous or cutaneous malignancy. Cancer, 50, 869-872

4. IARC Monographs, 26, 267-292, 1981

5. Habs, M., Schmähl, D. & Lin, P.Z. (1981) Carcinogenic activity in rats of combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil. Int. J. Cancer, 28, 91-96

6. IARC Monographs, Suppl. 6, 372-374, 1987


## Synonyms

- Amethopterin
- 4-Amino-10-methylfolic acid
- 4-Amino-$N^{10}$-methylpteroylglutamic acid
- Antifolan
- CL-14377
- *N*-[*p*-[(2,4-Diamino-6-pteridinyl)methyl]methylamino]-benzoyl L-(+)-glutamic acid
- *N*-(4-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino]-benzoyl)-L-glutamic acid
- *N*-[*p*-[(2,4-Diaminopteridin-6-yl-methyl)methylamino]benzoyl]-L-glutamic acid
- L-(+)-*N*-(*p*-[[(2,4-Diamino-6-pteridinyl)methyl]methyl-amino]benzoyl)glutamic acid
- Ledertrexate
- α-Methopterin
- A-Methopterin
- Methotrexate specia
- Methotrexatum
- Methylaminopterin
- MEXATE
- MTX
- NSC 740
- R 9985

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Last updated: 11 March 1998

# 5-METHOXYPSORALEN
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 242)

**CAS No.:** 484-20-8
**Chem. Abstr. Name:** 4-Methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one

**A. Evidence for carcinogenicity to humans** (*inadequate*)

In a survey of 87 persons employed in the production of bergamot oil (of which 5-methoxypsoralen is a constituent), 19% of 79 exposed workers and 16% of a comparison group of 31 people resident in the same area were observed to have 'keratomas' or 'epitheliomas' of the skin. Possible confounding effects of age, sex and outdoor employment were not considered in this analysis [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

5-Methoxypsoralen was tested in by skin application in combination with ultraviolet A radiation or solar-simulated radiation, producing skin papillomas and carcinomas; in these studies, no or few skin tumours were observed with ultraviolet A radiation or solar-simulated radiation alone. The studies were inadequate to evaluate the local and systemic carcinogenic effects of the compound itself [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of 5-methoxypsoralen in humans.

In the presence of ultra-violet A radiation, 5-methoxypsoralen induced chromosomal aberrations, sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*; sister chromatid exchanges, mutation and DNA cross-links in rodent cells *in vitro*; mutation, gene conversion and DNA cross-links in yeast; and mutation and prophage in bacteria [ref: 2].

5-Methoxypsoralen, tested in the absence of ultraviolet A radiation, was reported to be weakly mutagenic to bacteria [ref: 2].

**Overall evaluation**

5-Methoxypsoralen is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 40 (1986)

**References**

1. IARC Monographs, 40, 327-347, 1986

2. IARC Monographs, Suppl. 6, 377-379, 1987

**Synonyms**

- Bergaptan
- Bergapten
- Bergaptene
- Heraclin
- 6-Hydroxy-4-methoxy-5-benzofuranacrylic acid, delta-latone
- Majudin
- 5-Methoxy-6,7-furanocoumarin
- 5-MOP

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Last updated: 11 February 1998

# 8-METHOXYPSORALEN (METHOXSALEN) PLUS ULTRAVIOLET RADIATION (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 261)

**8-Methoxypsoralen**
**CAS No.**: 298-81-7
**Chem. Abstr. Name**: 7*H*-Furo[3,2-*g*][1]benzopyran-7-one, 9-methoxy-

**A. Evidence for carcinogenicity to humans** (*sufficient*)

The development of nonmelanocytic skin cancer (basal- and squamous-cell skin cancers) has been reported in patients treated with 8-methoxypsoralen and long-wave ultraviolet light (UVA) (PUVA) for psoriasis or mycosis fungoides [ref: 1-5]. Three cases of malignant melanomas of the skin have been reported in patients with psoriasis treated with PUVA [ref: 6,7]. The strongest evidence for a causal association between PUVA treatment and nonmelanocytic skin cancer comes from the follow-up of 1380 psoriatic patients treated in the USA. The standardized incidence ratio (SIR) for squamous-cell carcinoma increased from 4.1 (95% confidence interval, 2.3-6.8) at low doses to 22.3 (13.5-34.1) at medium doses and 56.8 (42.7-74.2) at high doses; this effect was independent of possible confounding effects of therapy with ionizing radiation and topical tar. The effect on basal-cell cancer was much weaker (high doses: SIR, 4.5; 2.8-6.9) [ref: 8]. One cohort study of 525 psoriatic patients treated with PUVA did not suggest an increase in the incidence of skin cancer (mean follow-up period, 2.1 years) [ref: 9]. This 'negative' result could have been due to lack of statistical power and to the low doses used in the study. Another study with a five-year follow up showed no skin tumour in 94 patients treated with PUVA for psoriasis or mycosis fungoides [ref: 10].

8-Methoxypsoralen alone did not alter the incidence of new skin cancer over two years in two small controlled trials of its use as a putative prophylactic for skin cancer [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

8-Methoxypsoralen was tested by oral and intraperitoneal administration and by skin application in combination with ultraviolet A radiation in mice, producing epidermal and dermal tumours [ref: 1,11-15]. When it was tested alone in mice by intraperitoneal administration [ref: 13] or by skin application [ref: 12,13], it did not induce skin tumours. The studies were inadequate to evaluate the systemic carcinogenicity of 8-methoxypsoralen.

**C. Other relevant data**

In patients treated with PUVA, neither chromosomal aberrations (one study) nor sister chromatid exchanges were observed [ref: 16].

8-Methoxypsoralen in combination with ultraviolet A radiation induced sister chromatid exchanges in epithelial cells of cheek pouches of hamsters treated *in vivo*. In a large number of studies, it induced chromosomal aberrations, sister chromatid exchanges, mutation, DNA damage and DNA cross-links in human cells *in vitro*. It transformed mouse C3H 10T1/2 cells. In rodent cells in culture, it induced chromosomal aberrations, micronuclei, sister chromatid exchanges, mutation, unscheduled DNA synthesis and DNA cross-links. It induced mitotic recombination and mutation in fungi and mutation and DNA damage in bacteria [ref: 16].

8-Methoxypsoralen in the absence of ultra-violet A radiation induced mutation in bacteria, but inconclusive results were obtained with respect to chromosomal aberrations and sister chromatid exchanges in human cells *in vitro*, gene mutation and DNA damage in rodent cells *in vitro* and mutation in yeast [ref: 16].

**Overall evaluation**

8-Methoxypsoralen (methoxsalen) plus ultraviolet radiation is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 24 (1980)

**References**


1. IARC Monographs, 24, 101-124, 1980

2. Roenigk, H.H., Jr & Caro, W.A. (1981) Skin cancer in the PUVA-48 cooperative study. J. Am. Acad. Dermatol., 4, 319-324

3. Stüttgen, G., Kentsch, V., Schalla, W. & Schneider, L. (1981) The risks of photochemotherapy (Ger.). Z. Hautkr., 56, 1379-1399

4. Abel, E.A., Deneau, D.G., Farber, E.M., Price, N.M. & Hoppe, R.T. (1981) PUVA treatment of erythrodermic and plaque type mycosis fungoides. J. Am. Acad. Dermatol., 4, 423-429

5. Stern, R., Zierler, S. & Parrish, J.A. (1982) Psoriasis and the risk of cancer. J. invest. Dermatol., 78, 147-149

6. Frenk, E. (1983) Malignant melanoma in a patient with severe psoriasis treated by oral methoxsalen photochemotherapy. Dermatologica, 167, 152-154

7. Marx, J.L., Auerbach, R., Possick, P., Myrow, R., Gladstein, A.H. & Kopf, A.W. (1983) Malignant melanoma *in situ* in two patients treated with psoralens and ultraviolet A. J. Am. Acad. Dermatol., 9, 904-911

8. Stern, R.S., Laird, N., Melski, J., Parrish, J.A., Fitzpatrick, T.B. & Bleich, H.L. (1984) Cutaneous squamous-cell carcinoma in patients treated with PUVA. New Engl. J. Med., 310, 1156-1161

9. Lassus, A., Reunala, T., Idanpää-Heikkilä, J., Juvakoski, T. & Salo, O. (1981) PUVA treatment and skin cancer: a follow-up study. Acta dermatol. venereol., 61, 141-145

10. Fitzsimons, C.P., Long, J. & MacKie, R.M. (1983) Synergistic carcinogenic potential of methotrexate and PUVA in psoriasis. Lancet, i, 235-236

11. Kripke, M.L., Morison, W.L. & Parrish, J.A. (1982) Induction and transplantation of murine skin cancers induced by methoxsalen plus ultraviolet (320-400 nm) radiation. J. natl Cancer Inst., 68, 685-690

12. Nagayo, K., Way, B.H., Tran, R.M. & Song, P.S. (1983) Photocarcinogenicity of 8-methoxypsoralen and aflatoxin $B_1$ with longwave ultraviolet light. Cancer Lett., 18, 191-198

13. Young, A.R., Magnus, I.A., Davies, A.C. & Smith, N.P. (1983) A comparison of the phototumorigenic potential of 8-MOP and 5-MOP in hairless albino mice exposed to solar simulated radiation. Br. J. Dermatol., 108, 507-518

14. Gibbs, N.K., Young, A.R. & Magnus, I.A. (1985) A strain of hairless mouse susceptible to tumorigenesis by TPA alone: studies with 8-methoxypsoralen and solar simulated radiation. Carcinogenesis, 6, 797-799

15. Hannuksela, M., Stenbäck, F. & Lahti, A. (1986) The carcinogenic properties of topical PUVA. A lifelong study in mice. Arch. Dermatol. Res., 278, 347-351

16. IARC Monographs, Suppl. 6, 380-385, 1987

**Synonyms for 8-Methoxypsoralen**

- Ammoidin
- Meladinin [VAN]
- Meladinine
- Meladoxen
- Meloxine
- Methoxa-Dome
- 9-Methoxy-7*H*-furo[3,2-*g*]benzopyran-7-one
- 6-Hydroxy-7-methoxy-5-benzofuranacrylic acid δ-lactone
- Methoxsalen
- 8-Methoxy-(furano-3',2':6,7-coumarin)
- 8-Methoxy-4'-5':6,7-furocoumarin
- 8-Methoxypsoralen
- 9-Methoxypsoralen
- 8-Methoxypsoralene
- 8-MOP
- Mopsoralen
- 8-MP
- Oxypsoralen
- Oxsoralen
- Soloxsalen
- Trioxun
- Xanthotoxin
- Xanthotoxine

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Last updated 12/23/1997

# 4,4'-METHYLENE BIS(2-METHYLANILINE) (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 248)

**CAS No.**: 838-88-0

**A. Evidence for carcinogenicity to humans** (*inadequate*)

A study of an Italian cohort of 906 dyestuffs workers employed between 1922 and 1970 revealed an impressive excess of deaths from bladder cancer (36 observed, 1.2 expected). Workers were classified into ten exposure categories. Among 53 workers employed in the manufacture of new fuchsin ('new' magenta) and safranine T, five died from bladder cancer, whereas 0.08 would have been expected. Their minimum length of employment was 12 years. Three of the five deaths occurred among workers engaged in the synthesis of *ortho*-toluidine and 4,4'-methylenebis(2-methylaniline), used as precursors in the production of fuchsin and safranine T, which was carried out in a separate building within the plant [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

4,4'-Methylene bis(2-methylaniline) was tested for carcinogenicity by oral administration in rats and dogs, inducing high incidences of hepatocellular carcinomas in animals of each species; neoplasms of the lung, mammary gland and skin in rats and of the lung in dogs were also reported [ref: 2-4].

**C. Other relevant data**

No data were available to the Working Group.

**Overall evaluation**

4,4'-Methylene bis(2-methylaniline) is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**

1. Rubino, G.F., Scansetti, G., Piolatto, G. & Pira, E. (1982) The carcinogenic effect of aromatic amines: an epidemiological study on the role of *o*-toluidine and 4,4'-methylene bis(2-methylaniline) in inducing bladder cancer in man. Environ. Res., 27, 241-254

2. IARC Monographs, 4, 73-77, 1974

3. Stula, E.F., Sherman, H., Zapp, J.A., Jr & Clayton, J.W., Jr (1975) Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline), and 4,4'-methylene-bis(2-methylaniline). Toxicol. appl. Pharmacol., 31, 159-176

4. Stula, E.F., Barnes, J.R., Sherman, H., Reinhardt, C.F. & Zapp, J.A., Jr (1978) Liver and lung tumors in dogs from 4,4'-methylene-bis(2-methylaniline). J. environ. Pathol. Toxicol., 1, 339-356

**Synonyms**

- 4,4'-Diamino-3,3'-dimethyldiphenylmethane
- 3,3'-Dimethyl-4,4'-diaminodiphenylmethane
- 3,3'-Dimethyldiphenylmethane-4,4'-diamine
- 2,2'-Dimethyl-4,4'-methylenedianiline
- Methylenebis(3-methylphenylene-4-amine)
- Methylenebis(*o*-methylaniline)
- Methylenebis(*o*-toluidine)
- Methylenebis(2-toluidine)
- 4,4'-Methylenedi-*o*-toluidine

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Last updated: 3 March 1998

# *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE (MNNG) (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.248)

**CAS No.:** 70-25-7

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Three cases of brain tumour (gliomas) and one of colon cancer have been reported from a genetics laboratory over a 13-year period. All the subjects were likely to have been exposed to MNNG for at least six to 15 years prior to death, but other carcinogens had been used in the laboratory [ref: 1,2].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

MNNG has been tested for carcinogenicity in mice, rats, hamsters, rabbits and dogs, producing tumours at many sites. It has a predominantly local carcinogenic effect and is carcinogenic in single-dose experiments. Following its oral administration, papillomas and squamous-cell carcinomas of the oesophagus and forestomach, adenocarcinomas of the stomach, small intestine and large bowel, and sarcomas of the gastrointestinal tract were reported [ref: 3]. These findings have been extended in more recent studies after oral administration to rats [ref: 4-7], hamsters [ref: 8,9] and dogs [ref: 10,11]. After subcutaneous injection in mice, it produced lung and liver tumours and haemangioendotheliomas [ref: 12]; after intrarectal instillation in rats and guinea-pigs [ref: 13-15] and after intrauterine and intravaginal application to rats, it produced local tumours [ref: 16].

**C. Other relevant data**

MNNG is an alkylating agent [ref: 17]. No data were available to evaluate the genetic and related effects of this compound in humans.

MNNG induced DNA strand breaks in various organs of rats treated *in vivo*. It did not cause dominant lethal mutations in mice, but it gave positive results for mutation in the mouse spot test; it induced chromosomal aberrations and micronuclei in bone-marrow cells of mice and sister chromatid exchanges in bone-marrow cells of mice and Chinese hamsters treated *in vivo*. It induced chromosomal aberrations, sister chromatid exchanges, DNA strand breaks and unscheduled DNA synthesis in human and rodent cells *in vitro* and induced mutation in cultured rodent cells. It gave positive results in several assays for cell transformation. MNNG induced somatic and sex-linked recessive lethal mutations in *Drosophila*. It caused chromosomal aberrations, sister chromatid exchanges and mutation in plants and recombination and mutation in fungi. It was mutagenic to and caused DNA damage in bacteria, and gave positive results in host-mediated assays using bacteria or yeast as indicators and mice as hosts [ref: 17].

**Overall evaluation**

*N*-Methyl-*N*'-Nitro-*N*-Nitrosoguanidine (MNNG) is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**

1. Pleven, C., Audran, R., Falcy, M., Efthymiou, M.-L. & Philbert, M. (1983) Glioblastomas and

chemical mutagenesis in biology laboratories. Report of 3 deaths in the same institute (Fr.). Arch. Mal. prof., 44, 411-418

2. Pleven, C., Falcy, M., Audran, R., Philbert, M. & Efthymiou, M.L. (1984) Occurrence of glioblastomas in people working in research laboratories using nitroso compounds (Fr.). J. Toxicol. med., 4, 249-257

3. IARC Monographs, 4, 183-195, 1974

4. Martin, M.S., Martin, F., Justrabo, E., Michiels, R., Bastien, H. & Knobel, S. (1974) Susceptibility of inbred rats to gastric and duodenal carcinomas induced by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. J. natl Cancer Inst., 53, 837-840

5. Kartasheva, L.A. & Bykorez, A.J. (1975) Induction of adenocarcinomas of the stomach in rats by *N*-methyl-*N*'-nitroso-*N*-nitroguanidine (Russ.). Vopr. Onkol., 21, 50-55

6. Habs, M., Deutsch-Wenzel, R., Preussmann, R. & Schmahl, D. (1978) Induction of gastric tumors in BD-IV rats by single application of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Z. Krebsforsch., 91, 183-188

7. Sherenesheva, N.I. (1979) Induction of gastrointestinal tumours in rats by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) (Russ.). Vopr. Onkol., 25, 72-74

8. Kogura, K., Sasadaira, H., Kawachi, T., Shimosato, Y., Tokunaga, A., Fujimura, S. & Sugimura, T. (1974) Further studies on induction of stomach cancer in hamsters by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Br. J. Cancer, 29, 132-142

9. Ketkar, M., Reznik, G. & Green, U. (1978) Carcinogenic effect of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG) in European hamsters. Cancer Lett., 4, 241-244

10. Fujita, M., Taguchi, T., Takami, M., Usugane, M., Takahashi, A. & Shiba, S. (1974) Carcinoma and related lesion in dog stomach induced by oral administration of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Gann, 65, 207-214

11. Koyama, Y., Omori, K., Hirota, T., Sano, R. & Ishihara, K. (1976) Leiomyosarcomas of the small intestine induced in dogs by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Gann, 67, 241-251

12. Fujii, K. & Nakadate, M. (1977) Tumor induction by a single subcutaneous injection of *N*-methyl-N'-nitro-*N*-nitrosoguanidine and its derivatives in newborn mice. Z. Krebsforsch., 90, 313-319

13. Nakano, H. (1973) Histopathological studies on rat colo-rectal carcinoma induced by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Tokohu J. exp. Med., 110, 7-21

14. Chlap, Z. & Przewlocki, F. (1979) A study of colon cancer in rats after rectal administration of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (Pol.). Pat. Pol., 30, 475-488

15. Narisawa, T., Wong, C.Q. & Weisburger, J.H. (1976) Large bowel carcinoma in strain-2 guinea pigs by intrarectal instillation of *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Gann, 67, 41-46

16. Tanaka, T. & Mori, H. (1983) Experimental induction of uterine cancer in rats by *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine. Pathol. Res. Pract., 178, 20-26

17. IARC Monographs, Suppl. 6, 394-398, 1987

**Synonyms**

- 1-Methyl-3-nitro-l-nitrosoguanidine
- *N*-Methyl-*N*-nitroso-*N*'-nitroguanidine
- MNG
- MNNG
- NG

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Last updated: 11 February 1998

# METHYL PARATHION
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 392)

**CAS No.**: 298-00-0
**Chem. Abstr. Name**: Phosphorothioic acid, *O*,*O*-dimethyl *O*-(4-nitrophenyl) ester

**A. Evidence for carcinogenicity to animals** (*evidence suggesting lack of carcinogenicity*)

Methyl parathion was tested adequately by oral administration in the diet of mice and rats. There was no increase in tumour incidence over that in controls [ref: 1].

**B. Other relevant data**

The incidences of chromosomal aberrations and of dominant lethal mutations were not increased in mice treated *in vivo* with methyl parathion. In mammalian cells, sister chromatid exchange and presumed gene mutations were induced, but neither chromosomal aberration nor unscheduled DNA synthesis was elicited. Methyl parathion was weakly or nonmutagenic in *Drosophila melanogaster* and in bacterial systems, but it was mutagenic in yeasts [ref: 1].

**Overall evaluation**

Methyl parathion is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 30 (1983)

**Reference**

1. IARC Monographs, 30, 131-152, 1983

**Synonyms**

- A-Gro
- Azofos
- Azophos
- Bay 11405
- Bladan M
- Cekumethion
- Dalf
- Demethylfenitrothion
- Dimethyl 4-nitrophenyl phosphorothionate
- Dimethyl *para*-nitrophenyl monothiophosphate
- Dimethyl *para*-nitrophenyl phosphorothionate
- Dimethyl *para*-nitrophenyl thiophosphate
- Dimethyl parathion
- Drexel methyl parathion 4E
- Drexel methyl parathion 601
- Dygun
- Dypar
- E 601

- Ekatox
- ENT 17292
- Folidol 80
- Folidol M
- Folidol M40
- Fosferno M50
- Gearphos
- M-Parathion
- Mepaton
- Meptox
- Metacid 50
- Metacide
- Metafos
- Metaphor
- Metaphos
- Methyl fosferno
- Methyl-E 605
- Methylthiophos
- Metron
- MPT
- NCI C02971
- Niletar
- Niran M-4
- Nitran
- Nitrox
- Nitrox 80
- *O*,*O*-dimethyl *O*-(*para*-nitrophenyl) phosphorothioate
- *O*,*O*-dimethyl *O*-(*para*-nitrophenyl) thionophosphate
- *O*,*O*-dimethyl *O*-(*para*-nitrophenyl) thiophosphate
- *O*,*O*-Dimethyl *O*-4-nitrophenyl phosphorothioate
- Oleovofotox
- Parapest M-50
- Parataf
- Parathion methyl homolog
- Parathion-methyl
- Paratox
- Paridol
- Partron M
- Penncap M
- Penncap MLS
- Phosphorothioic acid *O*,*O*-dimethyl *O*-(*para*-nitrophenyl) ester
- Sinafid M-48
- Tekwaisa
- Thiophenit
- Thylpar M-50
- Toll
- Unidol
- Vertac methyl parathion technisch 80%
- Vofatox
- Wofatox
- Wofotox

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Last updated: 11 March 1998

# METRONIDAZOLE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 250)

**CAS No.**: 443-48-1
**Chem. Abstr. Name**: 2-Methyl-5-nitro-1*H*-imidazole-1-ethanol

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Two epidemiological studies [ref: 1,2] of women treated with metronidazole showed some excesses of cancers of the uterine cervix, a neoplasm that has risk factors in common with vaginal trichomoniasis, the main indication in women for treatment with this drug. In one study [ref: 1], a greater excess of cervical cancer was observed in women with trichomoniasis who were not exposed to metronidazole than in those who were (relative risk, 2.1 *versus* 1.7). An excess of lung cancer (4 observed, 0.6 expected) seen in one of these studies [ref: 1] was not found in the other (2 observed, 2.6 expected) [ref: 3]. In the former, the excess was mainly of adenocarcinoma (3/4 cases) and was concentrated after at least ten years from first use of metronidazole (3 observed, 0.3 expected) [ref: 4]. Further follow-up and analysis of these data have suggested that the excess could be explained entirely by confounding with smoking [ref: 5]. Another study in which 12 280 users of metronidazole were followed up for two and one-half years gave a relative risk of 0.89 (95% confidence interval, 0.45-1.9) for all cancers [ref: 6].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Metronidazole has been tested for carcinogenicity by oral administration in mice and rats. It significantly increased the incidences of lung tumours in mice of each sex, of lymphomas in female mice [ref: 7,8] and of mammary, pituitary, testicular and liver tumours in rats [ref: 7,9,10]. It increased the incidence of colonic tumours induced in rats by subcutaneous administration of 1,2-dimethylhydrazine [ref: 11,12].

**C. Other relevant data**

Studies on bone-marrow cells and lymphocytes from a series of patients treated with metronidazole showed no increase in the incidence of chromosomal damage. Metronidazole was active in body fluid assays using sweat, faeces and urine from humans exposed *in vivo* and urine from rodents exposed *in vivo* [ref: 13].

Metronidazole did not induce micronuclei in bone-marrow cells of mice or rats, sister chromatid exchanges in bone-marrow cells of Chinese hamsters or unscheduled DNA synthesis in germ cells of male rabbits treated *in vivo*. Human cells exposed to metronidazole *in vitro* did not show increased incidences of chromosomal aberrations, whereas results with respect to sister chromatid exchanges were inconclusive. Metronidazole did not induce sister chromatid exchanges in cultured hamster cells; conflicting results were reported for the induction of mutation and DNA damage in rodent cells *in vitro*. It did not induce sex-linked recessive lethal mutations in *Drosophila* or recombination in yeast. It induced mutation in fungi and bacteria and induced prophage in bacteria [ref: 13].

**Overall evaluation**

Metronidazole is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 13 (1977)

## References


1. Beard, C.M., Noller, K.L., O'Fallon, W.M., Kurland, L.T. & Dockerty, M.B. (1979) Lack of evidence for cancer due to use of metronidazole. New Engl. J. Med., 301, 519-522

2. Friedman, G.D. & Ury, H.K. (1980) Initial screening for carcinogenicity of commonly used drugs. J. natl Cancer Inst., 65, 723-733

3. Friedman, G.D. (1980) Cancer after metronidazole. New Engl. J. Med., 302, 519

4. Beard, C.M. (1980) Cancer after metronidazole. New Engl. J. Med., 302, 520

5. Beard, C., Noller, K. & O'Fallon, W.M. (1985) Metronidazole and subsequent malignant neoplasms (Abstract). Am. J. Epidemiol., 122, 529

6. Danielson, D.A., Hannan, M.T. & Jick, H. (1982) Metronidazole and cancer. J. Am. med. Assoc., 247, 2498-2499

7. IARC Monographs, 13, 113-122, 1977

8. Cavaliere, A., Bacci, M., Amorosi, A., Del Gaudio, M. & Vitali, R. (1983) Induction of lung tumors and lymphomas in BALB/c mice by metronidazole. Tumori, 69, 379-382

9. Rustia, M. & Shubik, P. (1979) Experimental induction of hepatomas, mammary tumors, and other tumors with metronidazole in noninbred Sas:MRC(WI)BR rats. J. natl Cancer Inst., 63, 863-868

10. Cavaliere, A., Bacci, M. & Vitali, R. (1984) Induction of mammary tumors with metronidazole in female Sprague-Dawley rats. Tumori, 70, 307-311

11. Sloan, D.A., Fleiszer, D.M., Richards, G.K., Murray, D. & Brown, R.A. (1983) Increased incidence of experimental colon cancer associated with long-term metronidazole therapy. Am. J. Surg., 145, 66-70

12. A-Kareem, A.M., Fleiszer, D.M., Richards, G.K., Senterman, M.K. & Brown, R.A. (1984) Effect of long-term metronidazole (MTZ) therapy on experimental colon cancer in rats. J. surg. Res., 36, 547-552

13. IARC Monographs, Suppl. 6, 399-402, 1987


## Synonyms

- Acromona
- Anagiardil
- Atrivyl
- Bayer 5360
- Bexon
- Clont
- Cont
- Danizol
- Deflamon-wirkstoff
- Efloran
- Elyzol
- Entizol
- 1-(β-Ethylol)-2-methyl-5-nitro-3-azapyrrole

- Eumin
- Flagemona
- Flagesol
- Flagil
- Flagyl
- Flegyl
- Giatricol
- Gineflavir
- 1-Hydroxyethyl-2-methyl-5-nitroimidazole
- 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole
- 1-(β-Hydroxyethyl)-2-methyl-5-nitroimidazole
- Klion
- Maxibol silanes
- Meronidal
- 2-Methyl-5-nitro-1-imidazoleethanol
- 2-Methyl-5-nitroimidazole-1-ethanol
- Metronidaz
- Metronidazol
- Monagyl
- Nalox
- Neo-Tric
- Nida
- Novonidazol
- Orvagil
- RP 8823
- Sanatrichom
- SC 10295
- Takimetol
- Trichazol
- Trichex
- Trichocide
- Trichomol
- Trichomonacid pharmachim
- Trichopal
- Trichopol
- Tricocet
- Tricom
- Tricowas B
- Trikacide
- Trikamon
- Trikojol
- Trikozol
- Trimeks
- Trivazol
- Vagilen
- Vagimid
- Vertisal

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Last updated: 3 March 1998

# MINERAL OILS:

# UNTREATED AND MILDLY-TREATED OILS (Group 1)

# HIGHLY-REFINED OILS (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 252)

**Mineral oil**
**CAS No.**: 8002-05-9
**Chem. Abstr. Name**: Petroleum

**A. Evidence for carcinogenicity to humans** (*sufficient* for untreated and mildly-treated oils; *inadequate* for highly-refined oils)

Exposure to mineral oils that have been used in a variety of occupations, including mulespinning, metal machining and jute processing, has been associated strongly and consistently with the occurrence of squamous-cell cancers of the skin, and especially of the scrotum [ref: 1]. Production processes for these oils have changed over time, and with more recent manufacturing methods highly-refined products are produced that contain smaller amounts of contaminants, such as polycyclic aromatic hydrocarbons.

Excess mortality or morbidity from gastrointestinal malignancies was seen in two out of three cohort studies of metal workers (stomach cancer in two studies, large-bowel cancer in one): however, the only significant excess was for the sum of stomach cancer plus large-bowel cancer in one study. Four cases of scrotal cancer were detected in one relatively small cohort study of metal industry workers [ref: 1]. Among 682 turners with five or more years of exposure to mineral oils, five cases of squamous-cell carcinoma of the skin (four of the scrotum) occurred, with 0.3 expected [ref: 2]. In a case-control study, a relative risk of 4.9 was reported for the association of scrotal cancer with potential exposure of metal workers to mineral oils. Neither the actual levels of exposure nor the classification of the mineral oil to which the machine workers were potentially exposed was available in the reports of the epidemiological studies [ref: 1].

In a case-control study, an excess of sinonasal cancers was seen in toolsetters, set-up men and toolmakers [ref: 1]. In a series of 344 cases of scrotal cancer from 1936 to 1976, 62% had held occupations in which exposure to mineral oils was likely to have occurred. The median latent period was 34 years [ref. 3].

An examination of the incidence of second primary cancers among men with scrotal cancer demonstrated excess of respiratory, upper alimentary tract and skin cancers; when the occupations were grouped, the excess was largely confined to those with exposure to oil [ref: 1].

Excesses of bladder cancer have been reported in case-control studies in several countries among machinists and engineers, who were possibly exposed to cutting oils containing aromatic amines and additives [ref: 1].

With regard to printing pressmen, one of two cohort studies addressing lung cancer showed an excess and one of two proportionate mortality studies showed a small, statistically nonsignificant excess of lung cancer among newspaper pressmen but no excess among non-newspaper pressmen; the other study did not address lung cancer. One of three proportionate mortality studies on manual workers in the printing industry, not specifically addressing printing pressmen, did not show an increased lung cancer risk, whereas the other two studies found a statistically significant excess. One of two proportionate mortality studies of printing pressmen indicated a statistically significant

increase of deaths from rectal cancer, and the other showed a statistically nonsignificant increase of deaths from colon cancer; the cohort study considering colorectal cancers did not show an increased occurrence. One proportionate mortality study among newspaper and other commercial printing pressmen showed a statistically significant excess of mortality from cancers of the buccal cavity and pharynx, whereas no such excess was observed in a cohort study. One case-control study indicated a statistically significant excess of cancers of the buccal cavity and pharynx. The findings regarding other malignancies were inconsistent; scrotal cancers were not mentioned. The type and amount of exposure were usually not described; exposure to both mineral oils and carbon blacks (see p. 142) would probably have been involved [ref: 1].

In mortality statistics from the UK and from Washington State, USA, excesses of lung and skin cancer have been registered for jobs entailing exposure to mineral oils [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient* for untreated and mildly-treated oils; *inadequate* for highly-refined oils)

Vacuum-distillate fractions, acid-treated oils, mildly-treated solvent-refined oils, mildly-treated hydrotreated oils, solvent extracts (aromatic oils) and some cutting oils produced skin tumour after repeated skin applications to mice. Similar treatment with high-boiling catalytically-cracked oils produced skin tumours in rabbits and rhesus monkeys. Some severely solvent-refined oils did not produce skin tumours in mice. Highly-refined food-grade mineral oils did not produce skin tumours when applied to the skin of mice, although after intraperitoneal injection they produced plasma-cell neoplasms and reticulum-cell sarcomas in certain strains of mice [ref: 1]. It was agreed that, in accordance with the previous evaluation, 'the significant latter finding is difficult to interpret' [ref: 1].

**C. Other relevant data**

An increase in the frequency of chromosomal aberrations was observed in the peripheral blood lymphocytes of glass workers exposed to mineral oil mists. Urine from workers in a cold-rolling steel plant exposed to oil mists of solvent-refined oils was mutagenic to *Salmonella typhimurium* in the present of an exogenous metabolic system [ref: 4].

Special test protocols may be necessary to evaluate mineral oils adequately in short-term tests. Vacuum distillates from oil refining were reported to be mutagenic to *S. typhimurium* in the presence of an exogenous metabolic system. Positive findings were obtained when the concentration of the exogenous metabolic system was five to ten fold that used generally. Acid-treated oils were not mutagenic to *S. typhimurium in the presence of an exogenous metabolic system; solvent-refined oils were reported to be mutagenic in the presence of an exogenous metabolic system. Hydrotreated oil was reported to be mutagenic to S. typhimurium in the presence of an exogenous metabolic system, while white oils, highly-refined steel-hardening oil and solvent-refined steel-rolling oils were not. Unused crankcase oil was mutagenic to S. typhimurium in the presence of an exogenous metabolic system, while in other studies no mutagenic activity was found. Used crankcase oil from both gasoline and diesel engines was mutagenic to S. typhimurium both in the presence and absence of a metabolic system [ref: 4].*

*Two insulation oils from highly-refined mineral-base oils induced transformation of Syrian hamster embryo cells and enhanced transformation of mouse C3H 10T1/2 cells. Unused new, re-refined and used crankcase oils induced transformation in Syrian hamster embryo cells [ref: 4].*

***Overall evaluation***

*Untreated and mildly-treated oils are carcinogenic to humans (Group 1).*

*Highly-refined oils are not classifiable as to their carcinogenicity to humans (Group 3).*

*For definition of the italicized terms, see Preamble Evaluation.*

***Previous evaluation**: Vol. 33 (1984)*

***References***

*1. IARC Monograph, 33, 87-168, 1984*

*2. Järvholm, B., Fast, K., Lavenius, B. & Tomsic, P. (1985) Exposure to cutting oils and its relationship to skin tumors and premalignant skin lesions on the hands and forearms. Scand. J. Work Environ. Health, 11, 365-369*

*3. Waldron, H.A., Waterhouse, J.A.H. & Tessema, N. (1984) Scrotal cancer in the West Midlands, 1936-76. Br. J. ind. Med., 41, 437-444*

*4. IARC Monographs, Suppl. 6, 403, 1987*

***Synonym for Mineral oil***

- *Petroleum distillate*

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*Last updated: 9 February 1998*

# MOPP AND OTHER COMBINED CHEMOTHERAPY INCLUDING ALKYLATING AGENTS (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 254)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

In 1972, roughly five years after the introduction of intensive combined chemotherapy for Hodgkin's disease, the first report of subsequent acute nonlymphocytic leukaemia (ANLL) appeared [ref: 1]. Since then, investigators in more than 15 clinical centres and collaborative treatment groups in Europe and North America have performed a series of studies leading to the conclusion that the association is probably causal.

These studies are not easily compared with one another. The groups and subgroups of study subjects differ in distribution by age, stage at diagnosis, timing of initial therapy (both radiological and chemotherapeutic), interval between diagnosis and intensive chemotherapy, composition of the chemotherapeutic regimen and length of follow-up. Further, the methods of counting and allocating patients or person-years at risk, the criteria for diagnosis, the method of validating the separate identity of a second malignancy, the 'unexposed' group used as a reference standard, the method of statistical analysis, and the index used to summarize risk differences vary greatly from study to study. Finally, the extent to which such specific details are clearly described in the published reports is also variable.

Nonetheless, these reports are consistent in describing a strongly increased risk of ANLL after intensive treatment with combined chemotherapeutic regimens, particularly those containing alkylating agents. The most recent reports [ref: 2-18] describe a total of over 11 000 patients, reported roughly a decade after diagnosis, among whom more than 170 cases of ANLL have thus far occurred. About a quarter of these patients had received no intensive combined chemotherapy, yet all but a few leukaemia cases have occurred among those patients who did. Summary estimates of the relative risk of ANLL after intensive chemotherapy (relative to reasonably appropriate healthy populations) have been calculated to vary from 9 [ref: 11] through 40 [ref: 4,10] to well over 100 [ref: 6,9,16], precluding meaningful comparisons between studies, and estimates of the absolute (actuarial) risk observed in the first ten years range from 2-3% [ref: 3,4,10,14] through 5-6% [ref: 5,7-9,12] to 9-10% [ref: 2,13], again precluding direct comparisons between estimates. Observed variations in both relative risk and actuarial risk are probably due to differences in both methodology and exposure.

Although cases of leukaemia have been observed after radiotherapy in the absence of chemotherapy for Hodgkin's disease, the magnitude of the risk ratio is much lower, and may not even be elevated [ref: 6,19]. In contrast, the risk for ANLL is consistently high after chemotherapy even in the absence of radiation [ref: 7-9]. Although few untreated patient-years have been analysed recently, the relative absence of ANLL as an observed sequela of Hodgkin's disease prior to the era of intensive combined regimens [ref: 20,21], the absence of any relationship to histological subtype [ref: 13], and the appearance of ANLL during complete remission [ref: 5] emphasize the etiological role of chemotherapy, although interactions with stage of disease, with radiation or with factors important in the pathogenesis of Hodgkin's disease itself cannot be ruled out completely.

The only specific drug combination that has been used with sufficient frequency that it can be clearly linked to ANLL is MOPP (nitrogen mustard, vincristine, procarbazine and prednisone), although several reports describe excess cases not attributable to MOPP [ref: 9,11,14,16], and excesses of ANLL have appeared after treatment with other alkylating agent-containing combinations. The predominance of combined chemotherapy also precludes the identification of risk from individual constituents. Preliminary experience does indicate that risk for ANLL may be lower with some specific combinations, such as ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) [ref: 14,22,23].

Solid tumours, especially non-Hodgkin's lymphomas [ref: 10,24-27] and lung cancer [ref: 3,6,12,28,29], but including sarcomas, melanoma, malignancies of the central nervous system and carcinomas of the thyroid and gastrointestinal system, have also been reported in abundance after combined chemotherapy for Hodgkin's disease [ref: 3,6,7,10,12,29-32], but comparisons of observed to expected frequencies have not yielded consistent results. In contrast to leukaemia, solid tumours are more common in the general population, increase rapidly in frequency with age (and therefore the passage of time after treatment), are more diverse in known etiology, and are considered to appear with greater frequency after intensive radiotherapy [ref: 6]. Moreover, they are observed to appear with increasing frequency only after longer average duration of follow-up [ref: 32]. Some reports have shown increased risk after intensive chemotherapy [ref: 10], and the plausibility of a relationship is further suggested by multiple case reports of second malignancies that are unusual because of their rarity, either at an age [ref: 33] or on an absolute basis [ref: 9,24,31]. At present, it would appear that solid tumours occur among survivors of Hodgkin's disease in excess of the expected frequency; but, because too few patients have been followed into the second decade after treatment, it is too early to determine whether the increase can be better attributed to chance or to factors other than chemotherapy [ref: 32].

Combined chemotherapy containing alkylating agents for non-Hodgkin's lymphoma may also lead to ANLL [ref: 34-37], although the reports are not consistent and the documentation is less complete.

Treatment of nonhaematological malignancies may also cause second tumours, but most reported cases have occurred after the use of single agents [ref: 38], and combination regimens are less commonly used. Intensive combination therapy including alkylating agents for small-cell carcinoma of the lung [ref: 39,40], and possibly for cancer of the testis [ref: 41], may increase the risk for ANLL.

**B. Evidence for carcinogenicity to animals** (*inadequate*)

No data on MOPP were available to the Working Group. Combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil induced carcinogenic responses in several organs in rats [ref: 42]. See also the summaries of data on individual compounds: adriamycin, bleomycins, chlorambucil, cyclophosphamide, 5-fluorouracil, methotrexate, nitrogen mustard, prednisone, procarbazine hydrochloride, vinblastine sulphate and vincristine sulphate.

**C. Other relevant data**

For data on genetic and related effects, see the summaries on individual compounds, listed above.

**Overall evaluation**

MOPP and other combined chemotherapy including alkylating agents are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**References**

1. Arseneau, J.C., Sponzo, R.W., Levin, D.L., Schnipper, L.E., Bonner, H., Young, R.C., Canellos, G.P., Johnson, R.E. & DeVita, V.T. (1972) Nonlymphomatous malignant tumours complicating Hodgkin's disease. Possible association with intensive therapy. New Engl. J. Med., 287, 1119-1122

2. Aisenberg, A.C. (1983) Acute nonlymphocytic leukemia after treatment for Hodgkin's disease. Am. J. Med., 75, 449-454

3. Baccarani, M., Bosi, A., Papa, G. (1980) Second malignancy in patients treated for Hodgkin's disease. Cancer, 46, 1735-1740

4. Bergsagel, D.E., Alison, R.E., Bean, H.A., Brown, T.C., Bush, R.S., Clark, R.M., Chera, T., Dalley, D., DeBoer, G., Gospadarowicz, M., Hasselback, R., Perrault, D. & Rideout, D.F. (1982) Results of treating Hodgkin's disease without a policy of laparotomy staging. Cancer Treat. Rep., 66, 717-731

5. Brusamolino, E., Lazzarino, M., Salvaneschi, L., Canevari, A., Morra, E., Castelli, G., Pagnucco, G., Isernia, P. & Bernasconi, C. (1982) Risk of leukemia in patients treated for Hodgkin's disease. Eur. J. Cancer clin. Oncol., 18, 237-242

6. Boivin, J.F., Hutchison, G.B., Lyden, M., Godbold, J., Chorosh, J. & Schottenfeld, D. (1984) Second primary cancers following treatment of Hodgkin's disease. J. natl Cancer Inst., 72, 233-241

7. Coleman, C.N., Kaplan, H.S., Cox, R., Varghese, A., Butterfield, P. & Rosenburg, S.A. (1982) Leukaemias, non-Hodgkin's lymphomas and solid tumours in patients treated for Hodgkin's disease. Cancer Surv., 1, 733-744

8. Coltman, C.A., Jr & Dixon, D.O. (1982) Second malignancies complicating Hodgkin's disease. A Southwest Oncology Group 10-year follow-up. Cancer Treat. Rep., 66, 1023-1033

9. Glicksman, A.S., Pajak, T.F., Gottlieb, A., Nissen, N., Stutzman, L. & Cooper, M.R. (1982) Second malignant neoplasms in patients successfully treated for Hodgkin's disease: a Cancer and Leukemia Group B study. Cancer Treat Rep., 66, 1035-1044

10. Henry-Amar, M. (1983) Second cancers after radiotherapy and chemotherapy for early stages of Hodgkin's disease. J. natl Cancer Inst., 71, 911-916

11. Jacquillat, C., Auclerc, G., Weil, M., Auclerc, M.F. & Maral, J. (1983) Acute leukaemias and solid tumours in the course of Hodgkin's disease (Fr.). Bull. Cancer, 70, 61-66

12. Tester, W.J., Kinsella, T.J., Waller, B., Makuch, R.W., Kelley, P.A., Glatstein, E. & DeVita, V.T. (1984) Second malignant neoplasms complicating Hodgkin's disease: the National Cancer Institute experience. J. clin. Oncol., 2, 762-769

13. Pedersen-Bjergaard, J. & Larsen, S.O. (1982) Incidence of acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome up to 10 years after treatment of Hodgkin's disease. New Engl. J. Med., 307, 965-971

14. Valagussa, P., Santoro, A., Fossati Bellani, F., Franchi, F., Banfi, A. & Bonadonna, G. (1982) Absence of treatment-induced second neoplasms after ABVD in Hodgkin's disease. Blood, 59, 488-494

15. Prosnitz, L.R., Farber, L.R., Kapp, D.S., Bertino, J.R., Nordlund, M. & Lawrence, R. (1982) Combined modality therapy for advanced Hodgkin's disease: long-term follow-up data. Cancer Treat. Rep., 66, 871-879

16. Bartolucci, A.A., Liu, C., Durant, J.R. & Gams, R.A. (1983) Acute myelogenous leukemia as a second malignant neoplasm following the successful treatment of advanced Hodgkin's disease. Cancer, 52, 2209-2213

17. Andrieu, J.M., Montagnon, B., Asselain, B., Bayle-Weisgerber, C., Chastang, C., Teillet, F. & Bernard, J. (1980) Chemotherapy-radiotherapy association in Hodgkin's disease, clinical stages IA, $II_2A$: results of a prospective clinical trial with 166 patients. Cancer, 46, 2126-2130

18. Shishkin, I.P. (1984) Secondary tumours in patients with Hodgkin's disease following treatment (Russ.). Med. Radiol. (Moscow), 29, 24-28

19. Selby, P. & Horwich, A. (1986) Secondary leukaemia in Hodgkin's disease. Lancet, i, 1027-1028

20. Berg, J.W. (1967) The incidence of multiple primary cancers. 1. Development of further cancers in patients with lymphomas, leukemias, and myeloma. J. natl Cancer Inst., 38, 741-752

21. Newman, D.R., Maldonado, J.E., Harrison, E.G., Jr, Kiely, J.M. & Linman, J.W. (1970) Myelomonocytic leukemia in Hodgkin's disease. Cancer, 25, 128-134

22. Amadori, S., Papa, G., Anselmo, A.P., Fidani, P. & Mandelli, F. (1983) Acute promyelocytic leukemia following ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and radiotherapy for Hodgkin's disease. Cancer Treat. Rep., 67, 603-604

23. Valagussa, P., Santoro, A., Fossati-Bellani, F., Banfi, A., Bonadonna, G. & Veronesi, U. (1985) Second neoplasms in Hodgkin's disease (HD): progress report (Abstract No. 720). Proc. Am. Assoc. Cancer Res., 26, 182

24. Armitage, J.O., Dick, F.R., Goeken, J.A., Foucar, M.K. & Gingrich, R.D. (1983) Second lymphoid malignant neoplasms occurring in patients treated for Hodgkin's disease. Arch. intern. Med., 143, 445-450

25. Krikorian, J.G., Burke, J.S., Rosenberg, S.A. & Kaplan, H.S. (1979) Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. New Engl. J. Med., 300, 452-458

26. Jacquillat, C., Khayat, D., Desprez-Corely, J.P., Weil, M., Brocheriou, C., Auclerc, G., Chamseddine, N. & Bernard, J. (1984) Non-Hodgkin's lymphoma occurring after Hodgkin's disease. Four new cases and a review of the literature. Cancer, 53, 459-462

27. Miettinen, M., Franssila, K.O. & Saxén, E. (1983) Hodgkin's disease, lymphocytic predominance nodular. Increased risk for subsequent non-Hodgkin's lymphomas. Cancer, 51, 2293-2300

28. Kaldor, J.M., Day, N.E., Band, P., Choi, N.W., Clarke, E.A., Coleman, M.P., Hakama, M., Koch, M., Langmark, F., Neal, F.E., Pettersson, F., Pompe-Kirn, V., Prior, P. & Storm, H.H. (1987) Second malignancies following testicular cancer, ovarian cancer and Hodgkin's disease: an international collaborative study among cancer registries. Int. J. Cancer, 39, 571-585

29. Valagussa, P., Santora, A., Kenda, R., Bellani, F.F., Franchi, F., Banfi, A., Rilke, F. & Bonadonna, G. (1980) Second malignancies in Hodgkin's disease: a complication of certain forms of treatment. Br. med. J., i, 216-219

30. Nelson, D.F., Cooper, S., Weston, M.G. & Rubin, P. (1981) Second malignant neoplasms in patients treated for Hodgkin's disease with radiotherapy or radiotherapy and chemotherapy. Cancer, 48, 2386-2393

31. Tucker, M.A., Misfeldt, D., Coleman, C.N., Clark, W.H., Jr & Rosenberg, S.A. (1985) Cutaneous maligneant melanoma after Hodgkin's disease. Ann. intern. Med., 102, 37-41

32. Boivin, J.-F. & O'Brien, K. (1987) Solid cancer risk after treatment of Hodgkin's disease. Cancer (in press)

33. Brumbach, R.A., Gerber, J.E., Hicks, D.G. & Strauchen, J.A. (1984) Adenocarcinoma of the stomach following irradiation and chemotherapy for lymphoma in young patients. Cancer, 54, 994-998

34. Greene, M.H., Young, R.C., Merrill, J.M. & DeVita, V.T. (1983) Evidence of a treatment dose response in acute nonlymphocytic leukemia which occur after therapy of non-Hodgkin's lymphoma. Cancer Res., 43, 1891-1898

35. Gomez, G.A., Aggarwal, K.K. & Han, T. (1983) Post-therapeutic acute malignant myeloproliferative syndrome and acute nonlymphocytic leukemia in non-Hodgkin's lymphoma. Correlation with intensity of treatment. Cancer, 50, 2285-2288

36. Harousseau, J.L., Andrieu, J.M., Dumont, J., Montagnon, B. Asselain, B., Daniel, M.T. & Flandrin, G. (1980) Acute myeloblastic leukaemia during the course of malignant non-Hodgkin's lymphomas (Fr.). Nouv. Presse med., 9, 3513-3516

37. Pedersen-Bjergaard, J., Ersboll, J., Sørensen, H.M., Keiding, N., Larsen, S.O., Philip, P., Larsen, M.S., Schultz, H. & Nissen, N.I. (1985) Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphoma. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. Ann. intern. Med., 103, 195-200

38. Kyle, R.A. (1982) Second malignancies associated with chemotherapeutic agents. Semin. Oncol., 9, 131-142

39. Markman, M., Pavy, M.D. & Abeloff, M.D. (1982) Acute leukemia following intensive therapy for small-cell carcinoma of the lung. Cancer, 50, 672-675

40. May, J.T., Hsu, S.D. & Costanzi, J.J. (1981) Acute leukemia following combination chemotherapy for cancer of the lung. Oncology, 38, 134-137

41. van Imhoff, G.W., Steijfer, D.T., Breuning, M.H., Anders, G.J.P.A., Mulder, N.H. & Halie, M.R. (1986) Acute nonlymphocytic leukemia 5 years after treatment with cisplatin, vinblastine, and bleomycin for disseminated testicular cancer. Cancer, 57, 984-987

42. Habs, M., Schmähl, D. & Lin, P.Z. (1981) Carcinogenic activity in rats of combined treatment with cyclophosphamide, methotrexate and 5-fluorouracil. Int. J. Cancer, 28, 91-96

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Last updated: 9 February 1998

# MUSTARD GAS (SULPHUR MUSTARD)
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 259)

**CAS No.**: 505-60-2
**Chem. Abstr. Name**: 1,1'-Thiobis(2-chloroethane)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

The mortality of British and American veterans who were exposed to mustard gas during the First World War has been compared with that of other veterans who experienced respiratory infections; the effect of smoking could not be directly controlled for in either group. Cumulative lung cancer risk was not affected in UK veterans and was only modestly elevated (relative risk, 1.5, compared with the effect of cigarette smoking, roughly 10) in US veterans [ref: 1].

In contrast, mustard gas production workers in Japan during the Second World War have been found to have experienced an increase in the proportion of deaths attributed to lung cancer (three fold) compared to the local population [ref: 1,2], and especially in respiratory cancer (40 fold) in comparison with the general population [ref: 1]. Although sophisticated analytical methods were not used, the prevalence of smoking appeared to be comparable in the exposed and unexposed groups, and there was increased risk with increased duration of exposure [ref: 3]. British workers engaged in mustard gas production during the Second World War have also been followed up. Among 511 individuals, 11 cases of cancer (nine of the larynx and two of the pharynx) were identified, whereas one would have been expected [ref: 4].

**B. Evidence for carcinogenicity to animals** (*limited*)

Mustard gas was tested for carcinogenicity in mice, producing lung tumours after its inhalation or intravenous injection and local sarcomas after its subcutaneous injection [ref: 1].

**C. Other relevant data**

Mustard gas is a bifunctional alkylating agent [ref: 5]. No data were available on its genetic and related effects in humans.

Evidence of covalent binding to cellular DNA, RNA and protein *in vivo* was obtained in mice injected intraperitoneally with $^{35}$S-labelled mustard gas. It induced chromosomal aberrations and DNA damage in rodent cells *in vitro* and mutation in mouse lymphoma cells *in vitro* and in a host-mediated assay. It induced aneuploidy, heritable translocations, dominant lethal mutations and sex-linked recessive lethal mutations in *Drosophila*. It was mutagenic to fungi and induced DNA damage in bacteria [ref: 5].

**Overall evaluation**

Mustard gas (sulphur mustard) is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 9 (1975)

**References**

1. IARC Monographs, 9, 181-192, 1975

2. Shigenobu, T. (1980) Occupational cancer of the lungs - cancer of the respiratory tract among workers manufacturing poisonous gases (Jpn.). Jpn. J. thorac. Dis., 18, 880-885

3. Nishimoto, Y., Yamakido, M., Shigenobu, T., Onari, K. & Yukutake, M. (1983) Long term observation of poison gas workers with special reference to respiratory cancers. J. Univ. occup. environ. Health, 5 (Suppl.), 89-94

4. Manning, K.P., Skegg, D.C.G., Stell, P.M. & Doll, R. (1981) Cancer of the larynx and other occupational hazards of mustard gas workers. Clin. Otolaryngol., 6, 165-170

5. IARC Monographs, Suppl. 6, 403-405, 1987

**Synonyms**

- Bis(2-chloroethyl)sulphide
- Bis( β-chloroethyl)sulphide
- 1-Chloro-2-( β-chloroethylthio)ethane
- 2,2'-Dichlorodiethyl sulphide
- Di-2-chloroethyl sulphide
- β,β'-Dichloroethyl sulphide
- Schwefel-lost
- S-Lost
- S-Mustard
- Sulphur mustard
- Sulphur mustard gas
- Yellow cross liquid
- Yperite

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Last updated: 9 February 1998

# 1-NAPHTHYLAMINE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 260)

**CAS No.**: 134-32-7

**A. Evidence for carcinogenicity to humans** (*inadequate*)

An excess occurrence of bladder cancer was observed in workers who had been exposed to commercial 1-naphthylamine for five or more years who had not also been engaged in the production of 2-naphthylamine or benzidine. However, commercial 1-naphthylamine made at that time may have contained 4-10% 2-naphthylamine [ref: 1]. Among a cohort of 906 men employed for at least one year between 1922 and 1970 in a dyestuffs plant in Italy, a considerable excess of bladder cancer deaths (27 observed, 0.19 expected) was observed among 151 workers involved in the manufacture of 1- and 2-naphthylamine and benzidine [ref: 2]. A case-control study of bladder cancer in the UK showed a significant, exposure-related increased risk for dyestuffs workers. 1-Naphthylamine was plausibly concerned, but it was not possible to single out any compound from the combined exposure to arylamines [ref: 3].

In view of the contamination of the commercial product and the mixed nature of the exposures investigated, it is not possible to assess the carcinogenicity of 1-naphthylamine alone.

**B. Evidence for carcinogenicity to animals** (*inadequate*)

1-Naphthylamine was tested for carcinogenicity mice, hamsters and dogs by oral administration and in newborn mice by subcutaneous injection. No carcinogenic effect was observed following oral administration to hamsters [ref: 1] or dogs [ref: 1,4,5] or in a lung adenoma bioassay in mice [ref: 6]. Inconclusive results were obtained after oral administration to adult mice and subcutaneous injection of newborn mice [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of 1-naphthylamine in humans.

1-Naphthylamine did not induce micronuclei in bone-marrow cells of mice treated *in vivo*; it induced DNA strand breaks in mice, but not in rats. 1-Naphthylamine increased the incidence of chromosomal aberrations in cultured rodent cells, but the results for sister chromatid exchanges, mutation and DNA damage were inconclusive; no cell transformation was induced in Syrian hamster embryo cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*. It induced aneuploidy but not mutation in yeast; results for mitotic recombination were conflicting. It was mutagenic to bacteria [ref: 7].

**Overall evaluation**

1-Naphthylamine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**

1. IARC Monographs, 4, 87-96, 1974

2. Decarli, A., Peto, J., Piolatto, G. & La Vecchia, C. (1985) Bladder cancer mortality of workers exposed to aromatic amines: analysis of models of carcinogenesis. Br. J. Cancer, 51, 707-712

3. Boyko, R.W., Cartwright, R.A. & Glashan, R.W. (1985) Bladder cancer in dye manufacturing workers. J. occup. Med., 27, 799-803

4. Radomski, J.L., Deichmann, W.B., Altman, N.H. & Radmonski, T. (1980) Failure of pure 1-naphthylamine to induce bladder tumors in dogs. Cancer Res., 40, 3537-3539

5. Purchase, I.F.H., Kalinowski, A.E., Ishmael, J., Wilson, J., Gore, C.W. & Chart, I.S. (1981) Lifetime carcinogenicity study of 1- and 2-naphthylamine in dogs. Br. J. Cancer, 44, 892-901

6. Theiss, J.C., Shimkin, M.B. & Weisburger, E.K. (1981) Pulmonary adenoma response of strain A mice to sulfonic acid derivatives of 1- and 2-naphthylamines. J. natl Cancer Inst., 67, 1299-1302

7. IARC Monographs, Suppl. 6, 406-409, 1987

**Synonyms**

- 1-Aminonaphthalene
- Azoic diazo component 114
- Fast garnet B base
- Fast garnet base B
- Naphthalidam
- Naphthalidine
- α-Naphthylamine

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Last updated: 11 March 1998

# 2-NAPHTHYLAMINE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 261)

**CAS No.:** 91-59-8

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Case reports and epidemiological studies conducted independently in the 1950s and 1960s showed that occupational exposure to 2-naphthylamine, either alone or as an impurity in other compounds, is causally associated with the occurrence of bladder cancer [ref: 1].

Two studies in the USA examined cancer incidence and mortality in a group of chemical workers exposed mainly to 2-naphthylamine. In one, a remarkable and significantly increased incidence of bladder cancer was found (13 observed, 3.3 expected), which was not explained by smoking habits [ref: 2]. Investigation of mortality failed to pinpoint this increased risk and suggested an excess of oesophageal cancer, which, however, was not considered to be associated with the occupational exposure [ref: 3]. Two reports on one occupational population at a dyestuffs plant in Italy documented a very high bladder cancer risk linked specifically to 2-naphthylamine production (6 deaths observed, 0.04 expected) and a clear exposure-response relationship of the risk to exposures in the plant [ref: 4,5]. Incidence studies from Japan dealing with exposure to both 2-naphthylamine and benzidine showed apparently increased risks of cancer of the urinary tract and bladder and, possibly, an increased occurrence of second primary cancers at several sites, including the liver [ref: 6-8]. Case reports and ecological studies also documented the relationship between exposure to 2-naphthylamine, as well as to benzidine, and bladder cancer risk [ref: 9,10]. 2-Naphthylamine was most probably involved in the exposure to aryl amines reported in a UK study as producing a significantly increased bladder cancer risk, which was not accounted for by smoking habits [ref: 11].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

2-Naphthylamine was tested for carcinogenicity by oral administration in many animal species and by the mouse-lung adenoma bioassay. Following its oral administration, it induced bladder neoplasms in hamsters [ref: 1], dogs [ref: 1,12-14] and nonhuman primates [ref: 1], and liver tumours in mice [ref: 1]. A low incidence of bladder carcinomas was observed in rats after its oral administration [ref: 15]. In a lung adenoma bioassay in mice, 2-naphthylamine produced positive results [ref: 16].

**C. Other relevant data**

No data were available on the genetic and related effects of 2-naphthylamine in humans.

Mice and rabbits treated with 2-naphthylamine had increased incidences of sister chromatid exchanges; micronuclei were not induced in bone-marrow cells of mice treated *in vivo*. 2-Naphthylamine was mutagenic in the mouse spot test and induced DNA strand breaks in hepatocytes of treated rats. It formed DNA adducts in bladder and liver cells of dogs *in vivo*. It induced unscheduled DNA synthesis in human cells *in vitro* and chromosomal aberrations, sister chromatid exchanges, DNA strand breaks and unscheduled DNA synthesis in rodent cells *in vitro*. Equivocal results were obtained for mutation, but it caused morphological transformation in Syrian hamster embryo and virus-infected rat cells. 2-Naphthylamine induced aneuploidy in *Drosophila*, but equivocal results were found for sex-linked recessive lethal mutations. It caused aneuploidy, mutation and mitotic recombination in yeast and was mutagenic to plants and bacteria [ref: 17].

**Overall evaluation**

2-Naphthylamine is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 4 (1974)

**References**


1. IARC Monographs, 4, 97-111, 1974

2. Schulte, P.A., Ringen, K., Hemstreet, G.P., Altekruse, E.B., Gullen, W.H., Patton, M.G., Allsbrook, W.C., Jr, Crosby, J.H., West, S.S., Witherington, R., Koss, L., Bales, C.E., Tillet, D., Rooks, S.C.F., Stern, F., Stringer, W., Schmidt, V.A. & Brubaker, M.M. (1985) Risk assessment of a cohort exposed to aromatic amines. Initial results. J. occup. Med., 27, 115-121

3. Stern, F.B., Murthy, L.I., Beaumont, J.J., Schulte, P.A. & Halperin, W.E. (1985) Notification and risk assessment for bladder cancer of a cohort exposed to aromatic amines. III. Mortality among workers exposed to aromatic amines in the last beta-naphthylamine manufacturing facility in the United States. J. occup. Med., 27, 495-500

4. Rubino, G.F., Scansetti, G., Piolatto, G. & Pira, E. (1982) The carcinogenic effect of aromatic amines: an epidemiological study on the role of o-toluidine and 4,4'-methylene bis(2-methylaniline) in inducing bladder cancer in man. Environ. Res., 27, 241-254

5. Decarli, A., Peto, J., Piolatto, G. & La Vecchia, C. (1985) Bladder cancer mortality of workers exposed to aromatic amines: analysis of models of carcinogenesis. Br. J. Cancer, 51, 707-712

6. Tsuchiya, K., Okubo, T. & Ishizu, S. (1975) An epidemiological study of occupational bladder tumours in the dye industry of Japan. Br. J. ind. Med., 32, 203-209

7. Nakamura, J., Takamatsu, M., Doi, J., Ohkawa, T., Fujinaga, T., Ebisuno, S. & Sone, M. (1980) Clinical study on the occupational urinary tract tumor in Wakayama. Jpn. J. Urol., 71, 945-951

8. Morinaga, K., Oshima, A. & Hara, I. (1982) Multiple primary cancers following exposure to benzidine and beta-naphthylamine. Am. J. ind. Med., 3, 243-246

9. Budnick, L.D., Sokal, D.C., Falk, H., Logue, J.N. & Fox, J.M. (1984) Cancer and birth defects near the Drake Superfund site, Pennsylvania. Arch. environ. Health, 39, 409-413

10. Segnan, N. & Tanturri, G. (1976) A study on the geographical pathology of laryngeal, bladder and children cancer in the Province of Turin (Ital.). Tumori, 62, 377-386

11. Boyko, R.W., Cartwright, R.A., Chir, B. & Glashan, R.W. (1985) Bladder cancer in dye manufacturing workers. J. occup. Med., 27, 799-803

12. Romanenko, A.M. & Martynenko, A.G. (1972) Morphological peculiarities of vesical tumours induced by beta-naphthylamine in dogs (Russ.). Vopr. Onkol., 18, 70-75

13. Radomski, J.L., Krischer, C. & Krischer, K.N. (1978) Histologic and histochemical preneoplastic changes in the bladder mucosae of dogs given 2-naphthylamine. J. natl Cancer Inst., 60, 327-333

14. Purchase, I.F.H., Kalinowski, A.E., Ishmael, J., Wilson, J., Gore, C.W. & Chart, I.S. (1981) Lifetime carcinogenicity study of 1- and 2-naphthylamine in dogs. Br. J. Cancer, 44, 892-901

15. Hicks, R.M., Wright, R. & Wakefield, J.St J. (1982) The induction of rat bladder cancer by 2-naphthylamine. Br. J. Cancer, 46, 646-661

16. Theiss, J.C., Shimkin, M.B. & Weisburger, E.K. (1981) Pulmonary adenoma response of strain A mice to sulfonic acid derivaties of 1- and 2-naphthylamines. J. natl Cancer Inst., 67, 1299-1302

17. IARC Monographs, Suppl. 6, 410-414, 1987

**Synonyms**

- 2-Aminonaphthalene
- BNA
- Fast scarlet base B
- β-Naphthylamine

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Last updated: 9 February 1998

# 1-NAPHTHYLTHIOUREA (ANTU)
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 263)

**CAS No.**: 86-88-4
**Chem. Abstr. Name**: Thiourea, 1-naphthalenyl-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Cases of bladder tumours have been reported among rat catchers exposed to 1-naphthylthiourea (containing up to 0.2% 2-naphthylamine) [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

1-Naphthylthiourea was tested for carcinogenicity in mice and rats by administration in the diet. The studies were considered to be inadequate for evaluation [ref: 2].

**C. Other relevant data**

No data were available on the genetic and related effects of ANTU in humans. It did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro*. It was mutagenic to bacteria [ref: 3].

**Overall evaluation**

1-Naphthylthiourea (ANTU) is *not classifiable as to its carcinogenicity to humans (Group 3)*.

**Also see previous evaluation**: Vol. 30 (1983)

**References**

1. Davies, J.M., Thomas, H.F. & Manson, D. (1982) Bladder tumours among rodent operatives handling ANTU. Br. med. J., 285, 927-931

2. IARC Monographs, 30, 347-357, 1983

3. IARC Monographs, Suppl. 6, 415-416, 1987

**Synonyms**

- Alrato
- ANTU
- Anturat
- Bantu
- Chemical 109
- Dirax
- Kill kantz
- Kripid
- Krysid PI
- Krysidaptan
- α-Naphthylthiocarbamide
- α-Naphthothiourea

- *N*-(1-Naphthyl)-2-thiourea
- *N*-1-Naphthylthiourea
- 1-(1-Naphthyl)-2-thiourea
- 1-(1-Naphthyl)thiourea
- α-Naphthylthiourea
- Naphtox
- Rat-tu
- Rattrack
- Smeesana
- U 5227

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# NITROGEN MUSTARD
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 269)

**CAS No.:** 51-75-2
**Chem. Abstr. Name**: 2-Chloro-*N*-(2-chloroethyl)-*N*-methylethanamine

**A. Evidence for carcinogenicity to humans** (*limited*)

No epidemiological study of nitrogen mustard as a single agent was available to the Working Group. However, it is the principal alkylating agent in leukaemogenic combination chemotherapy given for Hodgkin's disease, and other alkylating agents are clearly leukaemogenic. The many case reports of cancer following topical application of nitrogen mustard cannot be interpreted with certainty because concurrent treatment with radiation and other potent drugs has been the rule rather than the exception, and occasionally such associations would be expected by chance.

Squamous-cell carcinomas of the skin following long-term topical application of nitrogen mustard alone or in combination with systemic therapy for mycosis fungoides [ref: 1-4] and psoriasis [ref: 5-7] have been observed to appear on skin surfaces not exposed to the sun.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Nitrogen mustard, administered mainly as the hydrochloride, has been tested for carcinogenicity in mice and rats by subcutaneous, intravenous and intraperitoneal administration and by skin painting. It produced mainly lung tumours and lymphomas in mice after subcutaneous, intravenous and intraperitoneal administration. Intravenous injection of nitrogen mustard to rats induced tumours in different organs [ref: 8]. Application by skin painting produced local tumours in mice in a dose-dependent manner [ref: 9,10].

**C. Other relevant data**

Nitrogen mustard is a bifunctional alkylating agent. In one study, it induced chromosomal aberrations in lymphocytes of treated patients [ref: 11].

Nitrogen mustard induced dominant lethal mutations and micronuclei in bone-marrow cells of mice exposed *in vivo* and alkylated DNA of ascites cells in experimental animals treated *in vivo*. It induced chromosomal aberrations, sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*. In rodent cells *in vitro*, it induced sister chromatid exchanges, chromosomal aberrations and DNA damage; studies on the induction of mutation were inconclusive. It transformed mouse C3H 10T1/2 cells. Nitrogen mustard induced aneuploidy and somatic mutation and recombination in *Drosophila*, chromosomal aberrations in plants, mitotic recombination and mutation in fungi, and mutation and DNA damage in fungi [ref: 11].

**Overall evaluation**

Nitrogen mustard is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 9 (1975)

**References**

1. Du Vivier, A, Vonderheid, E.C., Van Scott, E.J., Urbach, F. (1978) Mycosis fungoides, nitrogen mustard and skin cancer. Br. J. Dermatol., 99, 61-63

2. Kravitz, P.H. & McDonald, C.J. (1978) Topical nitrogen mustard induced carcinogenesis. Acta dermatol. venereol., 58, 421-425

3. Lee, L.A., Fritz, K.A., Golitz, L., Fritz, T.J. & Weston, W.L. (1982) Second cutaneous malignancies in patients with mycosis fungoides treated with topical nitrogen mustard. J. Am. Acad. Dermatol., 7, 590-598

4. Abel, E.A., Sendagorta, E. & Hoppe, R.T. (1986) Cutaneous malignancies and metastatic squamous cell carcinoma following topical therapies for mycosis fungoides. J. Am. Acad. Dermatol., 14, 1029-1038

5. Halprin, K.M., Comerford, M. & Taylor, J.R. (1982) Cancer in patients with psoriasis. J. Am. Acad. Dermatol, 7, 633-638

6. Ganor, S. (1983) Skin cancer in psoriatics treated with nitrogen mustard. J. Am. Acad. Dermatol., 8, 164

7. Halprin, K.M., Comerford, M. & Taylor, J.R. (1982) Skin cancer in psoriatics treated with nitrogen mustard. J. Am. Acad. Dermatol., 8, 164-165

8. IARC Monographs, 9, 193-207, 1975

9. Zackheim, H.S. & Smuckler, E.A. (1980) Tumorigenic effect of topical mechlorethamine, BCNU and CCNU in mice. Experientia, 36, 1211-1212

10. Epstein, J.H. (1984) Nitrogen mustard (mechlorethamine) and UVB photocarcinogenesis: a dose response effect. J. invest. Dermatol., 83, 320-322

11. IARC Monographs, Suppl. 6, 421-424, 1987

**Synonyms**

- *N*,*N*'-Bis(2-chloroethyl)-*N*-methylamine
- *N*,*N*-Bis(2-chloroethyl)methylamine
- Bis(2-chloroethyl)methylamine
- Bis(β-chloroethyl)methylamine
- Caryolysin
- Chloramine
- Chlormethine
- Cloramin
- β,β'-Dichlorodiethyl-N-methylamine
- Di(2-chloroethyl)methylamine
- 2,2'-Dichloro-*N*-methyl-diethylamine
- Embichin
- HN2
- MBA
- Mechlorethamine
- *N*-Methyl-bis(2-chloroethyl)amine
- *N*-Methyl-bis(β-chloroethyl)amine
- Methylbis(beta-chloroethyl)amine
- Methylbis(chloroethylamine)
- *N*-Methyl-2,2'-dichlorodiethylamine
- Methyldi(2-chloroethyl)amine
- Mustargen

- Mustine
- Mutagen

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Last updated: 11 February 1998

# OESTROGENS, NONSTEROIDAL
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 273)

**Diethylstilboestrol**
**CAS No.**: 56-53-1
**Chem. Abstr. Name**: (E)-4,4'-(1,2-Diethyl-1,2-ethenediyl)bisphenol

**Diethylstilboestrol dipropionate**
**CAS No.**:130-80-3
**Chem. Abstr. Name**: (E)-4,4'-(1,2-Diethyl-1,2-ethenediyl)bisphenol dipropionate

**Dienoestrol**
**CAS No.**:84-17-3
**Chem. Abstr. Name**: 4,4'-(1,2-Diethylidene-1,2-ethanediyl)bisphenol

**Hexoestrol**
**CAS No.:** 84-16-2

**Chlorotrianisene**
**CAS No.**: 569-57-3
**Chem. Abstr. Name**:1,1',l"-(1-Chloro-1-ethenyl-2-ylidene)-tris(4-methoxybenzene)

**Diethylstilboestrol**

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Diethylstilboestrol (DES) causes clear-cell adenocarcinoma of the vagina and cervix in women exposed in utero. There is sufficient evidence that administration of oestrogens for the control of symptoms of the climacteric is causally related to an increased incidence of endometrial carcinoma; DES is no different from other oestrogens in this respect [ref: 1].

There is also clear evidence that administration of DES in large doses during pregnancy increases the subsequent risk of breast cancer and that DES increases the risk of testicular cancer in males exposed *in utero*.

In four follow-up studies [ref: 2-5] of exposed and nonexposed groups of women, the possible effects of DES exposure during pregnancy on subsequent breast cancer risk have been evaluated. All have shown an increased risk in exposed women; two were randomized trials [ref: 2,3]. In one [ref: 2], there were 32 (4.6%) breast cancers among 693 women exposed to an average total dose of 12 g DES, and 21 (3.1%) breast cancers among 668 control (placebo) women. In the other [ref: 3], there were four (5.0%) breast cancers among 80 women exposed to an average total dose DES of 16 g (plus ethisterone, average total dose, 14 g), compared to none of 76 controls; all 156 women were diabetic. In two studies, an exposed group and a 'matched' unexposed group were followed-up [ref: 4,5]. One [ref: 4] found 118 (4.4%) breast cancer cases in 2680 women exposed to a mean DES dose of 5 g, and 80 (3.1%) among 2566 control women. The other [ref: 5] similarly showed 38 (2.5%) breast cancer cases among 1531 women exposed to a mean DES dose of 2 g, and 24 (1.7%) cases among the 1404 control women. The overall relative risk from these four studies is 1.5 ($p$ = 0.001).

A further group of 408 DES-exposed women (median dose, 1.5 g) was followed up and the eight breast cancer cases found were contrasted to the 8.1 cases expected on the basis of local breast cancer incidence rates [ref: 6]. If this study is considered together with the four studies described above, the overall relative risk is 1.4 ($p$ = 0.0016).

In all five papers [ref: 2-6], the possibility is discussed that there may be a long (15-20 years) 'latent' period before the first 'DES-induced' breast cancer would be seen. Clear evidence was found in a study [ref: 4] in which there was no difference in the breast cancer rates of exposed and unexposed women until 22 years after exposure, but an increasing difference thereafter. Similarly, in another study [ref: 3], there was no case in the exposed group in the first 18 years after exposure. In a further study [ref: 5], the relative risk was 1.3 before age 50 and 1.7 thereafter, and in another [ref: 6], three cases were reported with 5.1 expected before age 50 and five cases *versus* 3.0 expected thereafter. In contrast, however, a randomized study [ref: 2] showed 11 exposed cases and five nonexposed cases during the first 15 years of follow-up, compared to 21 exposed cases and 16 nonexposed cases thereafter. Further data are required to settle this issue.

The four follow-up studies [ref: 2-5] of exposed and nonexposed women also included information on other possibly 'hormone-related' cancers. The occurrence of endometrial cancer was not increased in any study. The study [ref: 2] of 693 women exposed to DES and 668 controls showed increases in the occurrence of cancer of the ovary (4 exposed, 1 nonexposed), cancer of the cervix (7 exposed, 3 non-exposed) and cancer of the colon-rectum (2 exposed, 1 nonexposed); there was also a risk for cancer at these sites in the study of 1531 women exposed to DES and 1404 controls [ref: 5] (6 exposed, 2 nonexposed; 9 exposed, 6 nonexposed; 11 exposed, 7 nonexposed for the three sites, respectively). A third study [ref: 4] showed, in contrast, no elevation of rates for cancer at any other site, and there were seven deaths from cervical cancer in the control group and none in the exposed group, suggesting that matching in the control group was 'inadequate'; the authors could not identify the matching problem, and, in particular, they found that the two groups were well matched on educational level. The data are too few to draw any firm conclusions.

A greater frequency of abnormalities of the reproductive tract has been found in males exposed prenatally to DES in comparison with nonexposed controls, although the data are few. Cryptorchidism, a major risk factor for testicular cancer, is one of the associated lesions [ref: 1]. Cancer of the testis has been investigated in five case-control studies of fetal exposure to DES [ref: 7-11]. One [ref: 7] showed that 5.1% (4/78) of cases and 1% of controls had been exposed to hormones (in all likelihood DES) for bleeding; the second [ref: 8] similarly found that 5.8% (11/190) *versus* 2.3% (7/304) had had such exposure; the third [ref: 9] found 1.9% (2/108) *versus* 0 (0/108) exposed to DES; the fourth [ref: 10] found 1.0% (2/202) *versus* 1.0% (2/206) exposed to DES; and the fifth [ref: 11] found 1.9% (4/211) *versus* 0.9% (2/214) exposed to DES. The combined relative risk is 2.5 ($p$ = 0.014).

A number of unusual tumours have been reported in women exposed to DES *in utero*: a fatal adenocarcinoma of the endometrium at age 26 [ref: 12]; a pituitary adenoma at age 18 [ref: 13]; an invasive squamous-cell carcinoma of the cervix at age 21 [ref: 14]; an invasive adenosquamous-cell carcinoma of the cervix at age 27 [ref: 15]; and an ovarian teratoma at age 12 [ref: 16].

There has been no further report to add to the six cases of primary breast cancer in males with prostatic cancer treated with DES [ref: 1]. A case has been reported of a Leydig-cell tumour developing in such a man treated with DES at 1 mg per day for 2.5 years [ref 17]. There has been a second case report of hepatic angiosarcoma in a man treated over a long period with DES for prostatic cancer [ref: 1,18], and a second case report of a hepatoma in a prostatic cancer patient treated with DES at 3 mg per day for 4.5 years (to diagnosis of hepatoma) [ref: 1,19]. Three renal carcinomas have been reported after exposure to DES for prostatic cancer [ref: 20,21].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

DES has been tested in mice, rats, hamsters, frogs and squirrel monkeys, producing tumours principally in oestrogen-responsive tissues [ref: 1]. Female newborn mice injected with DES developed epidermoid carcinomas and granular-cell myoblastomas of the cervix and squamous carcinomas of the vagina [ref: 22]. Mice treated prenatally with DES developed adenocarcinomas of the uterus, cervix and vagina, epidermoid carcinomas of the uterine cervix and vagina and ovarian and mammary tumours [ref: 23-28]. Female mice fed diets containing DES developed cervical and endometrial adenocarcinomas, mammary adenocarcinomas, osteosarcomas and mesotheliomas [ref: 29-33]. Mice treated subcutaneously with DES had a slightly increased incidence of lymphomas and subcutaneous fibrosarcomas [ref: 34,35]. Prenatal exposure to DES potentiated mammary tumorigenesis in rats given 7,12-dimethylbenz[a]anthracene at about 50 days of age [ref: 36]. Rats given DES by subcutaneous pellet developed mammary and pituitary tumours. When these animals

wee also treated with X-rays or neutrons, they developed a higher incidence of mammary tumours [ref: 37-39]. In other studies (subcutaneous, transplacental, oral), rats treated with DES developed mammary, hepatic and pituitary tumours [ref: 40-44]. When hamsters were treated prenatally with DES, females developed endometrial adenocarcinoma, squamous-cell papillomas of the cervix and vagina, and a mixed Mullerian tumour of the cervix (myosarcoma); in males, a leiomysarcoma of the seminal vesicles and a Cowper's gland adenoma were found [ref: 45]. Male hamsters castrated as adults and given DES subcutaneously developed renal tumours [ref: 46,47].

**C. Other relevant data**

No data were available on the genetic and related effects of DES in humans.

DES induced chromosomal aberrations in bone-marrow cells of mice treated *in vivo*, but data on induction of sister chromatid exchanges and micronuclei were equivocal; it induced sister chromatid exchanges in one study in rats. Unusual nucleotides were found in kidney DNA following chronic treatment of hamsters with DES. Aneuploidy was induced in human cells *in vitro*, but data on induction of sister chromatid exchanges. chromosomal aberrations and mutation were inconclusive; it induced DNA strand breaks, but not unscheduled DNA synthesis, except in a single study. Tests for transformation in rat and Syrian hamster embryo cells gave positive results, while results for mouse cells were negative. Aneuploidy and DNA strand breaks were induced in rodent cells *in vitro*, but results for chromosomal aberrations and sister chromatid exchanges were equivocal; DES did not induce mutation or unscheduled DNA synthesis, except in a single study in Syrian hamster embryo cells. It did not inhibit intercellular communication of Chinese hamster V79 cells. It induced aneuploidy in fungi, but, in most studies, it did not induce mutation, recombination or gene conversion. It did not induce mutation in a variety of bacterial and insect systems, but it was mutagenic in plants. DNA damage was not induced in fungi or bacteria. DES induced single-strand breaks in bacteriophage DNA in the presence of a horseradish peroxidase activation system [ref: 48].

**References**

1. IARC Monographs, 21, 131-134, 173-231, 1979

2. Bibbo, M., Haenszel, W.M., Wied, G.L., Hubby, M. & Herbst, A.L. (1978) A twenty-five-year follow-up of women exposed to diethylstilbestrol during pregnancy. New Engl. J. Med., 298, 763-767

3. Beral, V. & Colwell, L. (1980) Randomised trial of high doses of stilboestrol and ethisterone in pregnancy: Long-term follow-up of mothers. Br. med. J., 281, 1098-1101

4. Greenberg, E.R., Barnes, A.B., Resseguie, L., Barrett, J.A., Burnside, S., Lanza, L.L., Neff, R.K., Stevens, M., Young, R.H. & Colton, T. (1984) Breast cancer in mothers given diethylstilbestrol in pregnancy. New Engl. J. Med., 311, 1393-1398

5. Hadjimichael, O.C., Meigs, J.W., Falcier, F.W., Thompson, W.D. & Flannery, J.T. (1984) Cancer risk among women exposed to exogenous estrogens during pregnancy. J. natl Cancer Inst., 73, 831-834

6. Brian, D.D., Tilley, B.C., Labarthe, D.R., O'Fallon, W.M., Noller, K.L. & Kurland, L.T. (1980) Breast cancer in DES-exposed mothers. Absence of association. Mayo Clin. Proc., 55, 89-93

7. Henderson, B.E., Benton, B., Jing, J., Yu, M.C. & Pike, M.C. (1979) Risk factors for cancer of the testis in young men. Int. J. Cancer, 23, 598-602

8. Schottenfeld, D., Warshauer, M.E., Sherlock, S., Zauber, A.G., Leder, M. & Payne, R. (1980) The epidemiology of testicular cancer in young adults. Am. J. Epidemiol., 112, 232-246

9. Depue, R.H., Pike, M.C. & Henderson, B.E. (1983) Estrogen exposure during gestation and risk of testicular cancer. J. natl Cancer Inst., 71, 1151-1155

10. Brown, L.M., Pottern, L.M. & Hoover, R.N. (1986) Prenatal and perinatal risk factors for testicular cancer. Cancer Res., 46, 4812-4816

11. Moss, A.R., Osmond, D., Bacchetti, P., Torti, F.M. & Gurgin, V. (1986) Hormonal risk factors in testicular cancer. A case-control study. Am. J. Epidemiol., 124, 39-52

12. Barter, J.F., Austin, J.M., Jr & Shingleton, H.M. (1986) Endometrial adenocarcinoma after in utero diethylstilbestrol exposure. Obstet. Gynecol., 67 (Suppl.), 84S-85S

13. Cunningham, J.R., Gidwani, G.P., Gupta, M.S., Duchesneau, P.M. & Schumacher, O.P. (1982) Prolactin-secreting pituitary adenoma: occurrence following prenatal exposure to diethylstilbestrol. Cleveland Clin. Q., 49, 249-254

14. Lamb, E.J. (1977) Invasive squamous cell carcinoma of the cervix in a diethylstilbestrol-exposed offspring. Am. J. Obstet. Gynecol., 129, 924-925

15. Vandrie, D.M., Puri, S., Upton, R.T. & Demeester, L.J. (1983) Adenosquamous carcinoma of the cervix in a woman exposed to diethylstilbestrol *in utero*. Obstet. Gynecol., 61 (Suppl.), 84S-87S

16. Lazarus, K.H. (1984) Maternal diethylstilboestrol and ovarian malignancy in offspring. Lancet, i, 53

17. Deshmukh, A.S. & Hartung, W.H. (1983) Leydig cell tumor in patient on estrogen therapy. Urology, 21, 538-539

18. Ham, J.M., Pirola, R.C. & Crouch, R.L. (1980) Hemangioendothelial sarcoma of the liver associated with long-term estrogen therapy in a man. Dig. Dis. Sci., 25, 879-883

19. Brooks, J.J. (1982) Hepatoma associated with diethylstilbestrol therapy for prostatic carcinoma. J. Urol., 128, 1044-1045

20. Bellet, R.E. & Squitieri, A.P. (1974) Estrogen-induced hypernephroma. J. Urol., 112, 160-161

21. Nissenkorn, I., Servadio, C. & Avidor, I. (1979) Oestrogen-induced renal carcinoma. Br. J. Urol., 51, 6-9

22. Dunn, T.B. (1979) Cancer and other lesions in mice receiving estrogens. Recent Results Cancer Res., 66, 175-192

23. McLachlan, J.A. (1979) Transplacental effects of diethylstilbestrol in mice. Natl Cancer Inst. Monogr., 51, 67-72

24. McLachlan, J.A., Newbold, R.R. & Bullock, B.C. (1980) Long-term effects on the female mouse genital tract associated with prenatal exposure to diethylstilbestrol. Cancer Res., 40, 3988-3999

25. Lamb, J.C., IV, Newbold, R.R. & McLachlan, J.A. (1981) Visualization by light and scanning electron microscopy of reproductive tract lesions in female mice treated transplacentally with diethylstilbestrol. Cancer Res., 41, 4057-4062

26. Newbold, R.R. & MacLachlan, J.A. (1982) Vaginal adenosis and adenocarcinoma in mice exposed prenatally or neonatally to diethylstilbestrol. Cancer Res., 42, 2003-2011

27. Walker, B.E. (1983) Uterine tumors in old female mice exposed prenatally to diethylstilbestrol. J. natl Cancer Inst., 70, 477-484

28. Nagasawa, H., Mori, T. & Nakajima, Y. (1980) Long-term effects of progesterone or diethylstilbestrol with or without estrogen after maturity on mammary tumorigenesis in mice. Eur. J. Cancer, 16, 1583-1589

29. Highman, B., Greenman, D.L., Norvell, M.J., Farmer, J. & Shellenberger, T.E. (1980) Neoplastic and preneoplastic lesions induced in female C3H mice by diets containing diethylstilbestrol or 17β-estradiol. J. environ. Pathol. Toxicol., 4, 81-95

30. Highman, B., Roth, S.I. & Greenman, D.L. (1981) Osseous changes and oesteosarcomas in mice continuously fed diets containing diethylstilbestrol or 17β-estradiol. J. natl Cancer Inst., 67, 653-662

31. Greenman, D.L., Highman, B., Kodell, R.L., Morgan, K.T. & and Norvell, M. (1984) Neoplastic and nonneoplastic responses to chronic feeding of diethylstilbestrol in C3H mice. J. Toxicol. environ. Health, 14, 551-567

32. Greenman, D.L., Kodell, R.L., Highman, B., Schieferstein, G.J. & Norvell, M. (1984) Influence of strain and age on the induction of mammary tumours by diethylstilboestrol in C3H mice. Food chem. Toxicol., 22, 871-874

33. Greenman, D.L., Highman, B., Chen, J.J., Schieferstein, G.J. & Norvell, M.J. (1986) Influence of age on induction of mammary tumors by diethylstilbestrol in C3H/HeN mice with low murine mammary tumor virus titer. J. natl Cancer Inst., 77, 891-898

34. Boján, F., Rédai, I. & Gomba, S. (1979) Induction of lymphomas by urethane in combination with diethylstilboestrol in CFLP mice. Experientia, 35, 378-379

35. Ways, S. (1982) Local induction of fibrosarcomas by diethylstilbestrol. Int. Res. Commun. System med. Sci., 10, 796-797

36. Boylan, E.S. & Calhoon, R.E. (1979) Mammary tumorigenesis in the rat following prenatal exposure to diethylstilbestrol and postnatal treatment with 7,12-dimethylbenz(a)anthracene. J. Toxicol. environ. Health, 5, 1059-1071

37. Holtzman, S., Stone, J.P. & Shellabarger, C.J. (1979) Synergism of diethylstilbestrol and radiation in mammary carcinogenesis in female F344 rats. J. natl Cancer Inst., 63, 1071-1074

38. Holtzman, S., Stone, J.P. & Shellabarger, C.J. (1981) Synergism of estrogens and X-rays in mammary carcinogenesis in female ACI rats. J. natl Cancer Inst., 67, 455-459

39. Shellabarger, C.J., Chmelevsky, D., Kellerer, A.M., Stone, J.P. & Holtzman, S. (1982) Induction of mammary neoplasms in the ACI rat by 430-keV neutrons, X-rays, and diethylstilbestrol. J. natl Cancer Inst., 69, 1135-1146

40. Sumi, C., Yokoro, K. & Matsushima, R. (1983) Induction of hepatic tumors by diethylstilbestrol alone or in synergism with *N*-nitrosobutylurea in castrated male WF rats. J. natl Cancer Inst., 70, 937-942

41. Phelps, C. & Hymer, W.C. (1983) Characterization of estrogen-induced adenohypophyseal tumors in the Fischer 344 rat. Neuroendocrinology, 37, 23-31

42. Rothschild, T.C., Calhoon, R.E. & Boylan, E.S. (1985) Transplacental carcinogenicity of diethylstilbestrol (DES) in female ACI rats (Abstract No. 770). Proc. Am. Assoc. Cancer Res., 26, 195

43. Inoh, A., Kamiya, K., Fujii, Y. & Yokoro, K. (1985) Protective effects of progesterone and tamoxifen in estrogen-induced mammary carcinogenesis in ovariectomized W/FU rats. Jpn. J. Cancer Res. (Gann), 76, 699-704

44. Wanless, I.R. & Medline, A. (1982) Role of estrogens as promoters of hepatic neoplasia. Lab. Invest., 46, 313-320

45. Rustia, M. (1979) Role of hormone imbalance in transplacental carcinogenesis induced in Syrian golden hamsters by sex hormones. Natl Cancer Inst. Monogr., 51, 77-87

46. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

47. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

48. IARC Monographs, Suppl. 6, 250-256, 1987

**Dienoestrol**

**A. Evidence for carcinogenicity to animals** (*limited*)

Dienoestrol was tested in female guinea-pigs by subcutaneous injection and in female mice by intravaginal administration. Although these experiments indicated induction of 'uterine tumours' in guinea-pigs and of ovarian tumours in mice, they were regarded as inadequate [ref: 1]. Renal tumours were produced by administration of α-dienoestrol in male hamsters castrated as adults [ref: 2,3]. In noninbred rats, dienoestrol given prenatally and neonatally did not increase tumour incidence [ref: 4].

**B. Other relevant data**

No data were available on the genetic and related effects of dienoestrol in humans.

There are two stable stereoisomers of dienoestrol - Z,Z-dienoestrol (*cis*,*cis*-dienoestrol, β-dienoestrol) and E,E-dienoestrol (*trans*,*trans*-dienoestrol, α-dienoestrol). E,E-Dienoestrol is the principal constituent of dienoestrol-containing medications, whereas Z,Z-dienoestrol is a metabolite of diethylstilboestrol. Z,Z-Dienoestrol induced sister chromatid exchanges in human fibroblasts *in vitro*. Z,Z-Dienoestrol, but not E,E-dienoestrol, transformed cultured hamster cells. Z,Z-Dienoestrol produced single-strand breaks in hamster cells in the absence of an exogenous metabolic system, whereas both Z,Z- and E,E-dienoestrol gave weakly positive results in tests for unscheduled DNA synthesis in hamster cells only in the presence of a metabolic system. Z,Z-Dienoestrol did not induce single-strand breaks in bacteriophage DNA in the presence of a horseradish peroxidase activation system. Z,Z-Dienoestrol and E,E-dienoestrol were not mutagenic to bacteria [ref: 5].

**References**

1. IARC Monographs, 21, 161-171, 1979

2. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

3. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

4. Ird (Y.A. (1983) Blastomogenesis induced in rats by transplacental treatment with strogens (Russ.). Vopr. Onkol., 29, 61-66

5. IARC Monographs, Suppl. 6, 336-337, 1987

**Hexoestrol**

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Hexoestrol was tested for carcinogenicity in intact male hamsters and in males castrated as adults by subcutaneous implantation as a pellet, producing renal tumours, some of which were described as renal carcinomas, in 85-100% of tested animals [ref: 1-3].

**B. Other relevant data**

No data were available on the genetic and related effects of hexoestrol in humans. Unusual nucleotides were found in kidney DNA of hamsters treated with hexoestrol *in vivo*. The compound was not mutagenic to bacteria [ref: 4].

**References**

1. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

2. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

3. Liehr, J.G., Ballatore, A.M., Dague, B.B. & Ulubelen, A.A. (1985) Carcinogenicity and metabolic activation of hexestrol. Chem.-biol. Interactions, 55, 157-176

4. IARC Monographs, Suppl. 6, 336-337, 1987

**Chlorotrianisene**

**A. Evidence for carcinogenicity to animals** (*inadequate*)

Chlorotrianisene was tested in only one experiment in rats by oral administration. The data were insufficient to evaluate the carcinogenicity of this compound [ref: 1].

**B. Other relevant data**

No data were available to the Working Group.

**Reference**

1. IARC Monographs, 21, 139-146, 1979

**Overall evaluation**

Nonsteroidal oestrogens are *carcinogenic to humans (Group 1)*.

N.B. - This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.

For definition of the italicized terms, see Preamble Evaluation.

**Also previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

**Synonyms for Diethylstilboestrol**

- Acnestrol
- Antigestil
- Bio-des
- 3,4-Bis(*para*-hydroxyphenyl)-3-hexene
- Bufon
- Comestrol
- Cyren
- Cyren A
- Dawe's destrol
- DEB
- DES
- Desma
- Destrol
- DiBestrol '2' Premix
- Dicorvin
- DiEstryl
- α,α'-Diethylstilbenediol
- (E)-α,α'-Diethyl-4,4'-stilbenediol
- *trans*-α,α'-Diethyl-4,4'-stilbenediol
- *trans*-Diethylstilbesterol
- Diethylstilbestrol
- *trans*-Diethylstilbestrol
- *trans*-Diethylstilboestrol
- 4,4'-Dihydroxydiethylstilbene
- 4,4'-Dihydroxy-α,β-diethylstilbene
- Distilbene
- Domestrol
- Estilbin 'MCO'
- Estrobene
- Estromenin
- Estrosyn
- [Follidiene]
- Fonatol
- Grafestrol
- Gynopharm
- Hi-Bestrol
- Idroestril
- Iscovesco
- Menostilbeen
- Microest
- Milestrol
- Neo-Oestranol I
- Oekolp
- Oestrogen
- Oestrogenine
- Oestrol Vetag
- Oestromenin
- Oestromensyl
- Oestromon
- Pabestrol
- Palestrol
- Percutatrine Oestrogenique Iscovesco
- Rumestrol 1
- Rumestrol 2
- Sedestran
- Serral
- Sexocretin
- Sibol
- Sintestrol
- Stibilium
- Stilbestrol

- Stilbetin
- Stilboefral
- Stilboestrol
- Stilboestroform
- Stilbofollin
- Stilbol
- Stilkap
- Stil-Rol
- Synestrin
- Synthoestrin
- Synthofolin
- Syntofolin
- Tampovagan stilboestrol
- Tylosterone
- Vagestrol

**Synonyms for Diethylstilboestrol dipropionate**

- Clinestrol
- Cyren B
- Dibestil
- α,α,'-Diethyl-4,4'-stilbenediol dipropionate
- (E)-α,α'-Diethyl-4,4'-stilbenediol dipropionate
- α,α'-Diethyl-4,4'-stilbenediol trans-dipropionate
- α,α'-Diethyl-4,4'-stilbenediol dipropionyl ester
- Diethylstilbene dipropionate
- Diethylstilbesterol dipropionate
- Diethylstilbestrol dipropionate
- Diethylstilbestrol propionate
- Diethylstilboestrol dipropionate
- Diethylstilboestrol propionate
- Dihydroxydiethylstilbene dipropionate
- *para*,*para*'-Dipropionoxy-*trans*-α,β-diethylstilbene
- Estilben
- Estilbin
- Estrobene DF
- Estrobene DP
- Estrogenin
- Estrostilben
- Euvestin
- Gynolett
- Horfemine
- Neo-Oestranol II
- Neo-Oestronol II
- New-Oestranol 11
- Oestrogynaedron
- Orestol
- Pabestrol D
- Sinciclan
- Stilbestrol dipropionate
- Stilbestrol propionate
- Stilbestronate
- Stilboestrol dipropionate
- Stilboestrol DP
- Stilbofax
- Stilronate
- Synoestron
- Syntestrin
- Syntestrine
- Willestrol

**Synonyms for Dienoestrol**

- Agaldog
- 3,4-Bis(4-hydroxyphenyl)-2,4-hexadiene
- 3,4-Bis(*para*-hydroxyphenyl)-2,4-hexadiene
- Cycladiene
- Dehydrostilbestrol
- Dehydrostilboestrol
- Dienol
- 4,4'-(Diethylideneethylene)diphenol
- *para*,*para*'-(Diethylideneethylene)diphenol
- 4,4'-Dihydroxy-γ,δ-diphenyl-β,δ-hexadiene
- Dinovex
- Di(*para*-oxyphenyl)-2,4-hexadiene
- DV
- Estrodienol
- Estraguard
- Estroral
- Follidiene
- Follormon
- Gynefollin
- Hormofemin
- Isodienestrol
- Oestrasid
- Oestrodiene
- Oestrodienol
- Oestroral
- Oestrovis
- Para-dien
- Restrol
- Retalon
- Sexadien
- Synestrol
- Teserene
- Willnestrol

**Synonyms for Chlorotrianisene**

- Anisene
- Chlorestrolo
- Chlorotrianisine
- Chlorotrianizen
- Chlorotrisin
- Chlorotris-(*para*-methoxyphenyl)ethylene
- Chlortrianisen
- Clorestrolo
- Clorotrisin
- Hormonisene
- Khlortrianizen
- Merbentul
- Metace
- NSC-10108
- Rianil
- Tace
- TACE
- Tace-FN
- Tri-*para*-anisylchloroethylene
- Tris(*para*-methoxyphenyl)chloroethylene

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Last updated: 9 February 1998

# OESTROGEN-PROGESTIN REPLACEMENT THERAPY (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 308)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Progestins, when administered for at least ten days per 28-day oestrogen replacement therapy cycle, prevent adenomatous hyperplasia, a precursor of endometrial carcinoma, and cause regression of pre-existing adenomatous hyperplasia in some patients [ref: 1]. When administered alone, progestins are effective in the treatment of carcinoma *in situ* of the endometrium [ref: 2] and of more advanced disease [ref: 3,4].

Progestins increase the conversion of oestradiol-17β to oestrone, a biologically less active oestrogen [ref: 5], and they reduce the concentration of oestrogen receptors [ref: 6]. Maximal mitotic activity in the endometrium occurs during the follicular phase of the cycle; luteal-phase progesterone effectively stops mitotic activity and causes differentiation of endometrial cells to a secretory state [ref: 7].

Support for a protective effect of progestins against endometrial cancer risk is obtained from the results of studies of the effects of oral contraceptives on endometrial cancer risk. Case-control studies have consistently shown that, whereas ingestion of sequential oral contraceptives containing an oestrogen alone throughout most of the menstrual cycle increases risk, ingestion of combined oral contraceptives, in which each pill contains an oestrogen and a progestin, substantially decreases risk.

The effect of progestins on the breast is markedly different from that on the endometrium. Endometrial cancer risk is considerably reduced with combined oral contraceptives, but there is no evidence of a reduced risk of breast cancer, even after long periods of combined oral contraceptive use [ref: 8]. Maximal mitotic activity in breast tissue occurs during the luteal phase of the normal menstrual cycle in the face of maximal progesterone levels [ref: 9]. These results concerning the effects of combined oral contraceptives suggest strongly that progestins do not have an antioestrogen, anticancer effect on the breast. A number of studies [ref: 10-12] have addressed the relationship between oestrogen-progestin replacement therapy and cancer, but in each instance either the small size of the study or apparently inadequate study design or data analysis prevent conclusions from being drawn.

**B. Other relevant data**

No data were available to the Working Group.

**Overall evaluation**

Oestrogen-progestin replacement therapy is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

**Subsequent evaluation**: Vol. 72 (1999)

**References**

1. Gambrell, R.D., Jr (1982) Clinical use of progestins in the menopausal patient. Dosage and duration. J. reprod. Med., 27, 531-538

2. Kohorn, E.I. (1976) Gestagens and endometrial carcinoma. Gynecol. Oncol., 4, 398-411

3. Thornton, J.G., Brown, L.A., Wells, M. & Scott, J.S. (1985) Primary treatment of endometrial cancer with progestogen alone. Lancet, ii, 207-208

4. Mackillop, W.J. & Pringle, J.F. (1985) Stage III endometrial carcinoma: a review of 90 cases. Cancer, 56, 2519-2523

5. Tseng, L. & Gurpide, E. (1975) Induction of human endometrial estradiol dehydrogenase by progestins. Endocrinology, 97, 825-833

6. Hsueh, A.J.W., Peck, E.J., Jr & Clark, J.H. (1975) Progesterone antagonism of the oestrogen receptor and oestrogen-induced uterine growth. Nature, 254, 337-339

7. Novak, E.R. & Woodruff, J.D. (1979) Novak's Gynaecologic and Obstetric Pathology with Clinical and Endocrine Relations, Philadelphia, PA, W.B. Saunders, pp. 171-184

8. Kelsey, J.L. (1979) A review of the epidemiology of human breast cancer. Epidemiol. Rev., 1, 74-109

9. Anderson, T.J., Ferguson, D.J.P. & Raab, G.M. (1982) Cell turnover in the 'resting' human breast: influence of parity, contraceptive pill, age and laterality. Br. J. Cancer, 46, 376-382

10. Gambrell, R.D., Jr, Massey, F.M., Castaneda, T.A., Ugenas, A.J. & Ricci, C.A. (1979) Reduced incidence of endometrial cancer among postmenopausal women treated with progestogens. J. Am. Geriatr. Soc., 27, 389-394

11. Nachtigall, L.E., Nachtigall, R.H., Nachtigall, R.B. & Beckman, E.M. (1979) Estrogen replacement therapy. II. A prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. Obstet. Gynecol., 54, 74-79

12. Gambrell, R.D., Jr, Maier, R.C. & Sanders, B.I. (1983) Decreased incidence of breast cancer in postmenopausal estrogen-progestogen users. Obstet. Gynecol., 62, 435-443

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Last updated: 11 March 1998

# OESTROGEN REPLACEMENT THERAPY
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.280)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

A number of studies, utilizing a variety of designs, have shown a consistent, strongly positive association between exposure to a number of oestrogenic substances and risk of endometrial cancer, with evidence of positive dose-response relationships both for strength of medication and duration of use [ref: 1]. Consistent findings have also been seen in more recent studies [ref: 2-16]. The rise and fall of incidence of endometrial cancer in several areas of the USA was compatible with trends in oestrogen use [ref: 1,15].

Of the 20 epidemiological studies of oestrogen replacement therapy and breast cancer risk [ref: 16-35], nine show a positive relation between oestrogen use and breast cancer [ref: 17-20,22-24,28,33]. The increased risks tend to be small; for example, a 50% increase was found with 20 years of menopausal oestrogen replacement therapy use [ref: 24]. All except one [ref: 33] of the positive studies involved use of population controls (eight of the nine studies with population controls gave positive results), and most showed increased risk after prolonged use or after ten or more years since initial exposure. One study showed a positive association with current oestrogen use [ref: 28].

One possible reason that studies with hospital controls gave negative results and those with population controls positive results is that oestrogen replacement therapy may be used more frequently in hospitalized women than in the general population. However, in two studies involving use of both hospital and population control groups, one giving positive [ref: 29] and the other largely negative [ref: 25] results, similar results were obtained when hospital and population controls were used to estimate the relative risk. Three of the studies with negative results [ref: 26,27,34] probably did not permit the authors to address satisfactorily the question of long-term use of oestrogen replacement therapy. The large hospital-based study that showed a positive finding used as controls subjects with a large spectrum of acute conditions unrelated to any of the known or suspected risk factors for breast cancer [ref: 33].

One cohort study of 1439 women initially treated for benign breast disease showed increased risk for women who took exogenous oestrogens after biopsy, but not for those who had taken them before biopsy. The increased risk in the former group appeared to be associated with epithelial hyperplasia or calcification in the initial lesion [ref: 35].

**Overall evaluation**

Oestrogen replacement therapy is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

**Subsequent evaluation**: Vol. 72 (1999)

**References**

1. IARC Monographs, 21, 95-102, 147-159, 1979

2. Buring, J.E., Bain, C.J. & Ehrmann, R.L. (1986) Conjugated estrogen use and risk of endometrial cancer. Am. J. Epidemiol., 124, 434-441

3. Ewertz, M., Machado, S.G., Boice, J.D., Jr & Jensen, O.M. (1984) Endometrial cancer following treatment for breast cancer: A case-control study in Denmark. Br. J. Cancer, 50, 687-692

4. Henderson, B.E., Casagrande, J.T., Pike, M.C., Mack, T., Rosario, I. & Duke, A. (1983) The epidemiology of endometrial cancer in young women. Br. J. Cancer, 47, 749-756

5. Hulka, B.S., Fowler, W.C., Jr, Kaufman, D.G., Grimson, R.C., Greenberg, B.G., Hogue, C.J.R., Berger, G.S. & Pulliam, C.C. (1980) Estrogen and endometrial cancer: Cases and two control groups from North Carolina. Am. J. Obstet. Gynecol., 137, 92-101

6. Kelsey, J.L., LiVolsi, V.A., Holford, T.R., Fischer, D.B., Mostow, E.D., Schwartz, P.E., O'Connor, T. & White, C. (1982) A case-control study of cancer of the endometrium. Am. J. Epidemiol., 116, 333-342

7. La Vecchia, C., Franceschi, S., Gallus, G., DeCarli, A., Colombo, E., Mangioni, C. & Tognoni, G. (1982) Oestrogens and obesity as risk factors for endometrial cancer in Italy. Int. J. Epidemiol., 11, 120-126

8. La Vecchia, C., Franceschi, S., DeCarli, A., Gallus, G. & Tognoni, G. (1984) Risk factors for endometrial cancer at different ages. J. natl Cancer Inst., 73, 667-671

9. Öbrink, A., Bunne, G., Collén, J. & Tjernberg, B. (1981) Estrogen regimen of women with endometrial carcinoma. A retrospective case-control study at Radiumhemmet. Acta obstet. gynecol. scand., 60, 191-197

10. Shapiro, S., Kaufman, D.W., Slone, D., Rosenberg, L., Miettinen, O.S., Stolley, P.D., Rosenshein, N.B., Watring, W.G., Leavitt, T., Jr & Knapp, R.C. (1980) Recent and past use of conjugated estrogens in relation to adenocarcinoma of the endometrium. New Engl. J. Med., 303, 485-489

11. Shapiro, S., Kelly, J.P., Rosenberg, L., Kaufman, D.W., Helmrich, S.P., Rosenshein, N.B., Lewis, J.L., Jr, Knapp, R.C., Stolley, P.D. & Schottenfeld, D. (1985) Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. New Engl. J. Med., 313, 969-972

12. Spengler, R.F., Clarke, E.A., Woolever, C.A., Newman, A.M. & Osborn, R.W. (1981) Exogenous estrogens and endometrial cancer: a case-control study and assessment of potential biases. Am. J. Epidemiol., 114, 497-506

13. Stavraky, K.M., Collins, J.A., Donner, A. & Wells, G.A. (1981) A comparison of estrogen use by women with endometrial cancer, gynecologic disorders, and other illnesses. Am. J. Obstet. Gynecol., 141, 547-555

14. Weiss, N.S., Farewell, V.T., Szekely, D.R., English, D.R. & Kiviat, N. (1980) Oestrogens and endometrial cancer: effect of other risk factors on the association. Maturitas, 2, 185-190

15. Marrett, L.D., Meigs, J.W. & Flannery, J.T. (1982) Trends in the incidence of cancer of the corpus uteri in Connecticut, 1964-1969, in relation to consumption of exogenous estrogens. Am. J. Epidemiol., 116, 57-67

16. Vakil, D.V., Morgan, R.W. & Halliday, M. (1983) Exogenous estrogens and development of breast and endometrial cancer. Cancer Detect. Prev., 6, 415-424

17. Hoover, R., Gray, L.A., Sr, Cole, P. & MacMahon, B. (1976) Menopausal estrogens and breast cancer. New Engl. J. Med., 295, 401-405

18. Ross, R.K., Paganini-Hill, A., Gerkins, V.R., Mack, T.M., Pfeffer, R., Arthur, M. & Henderson, B.E. (1980) A case-control study of menopausal estrogen therapy and breast cancer. J. Am. med. Assoc., 243, 1635-1639

19. Hoover, R., Glass, A., Finkle, W.D., Azevedo, D. & Milne, K. (1981) Conjugated estrogens and breast cancer risk in women. J. natl Cancer Inst., 67, 815-820

20. Hulka, B.S., Chambless, L.E., Deubner, D.C. & Wilkinson, W.E. (1982) Breast cancer and estrogen replacement therapy. Am. J. Obstet. Gynecol., 143, 638-644

21. Gambrell, R.D., Jr, Maier, R.C. & Sanders, B.I. (1983) Decreased incidence of breast cancer in postmenopausal estrogen-progestogen users. Obstet. Gynecol., 62, 435-443

22. Hiatt, R.A., Bawol, R., Friedman, G.D. & Hoover, R. (1984) Exogenous estrogen and breast cancer after bilateral oophorectomy. Cancer, 54, 139-144

23. McDonald, J.A., Weiss, N.S., Daling, J.R., Francis, A.M. & Polissar, L. (1986) Menopausal estrogen use and the risk of breast cancer. Breast Cancer Res. Treat., 7, 193-199

24. Brinton, L.A., Hoover, R. & Fraumeni, J.F., Jr (1986) Menopausal oestrogens and breast cancer risk: an expanded case-control study. Br. J. Cancer, 54, 825-832

25. Nomura, A.M.Y., Kolonel, L.N., Hirohata, T. & Lee, J. (1986) The association of replacement estrogens with breast cancer. Int. J. Cancer, 37, 49-53

26. Sartwell, P.E., Arthes, F.G. & Tonascia, J.A. (1977) Exogenous hormones, reproductive history, and breast cancer. J. natl Cancer Inst., 59, 1589-1592

27. Ravnihar, B., Seigel, D.G. & Lindtner, J. (1979) An epidemiologic study of breast cancer and benign breast neoplasias in relation to the oral contraceptive and estrogen use. Eur. J. Cancer, 15, 395-405

28. Jick, H., Walker, A.M., Watkins, R.N., D'Ewart, D.C., Hunter, J.R., Danford, A., Madsen, S., Dinan, B.J. & Rothman, K.J. (1980) Replacement estrogens and breast cancer. Am. J. Epidemiol., 112, 586-594

29. Kelsey, J.L., Fischer, D.B., Holford, T.R., LiVolsi, V.A., Mostow, E.D., Goldenberg, I.S. & White, C. (1981) Exogenous estrogens and other factors in the epidemiology of breast cancer. J. natl Cancer Inst., 67, 327-333

30. Sherman, B., Wallace, R. & Bean, J. (1983) Estrogen use and breast cancer. Interaction with body mass. Cancer, 51, 1527-1531

31. Kaufman, D.W., Miller, D.R., Rosenberg, L., Helmrich, S.P., Stolley, P., Schottenfeld, D. & Shapiro, S. (1984) Noncontraceptive estrogen use and the risk of breast cancer. J. Am. med. Assoc., 252, 63-67

32. Horwitz, R.I. & Stewart, K.R. (1984) Effect of clinical features on the association of estrogens and breast cancer. Am. J. Med., 76, 192-198

33. La Vecchia, C., Decarli, A., Parazzini, F., Gentile, A., Liberati, C. & Franceschi, S. (1986) Non-contraceptive oestrogens and the risk of breast cancer in women. Int. J. Cancer, 38, 853-858

34. Wingo, P.A., Layde, P.M., Lee, N.C., Rubin, G. & Ory, H.W. (1987) The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. J. Am. med. Assoc., 257, 209-215

35. Thomas, D.B., Persing, J.P. & Hutchison, W.B. (1982) Exogenous estrogens and other risk factors for breast cancer in women with benign breast diseases. J. natl Cancer Inst., 69, 1017-1025

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Last updated: 9 February 1998

# OESTROGENS, STEROIDAL
# (Group 1)
# Evidence for carcinogenicity to humans (*sufficient*)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 280)

**Conjugated oestrogens**
**CAS No.**: N/A
**Chem. Abstr. Name**: N/A

**Sodium oestrone sulphate**
**CAS No.**: 438-67-5
**Chem. Abstr. Name**: 3-(Sulfooxy)estra-1,3,5(10)-trien-17-one sodium salt

**Sodium equilin sulphate**
**CAS No.**: 16680-47-0
**Chem. Abstr. Name**: 3-(Sulfooxy)estra-1,3,5(10),7-tetraen-17-one sodium salt

**Piperazine oestrone sulphate**
**CAS No.**: 17280-37-7
**Chem. Abstr. Name**: 3-(Sulfooxy)estra-1,3,5(10)-trien-17-one compd. with piperazine (1:1)

**Oestradiol-17** β
**CAS No.**: 50-28-2
**Chem. Abstr. Name**: (17 β)-Estra-1,3,5(10)-triene-3,17-diol

**Oestradiol 3-benzoate**
**CAS No.**: 50-50-0
**Chem. Abstr. Name**: Estra-1,3,5(10)-triene-3,17-diol(17β)-3-benzoate

**Oestradiol dipropionate**
**CAS No.**: 113-38-2
**Chem. Abstr. Name**: Estral,3,5(10)-triene-3,17-diol(17β)-dipropionate

**Oestradiol-17β-valerate**
**CAS No.**: 979-32-8
**Chem. Abstr. Name**: (17β)-Estra-1,3,5-triene-3,17-diol 17-pentanoate

**Polyoestradiol phosphate**
**CAS No.**: 28014-46-2
**Chem. Abstr. Name**: (17β)-Estra-1,3,5(10)-triene-3,17-diol polymer with phosphoric acid

**Oestriol**
**CAS No.**: 50-27-1
**Chem. Abstr. Name**: O(16 α,17 β)-Estra-1,3,5(10)-triene-3,16,17-triol

**Oestrone**
**CAS No.**: 53-16-7
**Chem. Abstr. Name**: 3-Hydroxyestra-1,3,5(10)-trien-17-one

**Oestrone benzoate**
**CAS No.**: 2393-53-5
**Chem. Abstr. Name**: 3-(Benzoyloxy)estra-1,3,5(10)-trien-17-one

**Ethinyloestradiol**
**CAS No.**: 57-63-6
**Chem. Abstr. Name**: (17α)-19-Norpregna-1,3,5(10)-trien-20yne-3,17-diol

**Mestranol**
**CAS No.**: 72-33-3
**Chem. Abstr. Name**: (17α)-3-Methoxy-19-norpregna-1,3,5(10)-trien-20-yn-17-ol

**Oestrogen replacement therapy**

**A. Evidence for carcinogenicity to humans** (*sufficient*)

A number of studies, utilizing a variety of designs, have shown a consistent, strongly positive association between exposure to a number of oestrogenic substances and risk of endometrial cancer, with evidence of positive dose-response relationships both for strength of medication and duration of use [ref: 1]. Consistent findings have also been seen in more recent studies [ref: 2-16]. The rise and fall of incidence of endometrial cancer in several areas of the USA was compatible with trends in oestrogen use [ref: 1,15].

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**References**

1. IARC Monographs, 21, 95-102, 147-159, 1979

2. Buring, J.E., Bain, C.J. & Ehrmann, R.L. (1986) Conjugated estrogen use and risk of endometrial cancer. Am. J. Epidemiol., 124, 434-441

3. Ewertz, M., Machado, S.G., Boice, J.D., Jr & Jensen, O.M. (1984) Endometrial cancer following treatment for breast cancer: A case-control study in Denmark. Br. J. Cancer, 50, 687-692

4. Henderson, B.E., Casagrande, J.T., Pike, M.C., Mack, T., Rosario, I. & Duke, A. (1983) The epidemiology of endometrial cancer in young women. Br. J. Cancer, 47, 749-756

5. Hulka, B.S., Fowler, W.C., Jr, Kaufman, D.G., Grimson, R.C., Greenberg, B.G., Hogue, C.J.R., Berger, G.S. & Pulliam, C.C. (1980) Estrogen and endometrial cancer: Cases and two control groups from North Carolina. Am. J. Obstet. Gynecol., 137, 92-101

6. Kelsey, J.L., LiVolsi, V.A., Holford, T.R., Fischer, D.B., Mostow, E.D., Schwartz, P.E., O'Connor, T. & White, C. (1982) A case-control study of cancer of the endometrium. Am. J. Epidemiol., 116, 333-342

7. La Vecchia, C., Franceschi, S., Gallus, G., DeCarli, A., Colombo, E., Mangioni, C. & Tognoni, G. (1982) Oestrogens and obesity as risk factors for endometrial cancer in Italy. Int. J. Epidemiol., 11, 120-126

8. La Vecchia, C., Franceschi, S., DeCarli, A., Gallus, G. & Tognoni, G. (1984) Risk factors for endometrial cancer at different ages. J. natl Cancer Inst., 73, 667-671

9. Öbrink, A., Bunne, G., Collén, J. & Tjernberg, B. (1981) Estrogen regimen of women with endometrial carcinoma. A retrospective case-control study at Radiumhemmet. Acta obstet. gynecol. scand., 60, 191-197

10. Shapiro, S., Kaufman, D.W., Slone, D., Rosenberg, L., Miettinen, O.S., Stolley, P.D., Rosenshein, N.B., Watring, W.G., Leavitt, T., Jr & Knapp, R.C. (1980) Recent and past use of conjugated estrogens in relation to adenocarcinoma of the endometrium. New Engl. J. Med., 303, 485-489

11. Shapiro, S., Kelly, J.P., Rosenberg, L., Kaufman, D.W., Helmrich, S.P., Rosenshein, N.B., Lewis, J.L., Jr, Knapp, R.C., Stolley, P.D. & Schottenfeld, D. (1985) Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. New Engl. J. Med., 313, 969-972

12. Spengler, R.F., Clarke, E.A., Woolever, C.A., Newman, A.M. & Osborn, R.W. (1981) Exogenous estrogens and endometrial cancer: a case-control study and assessment of potential biases. Am. J. Epidemiol., 114, 497-506

13. Stavraky, K.M., Collins, J.A., Donner, A. & Wells, G.A. (1981) A comparison of estrogen use by women with endometrial cancer, gynecologic disorders, and other illnesses. Am. J. Obstet. Gynecol., 141, 547-555

14. Weiss, N.S., Farewell, V.T., Szekely, D.R., English, D.R. & Kiviat, N. (1980) Oestrogens and endometrial cancer: effect of other risk factors on the association. Maturitas, 2, 185-190

15. Marrett, L.D., Meigs, J.W. & Flannery, J.T. (1982) Trends in the incidence of cancer of the corpus uteri in Connecticut, 1964-1969, in relation to consumption of exogenous estrogens. Am. J. Epidemiol., 116, 57-67

16. Vakil, D.V., Morgan, R.W. & Halliday, M. (1983) Exogenous estrogens and development of breast and endometrial cancer. Cancer Detect. Prev., 6, 415-424

17. Hoover, R., Gray, L.A., Sr, Cole, P. & MacMahon, B. (1976) Menopausal estrogens and breast cancer. New Engl. J. Med., 295, 401-405

18. Ross, R.K., Paganini-Hill, A., Gerkins, V.R., Mack, T.M., Pfeffer, R., Arthur, M. & Henderson, B.E. (1980) A case-control study of menopausal estrogen therapy and breast cancer. J. Am. med. Assoc., 243, 1635-1639

19. Hoover, R., Glass, A., Finkle, W.D., Azevedo, D. & Milne, K. (1981) Conjugated estrogens and breast cancer risk in women. J. natl Cancer Inst., 67, 815-820

20. Hulka, B.S., Chambless, L.E., Deubner, D.C. & Wilkinson, W.E. (1982) Breast cancer and estrogen replacement therapy. Am. J. Obstet. Gynecol., 143, 638-644

21. Gambrell, R.D., Jr, Maier, R.C. & Sanders, B.I. (1983) Decreased incidence of breast cancer in postmenopausal estrogen-progestogen users. Obstet. Gynecol., 62, 435-443

22. Hiatt, R.A., Bawol, R., Friedman, G.D. & Hoover, R. (1984) Exogenous estrogen and breast cancer after bilateral oophorectomy. Cancer, 54, 139-144

23. McDonald, J.A., Weiss, N.S., Daling, J.R., Francis, A.M. & Polissar, L. (1986) Menopausal estrogen use and the risk of breast cancer. Breast Cancer Res. Treat., 7, 193-199

24. Brinton, L.A., Hoover, R. & Fraumeni, J.F., Jr (1986) Menopausal oestrogens and breast cancer risk: an expanded case-control study. Br. J. Cancer, 54, 825-832

25. Nomura, A.M.Y., Kolonel, L.N., Hirohata, T. & Lee, J. (1986) The association of replacement estrogens with breast cancer. Int. J. Cancer, 37, 49-53

26. Sartwell, P.E., Arthes, F.G. & Tonascia, J.A. (1977) Exogenous hormones, reproductive history, and breast cancer. J. natl Cancer Inst., 59, 1589-1592

27. Ravnihar, B., Seigel, D.G. & Lindtner, J. (1979) An epidemiologic study of breast cancer and benign breast neoplasias in relation to the oral contraceptive and estrogen use. Eur. J. Cancer, 15, 395-405

28. Jick, H., Walker, A.M., Watkins, R.N., D'Ewart, D.C., Hunter, J.R., Danford, A., Madsen, S., Dinan, B.J. & Rothman, K.J. (1980) Replacement estrogens and breast cancer. Am. J. Epidemiol., 112, 586-594

29. Kelsey, J.L., Fischer, D.B., Holford, T.R., LiVolsi, V.A., Mostow, E.D., Goldenberg, I.S. & White, C. (1981) Exogenous estrogens and other factors in the epidemiology of breast cancer. J. natl Cancer Inst., 67, 327-333

30. Sherman, B., Wallace, R. & Bean, J. (1983) Estrogen use and breast cancer. Interaction with body mass. Cancer, 51, 1527-1531

31. Kaufman, D.W., Miller, D.R., Rosenberg, L., Helmrich, S.P., Stolley, P., Schottenfeld, D. & Shapiro, S. (1984) Noncontraceptive estrogen use and the risk of breast cancer. J. Am. med. Assoc., 252, 63-67

32. Horwitz, R.I. & Stewart, K.R. (1984) Effect of clinical features on the association of estrogens and breast cancer. Am. J. Med., 76, 192-198

33. La Vecchia, C., Decarli, A., Parazzini, F., Gentile, A., Liberati, C. & Franceschi, S. (1986) Non-contraceptive oestrogens and the risk of breast cancer in women. Int. J. Cancer, 38, 853-858

34. Wingo, P.A., Layde, P.M., Lee, N.C., Rubin, G. & Ory, H.W. (1987) The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. J. Am. med. Assoc., 257, 209-215

35. Thomas, D.B., Persing, J.P. & Hutchison, W.B. (1982) Exogenous estrogens and other risk factors for breast cancer in women with benign breast diseases. J. natl Cancer Inst., 69, 1017-1025

**Conjugated oestrogens**

**A. Evidence for carcinogenicity to animals** (*limited*)

Conjugated oestrogens were tested inadequately in rats by oral administration in one study [ref: 1]. In male hamsters castrated as adults, equilin administered as a subcutaneously implanted pellet produced renal tumours in 6/8 treated animals. In contrast, *d*-equilenin administered similarly did not induce renal tumours [ref: 2,3].

**B. Other relevant data**

No data were available on the genetic and related effects of conjugated oestrogens in humans.

A commercial preparation of conjugated oestrogens did not induce chromosomal aberrations in human lymphoblastoid cells *in vitro* or in Chinese hamster V79 cells exposed in diffusion chambers implanted into mice after oestrogen treatment. It was not mutagenic to bacteria [ref: 4].

**References**

1. IARC Monographs, 21, 147-159, 1979

2. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

3. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

4. IARC Monographs, Suppl. 6, 187, 1987

**Oestradiol-17β and esters**

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Oestradiol-17β and its esters were tested in mice, rats, hamsters and guinea-pigs by oral and subcutaneous administration. Administration to mice increased the incidences of mammary, pituitary, uterine, cervical, vaginal, testicular, lymphoid and bone tumours [ref: 1-5]. In rats, there was an increased incidence of mammary and/or pituitary tumours [ref: 1,6]. Oestradiol-17β produced a nonstatistically significant increase in the incidence of foci of altered hepatocytes and hepatic nodules induced by partial hepatectomy and administration of *N*-nitrosodiethylamine in rats [ref: 7]. In hamsters, a high incidence of malignant kidney tumours occurred in intact and castrated males [ref: 1,8-10] and in ovariectomized females, but not in intact females [ref: 1]. In guinea-pigs, diffuse fibromyomatous uterine and abdominal lesions were observed [ref: 1].

**B. Other relevant data**

No data were available on the genetic and related effects of oestradiol-17β in humans.

Oestradiol-17β did not induce chromosomal aberrations in bone-marrow cells of mice treated *in vivo*. Unusual nucleotides were found in kidney DNA of treated hamsters. It induced micronuclei but not aneuploidy, chromosomal aberrations or sister chromatid exchanges in human cells *in vitro*. In rodent cells *in vitro*, it induced aneuploidy and unscheduled DNA synthesis but was not mutagenic and did not induce DNA strand breaks or sister chromatid exchanges. Oestradiol-17β was not mutagenic to bacteria [ref: 11].

**References**

1. IARC Monographs, 21, 279-326, 1979

2. Huseby, R.A. (1980) Demonstration of a direct carcinogenic effect of estradiol on Leydig cells of the mouse. Cancer Res., 40, 1006-1013

3. Highman, B., Roth, S.I. & Greenman, D.L. (1981) Osseous changes and osteosarcomas in mice continuously fed diets containing diethylstilbestrol or 17β-estradiol. J. natl Cancer Inst., 67, 653-662

4. Highman, B., Greenman, D.L., Norvell, M.J., Farmer, J. & Shellenberger, T.E. (1980) Neoplastic and preneoplastic lesions induced in female C3H mice by diets containing diethylstilbestrol or 17β-estradiol. J. environ. Pathol. Toxicol., 4, 81-95

5. Nagasawa, H., Mori, T. & Nakajima, Y. (1980) Long-term effects of progesterone or diethylstilbestrol with or without estrogen after maturity on mammary tumorigenesis in mice. Eur. J. Cancer, 16, 1583-1589

6. Inoh, A., Kamiya, K., Fujii, Y. & Yokoro, K. (1985) Protective effects of progesterone and tamoxifen in estrogen-induced mammary carcinogenesis in ovariectomized W/FU rats. Jpn. J. Cancer Res. (Gann), 76, 699-704

7. Yager, J.D., Campbell, H.A., Longnecker, D.S., Roebuck, B.D. & Benoit, M.C. (1984) Enhancement of hepatocarcinogenesis in female rats by ethinyl estradiol and mestranol but not estradiol. Cancer Res., 44, 3862-3869

8. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

9. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

10. Liehr, J.G., Stancel, G.M., Chorich, L.P., Bousfield, G.R. & Ulubelen, A.A. (1986) Hormonal carcinogenesis: separation of estrogenicity from carcinogenicity. Chem.-biol. Interactions, 59, 173-184

11. IARC Monographs, Suppl. 6, 437-439, 1987

**Oestriol**

**A. Evidence for carcinogenicity to animals** (*limited*)

Oestriol was tested by subcutaneous implantation in castrated mice and in rats and hamsters. It increased the incidence and accelerated the appearance of mammary tumours in both male and female mice and produced kidney tumours in hamsters [ref: 1].

**B. Other relevant data**

No data were available on the genetic and related effects of oestriol in humans. It did not induce aneuploidy in cultured lymphocytes from one pregnant woman; results for induction of sister chromatid exchange were inconclusive. No effect was seen in lymphocytes from one man [ref: 2].

**References**

1. IARC Monographs, 21, 327-341, 1979

2. IARC Monographs, Suppl. 6, 440-441, 1987

**Oestrone**

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Oestrone was tested in mice by oral administration, in mice, rats and hamsters by subcutaneous injection and implantation, and in mice by skin painting. Its administration resulted in an increased incidence of mammary tumours in mice, in pituitary, adrenal and mammary tumours in rats, and in renal tumours in both castrated and intact male hamsters [ref: 1]. Oestrone implanted subcutaneously as a pellet produced renal tumours in 80% of treated male hamsters castrated as adults [ref: 2,3].

**B. Other relevant data**

No data were available on the genetic and related effects of oestrone in humans. It was not mutagenic to Chinese hamster cells *in vitro* [ref: 4].

**References**

1. IARC Monographs, 21, 343-362, 1979

2. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

3. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

4. IARC Monographs, Suppl. 6, 442-443, 1987

**Ethinyloestradiol**

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Ethinyloestradiol was tested in mice, rats, dogs and monkeys by oral administration and in rats by subcutaneous injection. In mice, it increased the incidences of pituitary tumours and of malignant mammary tumours in both males and females and produced malignant tumours of the uterus and cervix in females [ref: 1]. In rats, it increased the incidence of liver-cell tumours [ref: 1,2], pituitary chromophobe adenomas [ref: 2] and mammary adenocarcinomas [ref: 2,3]. Ethinyloestradiol administered as a subcutaneous injection of pellets produced a low but increased incidence of renal tumours in hamsters castrated as adults [ref: 4,5]. In rats, it induced foci of altered hepatocytes, a presumed preneoplastic lesion; when administered following initiation of hepatocarcinogenesis with *N*-nitrosodiethylamine, ethinyloestradiol enhanced the development of foci of altered hepatocytes and of hepatic nodules [ref: 6]. In female rats given partial hepatectomy and treated with *N*-nitrosodiethylamine, ethinyloestradiol potentiated the development of foci of altered hepatocytes and of hepatocellular carcinomas [ref: 7]. In *N*-nitrosodiethylamine-initiated rats, ethinyloestradiol increased the number of γ-glutamyl transpeptidase-positive hepatic foci [ref: 8]. Dietary administration of ethinyloestradiol combined with subcutaneous injections of 3,2'-dimethyl-4-aminobiphenyl caused a high incidence of prostatic carcinomas in male rats [ref: 9]. In rats, ethinyloestradiol significantly enhanced the development of tumours of the liver and kidneys induced by several agents [ref: 10].

**B. Other relevant data**

No data were available on the genetic and related effects of ethinyloestradiol alone in humans. See, however, the summary of data for combined oral contraceptives.

Ethinyloestradiol did not induce chromosomal aberrations in human lymphocytes, chromosomal

aberrations or mutation in Chinese hamster cells or unscheduled DNA synthesis in rat hepatocytes *in vitro*. Studies on cell transformation were inconclusive. It was weakly active in an assay for inhibition of intercellular communication in Chinese hamster V79 cells. It did not induce sex-linked recessive lethal mutations in *Drosophila* or mutation in yeast and did not induce mutation or DNA damage in bacteria [ref: 11].

**References**


1. IARC Monographs, 21, 233-255, 1979

2. Schardein, J.L. (1980) Studies of the components of an oral contraceptive agent in albino rats. I. Estrogenic component. J. Toxicol. environ. Health, 6, 885-894

3. Holtzman, S., Stone, J.P. & Shellabarger, C.J. (1981) Synergism of estrogens and X-rays in mammary carcinogenesis in female ACI rats. J. natl Cancer Inst., 67, 455-459

4. Li, J.J., Li, S.A., Klicka, J.K., Parsons, J.A. & Lam, L.K.T. (1983) Relative carcinogenic activity of various synthetic and natural estrogens in the Syrian hamster kidney. Cancer Res., 43, 5200-5204

5. Li, J.J. & Li, S.A. (1984) Estrogen-induced tumorigenesis in hamsters: roles for hormonal and carcinogenic activities. Arch. Toxicol., 55, 110-118

6. Wanless, I.R. & Medline, A. (1982) Role of estrogens as promoters of hepatic neoplasia. Lab. Invest., 46, 313-320

7. Yager, J.D., Campbell, H.A., Longnecker, D.S., Roebuck, B.D. & Benoit, M.C. (1984) Enhancement of hepatocarcinogenesis in female rats by ethinyl estradiol and mestranol but not estradiol. Cancer Res., 44, 3862-3869

8. Yager, J.D., Roebuck, B.D., Paluszcyk, T.L. & Memoli, V.A. (1986) Effects of ethinyl estradiol and tamoxifen on liver DNA turnover and new synthesis and appearance of gamma glutamyl transpeptidase-positive foci in female rats. Carcinogenesis, 12, 2007-2014

9. Shirai, T., Fukushima, S., Ikawa, E., Tagawa, Y. & Ito, N. (1986) Induction of prostate carcinoma *in situ* at high incidence on F344 rats by a combination of 3,2'-dimethyl-4-aminobiphenyl and ethinyl estradiol. Cancer Res., 46, 6423-6426

10. Shirai, T., Tsuda, H., Ogiso, T., Hirose, M. & Ito, N. (1987) Organ specific modifying potential of ethinyl estradiol on carcinogenesis initiated with different carcinogens. Carcinogenesis, 8, 115-119

11. IARC Monographs, Suppl. 6, 293-295, 1987


**Mestranol**

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Mestranol was tested in mice, rats, dogs and monkeys by oral administration. It increased the incidence of pituitary tumours and malignant mammary tumours in mice [ref: 1,2] and increased the incidence of malignant mammary tumours in female rats. Studies in monkeys were still in progress; although no tumour had been observed after seven years, no conclusive evaluation could be made [ref: 1]. Feeding of mestranol to rats following partial hepatectomy and treatment with *N*-nitrosodiethylamine enhanced the development of foci of altered hepatocytes and of hepatocellular carcinomas [ref: 3,4]. No significant increase in mammary tumour occurrence was seen in dogs treated with mestranol [ref: 5,6].

**B. Other relevant data**

No data were available on the genetic and related effects of mestranol alone in humans. See, however, the summary of data for combined oral contraceptives.

Mestranol did not induce DNA strand breaks in hepatocytes of rats or chromosomal aberrations in bone-marrow cells of mice treated *in vivo*. It did not induce chromosomal aberrations in human lymphocytes *in vitro*. It was weakly active in an assay for inhibition of intercellular communication in Chinese hamster V79 cells. It did not induce unscheduled DNA synthesis in cultured rat hepatocytes or sex-linked recessive lethal mutations in Drosophila. It was not mutagenic to bacteria [ref: 7].

**References**

1. IARC Monographs, 21, 257-278, 1979

2. El Etreby, M.F. & Neumann, F. (1980) Influence of sex steroids and steroid antagonists on hormone-dependent tumors in experimental animals. In: Iacobelli, S., King, R.J.B., Lindner, H.R. & Lippman, M.E., eds, Hormones and Cancer, New York, Raven Press, pp. 321-336

3. Yager, J.D., Jr & Yager, R. (1980) Oral contraceptive steroids as promoters of hepatocarcinogenesis in female Sprague-Dawley rats. Cancer Res., 40, 3680-3685

4. Yager, J.D., Campbell, H.A., Longnecker, D.S., Roebuck, B.D. & Benoit, M.C. (1984) Enhancement of hepatocarcinogenesis in female rats by ethinylestradiol and mestranol but not estradiol. Cancer Res., 44, 3862-3869

5. El Etreby, M.F. & Graf, K.-J. (1979) Effect of contraceptive steroids on mammary gland of beagle dog and its relevance to human carcinogenicity. Pharmacol. Ther., 5, 369-402

6. Kwapien, R.P., Giles, R.C., Geil, R.G. & Casey, H.W. (1980) Malignant mammary tumors in beagle dogs dosed with investigational oral contraceptive steroids. J. natl Cancer Inst., 65, 137-144

7. IARC Monographs, Suppl. 6, 369-371, 1987

**Overall evaluation**

Steroidal oestrogens are *carcinogenic to humans (Group 1)*.

N.B. - This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.

For definition of the italicized terms, see Preamble Evaluation.

**Also previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

### Synonyms for Conjugated oestrogens

- Amnestrogen
- Ces
- Climestrone
- Co-Estro
- Conest
- Conestron
- Conjes
- Equigyne
- Estratab

- Estrifol
- Estroate
- Estrocon
- Estromed
- Estropan
- Evex
- Femacoid
- Femest
- Fem H
- Femogen
- Formatrix
- Ganeake
- Genisis
- Glyestrin
- Kestrin
- Menest
- Menogen
- Menotab
- Menotrol
- Milprem
- MsMed
- Neo-Estrone
- Novoconestron
- Oestrilin
- Oestro-Feminal
- Oestropak Morning
- Ovest
- Palopause
- Par Estro
- Piperazine oestrone sulphate
- PMB
- Premarin
- Presomen
- Promarit
- SK-Estrogens
- Sodestrin-H
- Sodium equilin sulphate
- Tag-39
- Transannon
- Trocosone
- Zeste

**Synonyms for Sodium oestrone sulphate**

- Conestoral
- Estrone hydrogen sulfate sodium salt
- Estrone sodium sulfate
- Estrone sulfate sodium
- Evex
- Morestin
- Oestrone hydrogen sulphate sodium salt
- Oestrone sodium sulphate
- Oestrone sulphate sodium
- Sodium estrone 3-monosulfate
- Sodium estrone sulfate
- Sodium estrone-3-sulfate
- Sodium oestrone 3-monosulphate
- Sodium oestrone sulphate
- Sodium oestrone-3-sulphate

**Synonyms for sodium equilin sulphate**

- Equilin sodium sulfate

- Equilin sodium sulphate
- Estra-1,3,5(l0),7-tetraen-17-one hydrogen sulfate sodium salt
- Oestra-1,3,5(10),7-tetraen-17-one hydrogen sulphate sodium salt
- Sodium equilin 3-monosulfate
- Sodium equilin 3-monosulphate
- Sodium equilin sulfate

**Synonyms for Piperazine oestrone sulphate**

- Estrone, hydrogen sulfate, compd. with piperazine (1:1)
- Harmogen
- Ogen
- Oestrone, hydrogen sulphate, compd. with piperazine (1:1)
- Piperazine estrone sulfate
- Piperazine 17-oxo-oestra-1,3,5(10)-trien-3-yl sulphate
- Sulestrex
- Sulestrex Piperazine

**Synonyms for Oestradiol-17 β**

- Altrad
- Aquadiol
- Aquagen
- Bardiol
- Corpagen
- C-Progynova
- Dihydrofollicular hormone
- Dihydrofolliculin
- Dihydromenformon
- Dihydrotheelin
- 3,17β-Dihydroxyestra-1,3,5-triene
- 3,17β-Dihydroxyestra-1,3,5(10)-triene
- dihydroxyestrin
- 3,17β-Dihydroxyoestra-1,3,5-triene;
- β-Dihydroxyoestra-1,3,5(10)-triene
- Dihydroxyoestrin
- Dimenformon
- Diogyn
- Diogynets
- E(2)
- 3,17-Epidihydroxyestratriene
- Estrace
- Estradiol
- β-Estradiol
- 17β-eEtradiol
- Estradiol-17β
- 3,17β-Estradiol
- d-3,17β-Estradiol
- *cis*-Estradiol
- Estra-1,3,5(10)-triene-3,17β-diol
- Estraldine
- Estrobe
- Estrovite
- Femestral
- Femogen
- Follicyclin
- Ginosedol
- Gynergon
- Gynoestryl
- Lamdiol
- Lip-Oid
- Macrodiol
- Macrol

- Microdiol
- Nordicol
- Oestergon
- Oestradiol
- β-Oestradiol
- 17β-Oestradiol
- 3,17β-Oestradiol
- d-3,17β-Oestradiol
- *cis*-oestradiol
- Oestra-1,3,5(10)-triene-3,17 β-diol
- Oestroglandol
- Ormogamma
- Ovahormon
- Ovasterol
- Ovastevol
- Ovocyclin
- Ovocylin
- Perlatanol
- Primofol
- Profoliol
- Progynon
- Progynon-DH
- Propagon-E
- Syndiol
- Test-Estrin

**Synonyms for Oestradiol 3-benzoate**

- Benovocylin
- Benzhormovarine
- Benzoestrofol
- Benzofoline
- Benzo-Gynoestryl
- De Graafina
- Diffollisterol
- Difolliculine
- Dimenformon benzoate
- Diogyn B
- Eston-B
- Estradiol benzoate
- β-Estradiol benzoate
- β-Estradiol 3-benzoate
- 17β-Estradiol 3-benzoate
- Estradiol monobenzoate
- 1,3,5(10)-Estratriene-3,17β-diol 3-benzoate
- Femestrone
- Follicormon
- Follidrin
- Graafina
- Gynecormone
- Gynformone
- Hidroestron
- Hormogynon
- Oestradiol benzoate
- β-Oestradiol benzoate
- β-Oestradiol 3-benzoate
- 17β-Oestradiol 3-benzoate
- Oestradiol monobenzoate
- 1,3,5(10)-Oestratriene-3, 17β-diol 3-benzoate
- Oestroform (BDH)
- Ovahormon benzoate
- Ovasterol-B
- Ovex
- Ovocyclin benzoate

- Ovocyclin M
- Ovocyclin-MB
- Primogyn B
- Primogyn Boleosum
- Primogyn I
- Progynon B
- Progynon-B
- Progynon benzoate
- Recthormone Oestradiol
- Solestro
- Unistradiol

**Synonyms for Oestradiol diproprionate**

- Agofollin
- Dimenformon dipropionate
- Diovocyclin
- Diovocylin
- Diprostron
- Endofollicolina D.P.
- Estradiol dipropionate
- β-Estradioldipropionate
- 17β-Estradiol dipropionate
- 3,17β-Estradiol dipropionate
- Estroici
- Estronex
- Follicyclin P
- Nacyclyl
- Oestradiol 3,17-dipropionate
- β-Oestradiol dipropionate
- 17β-Oestradiol dipropionate
- 3,17β-Oestradiol dipropionate
- Ovocyclin dipropionate
- Ovocyclin P
- Ovocyclin-P
- Progynon-DP

**Synonyms for Oestradiol-17β-valerate**

- Ardefem
- Atladiol
- Bimone-L.A.
- Cyclo-Progynova
- Deladiol
- Deladumone
- Delahormone unimatic
- Delestrogen
- Delestrogen 4X
- Depogen
- Diol-20
- Dioval
- Ditate
- Ditate DS
- Duoval-P.A.
- Dura-Estradiol
- Duragen
- Duratrad
- Estate
- Estradiol-L.A.
- Estradiol valerate
- Estradiol 17-valerate
- Estradiol 17β-valerate
- Estradiol valerianate

- Estra-L
- Estratab
- Estraval
- Estraval-P.A.
- Estroval-10
- Eval
- Femogen
- Femogen-L.A.
- Femogex
- Lastrogen
- Mal-O-Fem LA
- Neofollin
- Oestradiol retard Pharlon
- Oestradiol valerate
- Oestradiol 17-valerate
- Oestradiol 17β-valerate
- Oestradiol valerianate
- Oestragynol sine
- Pharlon
- Primogyn-Depot
- Progynon-Depot
- Progynova
- Rep-Estra
- Repestrogen
- Rep-Estro Med
- Retestrin
- Span-Est
- Teev
- Testadiate
- Valergen
- Valertest No. 1
- Valertest No. 2
- 17β-Valeryl-oxyoestra-1,3,5(10)-trien-3-ol

**Synonyms for Polyoestradiol phosphate**

- Estradiol phosphate polymer
- Estradiol polyester with phosphoric acid
- Oestradiol phosphate polymer
- Oestradiol polyester with phosphoric acid
- PEP
- Poly(estradiolphosphate)
- Poly(oestradiol phosphate)

**Synonyms for Oestriol**

- Aacifemine
- Destriol
- Deuslon-A
- 1,3,5-Estratriene-3β,16,17β-triol
- Estra-1,3,5(10)-triene-3,16α,17β-triol
- Estra-1,3,5(10)-triene-3,16α,17β-triol
- Estratriol
- Estriol
- 16α,17β-Estriol
- 3,16α,17β-Estriol
- Follicular hormone hydrate
- Hemostyptanon
- Holin
- Hormomed
- Hormonin
- 16α-Hydroxy-estradiol
- 16α-Hydroxyoestradiol

- Klimoral
- NSC-12169
- OE3
- 1,3,5-Oestratriene-3β,16,17β-triol
- Oestra-1,3,5(10)-triene-3,16α,17β-triol
- Oestra-1,3,5(10)-triene-3,16α,17 β-triol
- Oestratriol
- 16α,17 β-Oestriol
- 3,16α,17β-Oestriol
- Orgastyptin
- Ovesterin
- Ovestin
- Ovestrion
- Stiptanon
- Synapause
- Theelol
- Tridestrin
- 3,16α,17β-Trihydroxyestra-1,3,5(10)-triene
- 3,16α,-17β-Trihydroxyoestra-1,3,5(10)-triene
- 3,16α,17β-Trihydroxy-1,3,5-estratriene
- Trihydroxyestrin
- 3,16α,17β-Trihydroxy-1,3,5-oestratriene
- Trihydroxyoestrin
- Triodurin
- Triovex

**Synonyms for Oestrone**

- Andrestraq
- Aquacrine
- A.T.V.
- Bestrone
- Centrogen-20
- Cormone
- Crinovaryl
- Cristallovar
- Crystogen
- Destrone
- Di-Est Modified
- Di-Met
- Disynformon
- Duogen
- E(1)
- Endofolliculina
- Esterone
- 1,3,5-Estratrien-3-ol-17-one
- Estrol
- Estrolin
- Estromone
- Estron
- Estrone
- Estronol
- Estrovag
- Estrovarin
- Estrugenone
- Estrusol
- Evagen
- Femestrone injection
- Femidyn
- Femogen
- Femspan
- Folikrin
- Folipex
- Folisan

- Follestrine
- Follestrol
- Follicormone
- Follicular hormone
- Folliculin
- Follicunodis
- Follidrin
- Follikulin
- Foygen
- Glandubolin
- Glyestrin
- Gravigen
- Hiestrone
- Hormofollin
- Hormovarine
- Kestrin
- Kestrone
- Ketodestrin
- Ketohydroxyestrin
- Ketohydroxyoestrin
- Kolpon
- Mal-O-Fem
- Menagen
- Menformon
- Mer-Estrone
- Neo-Genic DA
- 1,3,5-Oestratrien-3-ol-17-one
- Oestrilin
- Oestrin
- Oestroform
- Oestroglandol
- Oestroperos
- Ovex
- Ovifollin
- Perlatan
- Solestrin
- Solliculin
- Spanestrin
- Testagen
- Theelin
- Thelestrin
- Thelykinin
- Tokokin
- Thynestron
- Tri-Es
- Tri-Estrin
- Unden
- Urestrin
- Wehgen
- Wynestron

**Synonyms for Ethinyloestradiol**

- Amenoron
- Brevicon
- Brevicon 28-Day
- Cavomen-F
- Chee-O-Gen
- Chee-O-Genf
- Climatone
- Declimone
- Demulen
- Demulen 28
- Diogyn-E

- Dylofor
- Edrol
- EE
- EE2
- EED
- Esteed
- Estigyn
- Estinyl
- Eston-E
- Estoral
- Estorals
- Ethidol
- Ethinoral
- Ethinylestradiol
- 17-Ethinylestradiol
- 17α-Ethinylestradiol
- 17α-Ethinyl-17β-estradiol
- 17-Ethinyl-3,17-estradiol
- Ethinylestriol
- 17-Ethinyloestradiol
- 17α-Ethinyloestradiol
- 17α-Ethinyl-17 β-oestradiol
- 17-Ethinyl-3,17-oestradiol
- Ethinyloestriol
- Ethy
- Ethy 11
- Ethynylestradiol
- 17-Ethynylestradiol
- 17α-Ethynylestradiol
- 17α-Ethynyl-1,3,5(10)-estratriene-3,17β-diol
- Ethynyloestradiol
- 17-Ethynyloestradiol
- 17α-Ethynyloestradiol
- 17α-Ethynyl-1,3,5(10)-oestratriene-3,17β-diol
- Eticyclin
- Eticyclol
- Etifollin
- Etinestrol
- Etinestryl
- Etinoestryl
- Etistradiol
- Etivex
- Feminone
- Follicoral
- Follikoral
- Ginestrene
- Gynetone
- Gynolett
- Gynostat
- Halodrin
- Inestra
- Kolpolyn
- Linoral
- Loestrin
- Loestrin 21
- Lo/Ovral
- Lo/Ovral-28
- Lynoral
- Menolet Sublets
- Menolyn
- Menopax
- Menopax Forte
- Mepilin
- Metroval
- Mixogen

- Modicon
- Modicon 28
- Neo-Estrone
- Nogest-S
- 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol
- Norlestrin 21
- Norlestrin 28
- Norlestrin Fe
- Normaoestren
- Norma-ostren
- Novestrol
- Oestradin
- Oradiol
- Orestralyn
- Os-cal Mone
- Ovcon 35
- Ovcon 50
- Ovral
- Ovral 28
- Palonyl
- Perovex
- Primogyn
- Primogyn C
- Primogyn M
- Progynon C
- Progynon M
- Roldiol
- Spanestrin
- Test-Estrin
- Trimone Sublets
- Ylestrol
- Zorane

**Synonyms for Mestranol**

- Conovid
- C-Quens
- Demulen
- Devocin
- EE3ME
- Emetin
- Enavid
- Enavid E
- Enovid
- Enovid-E
- Enovid-E21
- Ethinylestradiol 3-methyl ether
- 17α-Ethinylestradiol 3-methyl ether
- Ethinyloestradiol 3-methyl ether
- 17α-Ethinyloestradiol 3-methyl ether
- Ethynylestradiol methyl ether
- Ethynylestradiol 3-methyl ether
- 17-Ethynylestradiol 3-methyl ether
- 17α-Ethynylestradiol methyl ether
- 17α-Ethynylestradiol 3-methyl ether
- 17α-Ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol
- Ethynyloestradiol methyl ether
- Ethynyloestradiol 3-methyl ether
- 17-Ethynyloestradiol 3-methyl ether
- 17α-Ethynyloestradiol methyl ether
- 17α-Ethynyloestradiol 3-methyl ether
- 17α,-Ethynyl-3-methoxy-1,3,5(10)-oestratrien-17β-ol
- Inostral
- Lyndiol 2.5

- Menophase
- 3-Methoxy-17α-ethinylestradiol
- 3-Methoxy-17α-ethinyloestradiol
- 3-Methoxyethynylestradiol
- 3-Methoxy-17α-ethynylestradiol
- 3-Methoxyethynyloestradiol
- 3-Methoxy-17α-ethynyloestradiol
- 3-Methoxy-19-nor-17α,-pregna-1,3,5(10)-trien-20-yn-17-ol
- 3-Methylethynylestradiol
- 3-Methylethynyloestradiol
- -MVE
- Metrulen
- Norinyl
- Norinyl 1
- Norinyl 2
- Norquen
- Ortho-Novin 2
- Ortho-Novum
- Ovanon
- Ovastol
- Ovulen
- Ovulen-21
- Ovulen-28
- Previson
- SC 4725
- Sequens
- Sophia
- Syntex menophase

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Last updated: 9 February 1998

# ORAL CONTRACEPTIVES, COMBINED
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 296)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

There is sufficient evidence that combined oral contraceptives cause benign and malignant liver tumours. There is also conclusive evidence that these agents protect against cancers of the ovary and endometrium.

**Liver cancer**

Numerous case reports and series of hepatic-cell adenomas occurring almost exclusively in women who had used combined oral contraceptives strongly suggest that such benign tumours may result from exposure to these products [ref: 1]. Two case-control studies [ref: 1] have shown that risk of hepatic-cell adenomas increases strongly with duration of use and have provided estimates of the relative risk in users for more than seven and nine years duration of 500 [ref: 2] and 25 [ref:3], respectively. The many reports of focal nodular hyperplasia occurring in users of oral contraceptives could also represent a causal relationship, but these lesions also occur in men and older women, and no case-control study on these populations has been conducted.

Reports of hepatocellular carcinomas occurring in conjunction with liver-cell adenomas in users of oral contraceptives have been published [ref: 1]. In addition, three case-control studies of hepatocellular carcinomas, one in the USA [ref: 4] and two in the UK [ref: 5,6], have shown strong trends of increasing risk with duration of use. Relative risks (95% confidence limits) in the three studies in users of more than five, eight and eight years' duration, respectively, were estimated to be [13.5 (1.2-152.2)] [ref: 4], 7.2 (2.0-25.7) [ref: 5] and 20.1 (2.3-175.7) [ref: 4], respectively. When data for all three studies are combined, relative risks of 2.5 (1.1-5.5) and 10.0 (3.7-27.2) in 'ever' users and users for more than five to eight years (depending on the study) were derived by the Working Group. Although all three case-control studies of liver cancers and oral contraceptives are small and have methodological deficiencies that could have resulted in biased results, the magnitude of the relative risks and the consistency of the results provide strong evidence that the results are not spurious. Case reports of cholangiocarcinoma in users of oral contraceptives have also been published, but one case-control study of 11 cases [ref: 6] showed no association with use of oral contraceptives [(relative risk, 0.3 in women who ever used oral contraceptives; 0.9 in users of four or more years)].

**Ovarian cancer**

Ten case-control studies have provided the following estimates of the relative risk (95% confidence limits) for ovarian cancer in women who had ever used combined oral contraceptives: 0.6 [0.3-1.1] [ref: 7], [0.7 (0.4-1.1)] [ref: 8], 0.8 (0.4-1.5) [ref: 9], 0.5 (0.2-1.5) [ref: 10], 0.6 [0.4-1.0] [ref: 11], 0.7 (0.4-1.1) [ref: 12], 0.4 (0.2-1.0) [ref: 13], 0.6 (0.4-0.9) [ref: 14], 0.6 (0.4-0.9) [ref: 15] and 0.6 (0.4-1.0) [ref: 16]. Six of these studies assessed risk in relation to duration of use and five provide at least some evidence that the risk declines with years of exposure, although this trend is less striking than that for endometrial cancer (see below). Relative risks in women who had used combined oral contraceptives for up to or more than five, five, seven and nine years were found in four different studies to be 0.3 (0.1-0.8) [ref: 14], 0.4 (0.2-0.6) [ref: 15], 0.6 [0.3-1.4] [ref: 8] and 0.4 (0.2-1.3) [ref: 11].

**Endometrial cancer**

Five case-control studies have provided the following estimates of the relative risk (95% confidence limits) for endometrial cancer in women who had ever used combined oral contraceptives: 0.5 (0.1-1.0) [ref: 17], 0.4 (0.2-0.8) [ref: 18], 0.4 [0.2-1.2] [ref: 19], 0.5 (0.3-0.8) [ref: 20] and 0.6 (0.2-

1.3) [ref: 16]. Three of these [ref: 18-20], and two others [ref: 21,22], assessed risk in relation to duration of use, and all showed a decline in risk with duration of exposure. Relative risks in users of five or more years' duration were estimated in two studies to be 0.3 (0.1-1.3) [ref: 19] and 0.6 (0.4-0.9) [ref: 20], and one study showed a relative risk of 0.1 [ref: 22] in women with six or more years of use.

**Cervical cancer**

Four case-control studies [ref: 23-26] of cervical squamous dysplasia provide estimates of relative risk in women who had ever used combined oral contraceptives ranging from 1.2 to 3, and the lower limit of the 95% confidence limits of two of the estimates was greater than one. Relative risks (95% confidence limits) from two cohort studies were [5.0 (1.2-20.8)] [ref: 1], 1.5 [(0.8-2.6)] [ref: 27] and 1.1 [(0.8-1.7)] [ref: 28]. Relative risks for squamous dysplasia were found to increase with duration of use in two [ref: 24,26] of three case-control studies in which risk in relation to length of exposure was considered, and those for women who had used oral contraceptives for more than four years were found in two cohort studies to be [4.9 (1.1-21.8) [ref: 1]] and 2.0 [(1.1-3.6)] [ref: 27].

Four case-control studies of cervical carcinoma *in situ* [ref: 1,23-25] provide estimates of relative risks in women who had ever used combined oral contraceptives ranging from 0.6 to 1.1 [ref: 25], with 95% confidence limits that include 1.0; but one additional such study yielded an estimated relative risk of [1.6 (1.2-2.0)] [ref: 1], and estimates from three cohort studies were [3.7 (1.5-9.0)] [ref: 1], 1.6 [(0.8-3.0)] [ref: 27] and 1.2 (0.8-1.7) [ref: 28]. One case-control study showed a strong increase in risk for carcinoma *in situ* with duration of use [ref: 24], but two others did not [ref: 1,25]. Relative risks in users of more than four years' duration were estimated in two cohort studies to be [5.4 (2.1-13.7)] [ref: 1] and 1.7 [(0.9-3.2)] [ref: 27]. Another cohort study [ref: 1] showed the risk of progression from dysplasia to carcinoma in situ to be six times greater in users than in nonusers of oral contraceptives.

Three case-control studies of invasive cervical cancer yielded relative risks in women who had ever used combined oral contraceptives of 1.2 (1.0-1.4) [ref: 29], 1.5 (1.1-2.1) [ref: 30] and 1.7 (0.8-3.6) [ref: 16]; and three cohort studies gave incidence rates of invasive cervical cancer per 1000 women years in users and nonusers of oral contraceptives of 0.20 and 0 [ref: 27], 0.15 and 0.07 [ref: 31] and 0.12 and 0 [ref: 28]. All three case-control studies also showed that risk increased with duration of use; and the two in which relative risks were assessed in women who had used oral contraceptives for more than five years gave values of 1.5 (1.1-2.1) [ref: 29] and [1.9 (1.3-2.7)] [ref: 30].

There is evidence that one or more sexually transmitted, infective agents play an important role in the development of cervical cancer. Since this agent(s) has not been unequivocally identified, and, in particular, was not considered in the studies under review, surrogate measures were used to reflect degree of sexual activity and to adjust for this. Any observed effect of oral contraceptives on risk of cervical cancer may therefore be confounded by an association of oral contraceptive use with exposure to the putative infective agent. Since the specific factor by which the analysis should be adjusted is not known, the Working Group considered that adjusting for age at first intercourse and number of sexual partners may not be sufficient to remove the confounding and, therefore, that they could not regard a causal association of oral contraceptives and cervical cancer as proven.

**Breast cancer**

Relative risks for breast cancer in women who had ever used combined oral contraceptives have been assessed in 18 case-control studies [ref: 1,16,32-43] and in seven cohort studies [ref: 1,44-47]. All provide point estimates of relative risk close to unity, with 95% confidence intervals that include 1.0. Six case-control studies have provided estimates of the relative risk in women who had used combined oral contraceptives for more than a decade: four [ref: 36,39,40,43] yield relative risks between 0.7 and 1.1 with 95% confidence limits that included 1.0 in users of ten or more years' duration; another [ref: 48] provides a relative risk estimate of 2.2 (1.2-4.0) in users of 12 or more years' duration; and one [ref: 42] gives a relative risk of 0.6 (0.4-0.9) in women who had used oral contraceptives for 15 or more years. Eight case-control studies [ref: 16,36-38,40,42,43,48] and two cohort studies [ref: 44,45] give estimated relative risks for breast cancer ten or more to 20 or more years after initial exposure to combined oral contraceptives, and all are close to 1.0, with 95% confidence intervals that include unity. Eleven case-control studies have assessed risk for breast

cancer among women who had used combined oral contraceptives before their first full-term pregnancy. The results are inconsistent, six studies [ref: 39,40,43,47,49,50] showing no significant elevation in risk, three [ref: 34,37,51] showing a significant trend of increasing risk with duration of use, and two [ref: 48,52] showing an increased risk without a significant trend. The reasons for these discrepant findings have not been identified. Five case-control studies have assessed risk in women who had used combined oral contraceptives before 25 years of age. The initial study of this issue showed a strong trend of increasing risk with years of use before age 25 [ref: 53]. A subsequent study from Sweden [ref: 54] showed a relative risk of 3.3 in women who had ever used oral contraceptives at age 20-24, but ascertainment of prior use was not comparable for cases and controls, rendering this finding suspect. Another study from Norway and Sweden [ref: 48] gave a relative risk of 2.7 in women who had used oral contraceptives for eight or more years before the age of 25, but the confidence limits for this included 1.0 (0.7-11.0), and no consistent trend of increasing risk with duration of use was observed. The fourth study, from New Zealand [ref: 43], showed a nonsignificant ($p$ = 0.4) trend of declining risk with duration of use before age 25 and estimated the relative risk in users of six or more years to be 0.6. The fifth study [ref: 50] gave relative risks of 1.0 to 1.3 in six categories of duration of use (< 12, 13-48 and > 48 months in women less than 20 and in women 20-24 years of age) but no trend of increasing risk with duration of use. Risk was also initially reported to be particularly enhanced by use before age 25 [ref: 53] of oral contraceptives with a high progestogen potency, but the authors' classification has been disputed; and results from a large collaborative study in the USA do not confirm their findings [ref: 50].

**Other tumours**

The relative risk for malignant melanoma in women who had ever taken oral contraceptives has been estimated in eight case-control [ref: 1,55-61] and in three cohort [ref: 55,62,63] studies. Values from all the case-control studies were close to unity, with 95% confidence limits that included 1.0. Values from the three cohort studies were 0.3 [0.1-0.8] [ref: 55], 1.5 (0.7-2.9) [ref: 62] and 3.5 (1.4-9.0) [ref: 63]. The reasons for these widely discrepant results are unknown. Trends of increasing risk with duration of use have been observed in some investigations but not in others. The two case-control studies in which analyses were performed to estimate the relative risk in users of more than two [ref: 56] and five [ref: 59] years' duration, ten or more years after initial exposure, showed elevated risks of 2.3 (0.8-6.9) and 1.5 (1.0-2.1), respectively. Two case-control studies showed trends of increasing risk specifically for superficial spreading melanoma with increasing duration of use [ref: 57,60], although a third did not [ref: 63]. Also, two studies have shown relative risks for superficial spreading-type melanoma to be increased in users of five or more years' duration after latent periods of over ten [ref: 59] and 12 [ref: 57] years: [1.6 (1.0-2.6)] and 4.4 (2.0-9.7), respectively.

Two case-control studies and two prospective studies have shown no increase in risk for pituitary adenomas [ref: 1,64,65].

Women who took oral contraceptives after evacuation of a hydatidiform mole were reported in one study [ref: 1] subsequently to have developed trophoblastic tumours more frequently than women who had used other methods of contraception after a molar evacuation, but this was not confirmed in another investigation [ref: 66].

A single case-control study showed a reduction in risk for carcinomas of the colon and rectum with duration of use of combined oral contraceptives [ref: 67], but two cohort studies showed no alteration in risk for these neoplasms in users [ref: 63,68].

A protective effect of combined oral contraceptives against both fibroadenoma and fibrocystic disease of the breast has been found in many investigations [ref: 1,63,69-72], although a single recent study found an increase in risk for the latter condition in postmenopausal women [ref: 73]. One study showed no protective effect of oral contraceptives against fibrocystic disease with atypical histological features [ref: 1], but one subsequent investigation did [ref: 70].

A reduction in risk for retention cysts of the ovary has been documented in two cohort studies and in one case-control study [ref: 1]. A reduction in risk for uterine leiomyoma has been documented in one case-control study [ref: 74].

**B. Evidence for carcinogenicity to animals** (*sufficient* for norethynodrel in combination with mestranol; limited for chlormadinone acetate in combination with mestranol or ethinyloestradiol, for ethynodiol acetate in combination with mestranol or ethinyloestradiol, for megestrol acetate in combination with ethinyloestradiol, for norethisterone in combination with mestranol or ethinyloestradiol, for progesterone in combination with oestradiol-17β, and for investigational contraceptives; *inadequate* for lynoestrenol in combination with mestranol and for norgestrel in combination with ethinyloestradiol)

**Chlormadinone acetate and oestrogens**

Chlormadinone acetate, in combination with mestranol, was tested for carcinogenicity by oral administration to mice; an increased incidence of pituitary tumours was observed in animals of each sex. Oral administration of chlormadinone acetate in combination with ethinyloestradiol to mice resulted in an increased incidence of mammary tumours in intact and castrated males [ref: 75].

**Ethynodiol diacetate and oestrogens**

Following oral administration of ethynodiol diacetate plus mestranol to mice, increased incidences of pituitary tumours were observed in animals of each sex. Ethynodiol diacetate plus ethinyloestradiol was tested for carcinogenicity by oral administration to mice and rats. In mice, it induced increased incidences of pituitary tumours in animals of each sex and of malignant tumours of connective tissues of the uterus. In rats, malignant mammary tumours were produced in animals of each sex [ref: 76].

**Lynoestrenol and oestrogens**

Lynoestrenol, in combination with mestranol, was tested in mice and female rats by oral administration. A slight, nonsignificant increase in the incidence of malignant mammary tumours was observed in female mice [ref: 77].

**Megestrol acetate and oestrogens**

Megestrol acetate plus ethinyloestradiol was tested for carcinogenicity by oral administration to mice and rats. In mice, increased incidences of malignant mammary tumours were observed in animals of each sex. No increase in tumour incidence was observed in rats [ref: 78].

**Norethisterone and oestrogens**

Norethisterone acetate plus ethinyloestradiol was tested for carcinogenicity by oral administration to mice, rats and monkeys. In mice, pituitary tumours were observed in animals of each sex. In rats, increased incidences of benign mammary tumours were found in males in one study and of benign liver-cell and mammary tumours in animals of each sex in the other [ref: 79]. Norethisterone acetate plus ethinyloestradiol administered orally to rats induced endometrial carcinomas [ref: 80]. Oral administration of norethisterone acetate plus ethinyloestradiol to female rats for 12 months resulted in hyperplastic nodules of the liver in all animals and a hepatocellular carcinoma in one (preliminary results) [ref: 81]. Norethisterone acetate and ethinyloestradiol given orally to monkeys for ten years did not produce malignant tumours [ref: 82].

Norethisterone plus mestranol was tested for carcinogenicity in mice and rats by oral administration. In mice, pituitaty tumours developed in animals of each sex. In rats, an increased incidence of malignant mammary tumours was found in females. Norethisterone plus ethinyloestradiol, tested in mice by oral administration, induced an increased incidence of pituitary tumours in females [ref: 79].

**Norethynodrel and oestrogens**

Norethynodrel in combination with mestranol was tested for carcinogenicity in mice, rats, hamsters and monkeys orally and by subcutaneous implantation. Increased incidences of pituitary, mammary, vaginal and cervical tumours were found in female mice and of pituitary tumours in male mice. In

castrated male mice, the combined treatment resulted in an increase in the incidence of mammary tumours. In rats, benign liver-cell tumours were observed in males and pituitary tumours and malignant mammary tumours in animals of each sex. A study of hamsters was of too short a duration to be considered for evaluation. The combined treatment given to *Macaca mulatta* monkeys for five years did not increase the incidence of mammary tumours [ref: 83].

**Norgestrel and oestrogens**

Norgestrel plus ethinyloestradiol was tested for carcinogenicity in mice and rats by oral administration. No increase in the incidence of tumours was observed in either species [ref: 84].

**Progesterone and oestrogen**

Neonatal exposure of mice to progesterone plus oestradiol-17β resulted in an increased incidence of mammary tumours [ref: 85].

**Investigational oral contraceptives**

Three investigational oral contraceptives (ethynerone, chloroethynyl norgestrel or anagestone acetate plus mestranol) were tested for carcinogenicity by oral administration to dogs. An increased incidence of malignant mammary tumours was observed after treatment with chloroethynyl norgestrel plus mestranol or with anagestone acetate plus mestranol; no difference in the total number of mammary-gland nodules was observed with these two contraceptives. One dog given ethynerone plus mestranol had 14 malignant mammary fibrosarcomas [ref: 86].

**C. Other relevant data**

The results reported in the available studies related to a variety of different oral contraceptives.

Several studies showed no increase in the incidence of structural chromosomal changes in lymphocytes taken from women after oral contraceptive use (norethisterone with mestranol or ethynodiol diacetate with mestranol). In contrast to an earlier report, no increase in the incidence of sister chromatid exchanges was observed in 52 women taking oral contraceptives as compared with 63 controls when results were adjusted for smoking [ref: 87].

No significant difference in the frequency of abnormal karyotypes or in sex ratio was seen in a study of spontaneous abortuses of women who had taken oral contraceptives; the contraceptives used were norgestrel, norethisterone acetate or medroxyprogesterone acetate in combination with ethinyloestradiol; or ethynodiol acetate, megestrol acetate or lynoestrenol in combination with mestranol. Similarly, a large cohort study showed no increase in risk for chromosomal anomalies in live births and abortuses of oral contraceptive users [ref: 87].

High doses of one oral contraceptive (lynoestrenol and mestranol) administered to two strains of female mice induced dominant lethal mutations, whereas high doses of another (norethisterone and ethinyl oestradiol) did not. In a later report using even higher doses of the oral contraceptive that induced dominant lethal mutations and of another (norethisterone acetate and ethinyloestradiol), the same authors reported no increase in the incidence of dominant lethal, recessive lethal or visible mutations in mice. Combinations of progestins (norethynodrel and ethynodiol diacetate) and oestrogens (mestranol and ethinyloestradiol) did not induce sex-linked recessive lethal mutations in *Drosophila* [ref: 87].

**Overall evaluation**

Combined oral contraceptives are *carcinogenic to humans (Group 1)*.

N.B. - There is also conclusive evidence that these agents have a protective effect against cancers of the ovary and endometrium.

For definition of the italicized terms, see Preamble Evaluation.

**Also previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

**Subsequent evaluation**: Vol. 72 (1999)

**References**


1. IARC Monographs, 21, 103-129, 133-134, 1979

2. Rooks, J.B., Ory, H.W., Ishak, K.G., Strauss, L.T., Greenspan, J.R. & Tyler, C.W., Jr (1977) The association between oral contraception and hepatocellular adenoma - a preliminary report. Int. J. Gynaecol. Obstet., 15, 143-144

3. Edmondson, H.A., Henderson, B. & Benton, B. (1976) Liver-cell adenomas associated with use of oral contraceptives. New Engl. J. Med., 294, 470-472

4. Henderson, B.E., Preston-Martin, S., Edmondson, H.A., Peters, R.L. & Pike, M.C. (1983) Hepatocellular carcinoma and oral contraceptives. Br. J. Cancer, 48, 437-440

5. Neuberger, J., Forman, D., Doll, R. & Williams, R. (1986) Oral contraceptives and hepatocellular carcinoma. Br. med. J., 292, 1355-1357

6. Forman, D., Vincent, T.J. & Doll, R. (1986) Cancer of the liver and the use of oral contraceptives. Br. med. J., 292, 1357-1361

7. Newhouse, M.L., Pearson, R.M., Fullerton, J.M., Boesen, E.A.M. & Shannon, H.S. (1977) A case control study of carcinoma of the ovary. Br. J. prev. soc. Med., 31, 148-153

8. Casagrande, J.T., Pike, M.C., Ross, R.K., Louie, E.W., Roy, S. & Henderson, B.E. (1979) 'Incessant ovulation' and ovarian cancer. Lancet, ii, 170-173

9. Willett, W.C., Bain, C., Hennekens, C.H., Rosner, B. & Speizer, F.E. (1981) Oral contraceptives and risk of ovarian cancer. Cancer, 48, 1684-1687

10. Hildreth, N.G., Kelsey, J.L., LiVolsi, V.A., Fischer, D.B., Holford, T.R., Mostow, E.D., Schwartz, P.E. & White, C. (1981) An epidemiologic study of epithelial carcinoma of the ovary. Am. J. Epidemiol., 114, 398-405

11. Weiss, N.S., Lyon, J.L., Liff, J.M., Vollmer, W.M. & Daling, J.R. (1981) Incidence of ovarian cancer in relation to the use of oral contraceptives. Int. J. Cancer, 28, 669-671

12. Franceschi, S., La Vecchia, C., Helmrich, S.P., Mangioni, C. & Tognoni, G. (1982) Risk factors for epithelial ovarian cancer in Italy. Am. J. Epidemiol., 115, 714-719

13. Cramer, D.W., Hutchison, G.B., Welch, W.R., Scully, R.E. & Knapp, R.C. (1982) Factors affecting the association of oral contraceptives and ovarian cancer. New Engl. J. Med., 307, 1047-1051

14. Rosenberg, L., Shapiro, S., Slone, D., Kaufman, D.W., Helmrich, S.P., Miettinen, O.S., Stolley, P.D., Rosenshein, N.B., Schottenfeld, D. & Engle, R.L., Jr (1982) Epithelial ovarian cancer and combination oral contraceptives. J. Am. med. Assoc., 247, 3210-3212

15. Centers for Disease Control Cancer and Steroid Hormone Study (1983) Oral contraceptive use and the risk of ovarian cancer. J. Am. med. Assoc., 249, 1596-1599

16. La Vecchia, C., Decarli, A., Fasoli, M., Franceschi, S., Gentile, A., Negri, E., Parazzini, F. & Tognoni, G. (1986) Oral contraceptives and cancers of the breast and of the female genital tract. Interim results from a case-control study. Br. J. Cancer, 54, 311-317

17. Weiss, N.S. & Sayvetz, T.A. (1980) Incidence of endometrial cancer in relation to the use of oral contraceptives. New Engl. J. Med., 302, 551-554

18. Kaufman, D.W., Shapiro, S., Slone, D., Rosenberg, L., Miettinen, O.S., Stolley, P.D., Knapp, R.C., Leavitt, T., Jr, Watring, W.G., Rosenshein, N.B., Lewis, J.L., Jr, Schottenfeld, D. & Engle, R.L., Jr (1980) Decreased risk of endometrial cancer among oral-contraceptive users. New Engl. J. Med., 303, 1045-1047

19. Hulka, B.S., Chambless, L.E., Kaufman, D.G., Fowler, W.C., Jr & Greenberg, B.G. (1982) Protection against endometrial carcinoma by combination-product oral contraceptives. J. Am. med. Assoc., 247, 475-477

20. Centers for Disease Control Cancer and Steroid Hormone Study (1983) Oral contraceptive use and the risk of endometrial cancer. J. Am. med. Assoc., 249, 1600-1604

21. Kelsey, J.L., LiVolsi, V.A., Holford, T.R., Fischer, D.B., Mostow, E.D., Schwartz, P.E., O'Connor, T. & White, C. (1982) A case-control study of cancer of the endometrium. Am. J. Epidemiol., 116, 333-342

22. Henderson, B.E., Casagrande, J.T., Pike, M.C., Mack, T., Rosario, I. & Duke, A. (1983) The epidemiology of endometrial cancer in young women. Br. J. Cancer, 47, 749-756

23. Thomas, D.B. (1972) Relationship of oral contraceptives to cervical carcinogenesis. Obstet. Gynecol., 40, 508-518

24. Ory, H.W., Conger, S.B., Naib, Z., Tyler, C.W., Jr & Hatcher, R.A. (1977) Preliminary analysis of oral contraceptives use and risk for developing premalignant lesions of the uterine cervix. In: Garattini, S. & Berendes, H.W., eds, Pharmacology of Steroid Contraceptive Drugs, New York, Raven Press, pp. 211-218

25. Fasal, E., Simmons, M.E. & Kampert, J.B. (1981) Factors associated with high and low risk of cervical neoplasia. J. natl Cancer Inst., 66, 631-636

26. Clarke, E.A., Hatcher, J., McKeown-Eyssen, G.E. & Lickrish, G.M. (1985) Cervical dysplasia: association with sexual behavior, smoking, and oral contraceptive use? Am. J. Obstet. Gynecol., 151, 612-616

27. Vessey, M.P., McPherson, K., Lawless, M. & Yeates, D. (1983) Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill. Lancet, ii, 930-934

28. Andolsek, L., Kovácic, J., Kozuh, M. & Litt, B. (1983) Influence of oral contraceptives on the incidence of premalignant and malignant lesions of the cervix. Contraception, 28, 505-519

29. WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1985) Invasive cervical cancer and combined oral contraceptives. Br. med. J., 290, 961-965

30. Brinton, L.A., Huggins, G.R., Lehman, H.F., Mallin, K., Savitz, D.A., Trapido, E., Rosenthal, J. & Hoover, R. (1986) Long-term use of oral contraceptives and risk of invasive cervical cancer. Int. J. Cancer, 38, 339-344

31. Kay, C.R. (1983) Oral contraceptives and cancer. Lancet, ii, 1018

32. Henderson, B.E., Powell, D., Rosario, I., Keys, C., Hanisch, R., Young, M., Casagrande, J., Gerkins, V. & Pike, M.C. (1974) An epidemiologic study of breast cancer. J. natl Cancer Inst., 53, 609-614

33. Ravnihar, B., Seigel, D.G. & Lindtner, J. (1979) An epidemiologic study of breast cancer and benign breast neoplasias in relation to the oral contraceptive and estrogen use. Eur. J. Cancer, 15, 395-405

34. Pike, M.C., Henderson, B.E., Casagrande, J.T., Rosario, I. & Gray, G.E. (1981) Oral contraceptive use and early abortion as risk factors for breast cancer in young women. Br. J. Cancer, 43, 72-76

35. Kelsey, J.L., Fisher, D.B., Holford, T.R., LiVolsi, V.A., Mostow, E.D., Goldenberg, I.S. & White, C. (1981) Exogenous estrogens and other factors in the epidemiology of breast cancer. J. natl Cancer Inst., 67, 327-333

36. Brinton, L.A., Hoover, R., Szklo, M. & Fraumeni, J.F., Jr (1982) Oral contraceptives and breast cancer. Int. J. Epidemiol., 11, 316-322

37. Harris, N.V., Weiss, N.S., Francis, A.M. & Polissar, L. (1982) Breast cancer in relation to patterns of oral contraceptive use. Am. J. Epidemiol., 116, 643-651

38. Vessey, M., Baron, J., Doll, R., McPherson, K. & Yeates, D. (1983) Oral contraceptives and breast cancer: final report of an epidemiological study. Br. J. Cancer, 47, 455-462

39. Hennekens, C.H., Speizer, F.E., Lipnick, R.J., Rosner, B., Bain, C., Belanger, C., Stampfer, M., Willett, W. & Peto, R. (1984) A case-control study of oral contraceptive use and breast cancer. J. natl Cancer Inst., 72, 39-42

40. Rosenberg, L., Miller, D.R., Kaufman, D.W., Helmrich, S.P., Stolley, P.D., Schottenfeld, D. & Shapiro, S. (1984) Breast cancer and oral contraceptive use. Am. J. Epidemiol., 119, 167-176

41. Talamini, R., La Vecchia, C., Franceschi, S., Colombo, F., Decarli, A., Grattoni, E., Grigoletto, E. & Tognoni, G. (1985) Reproductive and hormonal factors and breast cancer in a northern Italian population. Int. J. Epidemiol., 14, 70-74

42. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development (1986) Oral-contraceptive use and the risk of breast cancer. New Engl. J. Med., 315, 405-411

43. Paul, C., Skegg, D.C.G., Spears, G.F.S. & Kaldor, J.M. (1986) Oral contraceptives and breast cancer: a national study. Br. med. J., 293, 723-726

44. Vessey, M.P., McPherson, K. & Doll, R. (1981) Breast cancer and oral contraceptives: findings in Oxford-Family Planning Association contraceptive study. Br. med. J., 282, 2093-2094

45. Trapido, E.J. (1981) A prospective cohort study of oral contraceptives and breast cancer. J. natl Cancer Inst., 67, 1011-1015

46. Royal College of General Practitioners (1981) Breast cancer and oral contraceptives: findings in Royal College of General Practitioners' study. Br. med. J., 282, 2089-2093

47. Lipnick, R.J., Buring, J.E., Hennekens, C.H., Rosner, B., Willett, W., Bain, C., Stampfer, M.J., Colditz, G.A., Peto, R. & Speizer, F.E. (1986) Oral contraceptives and breast cancer. A prospective cohort study. J. Am. med. Assoc., 255, 58-61

48. Meirik, O., Adami, H.-O., Christoffersen, T., Lund, E., Bergström, R. & Bergsjö, P. (1986) Oral contraceptive use and breast cancer in young women. A joint national case-control study in Sweden and Norway. Lancet, ii, 650-654

49. Vessey, M.P., McPherson, K., Yeates, D. & Doll, R. (1982) Oral contraceptive use and abortion before first term pregnancy in relation to breast cancer risk. Br. J. Cancer, 45, 327-331

50. Stadel, B.V., Webster, L.A., Rubin, G.L., Schlesselman, J.J. & Wingo, P.A. (1985) Oral contraceptives and breast cancer in young women. Lancet, ii, 970-973

51. McPherson, K., Neil, A., Vessey, M.P. & Doll, R. (1983) Oral contraceptives and breast cancer. Lancet, ii, 1414-1415

52. Paffenbarger, R.S., Jr, Kampert, J.B. & Chang, H.-G. (1980) Characteristics that predict risk of breast cancer before and after the menopause. Am. J. Epidemiol., 112, 258-268

53. Pike, M.C., Krailo, M.D., Henderson, B.E., Duke, A. & Roy, S. (1983) Breast cancer in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet, ii, 926-930

54. Olsson, H., Olsson, M.L., Möller, T.R., Ranstam, J. & Holm, P. (1985) Oral contraceptive use and breast cancer in young women in Sweden. Lancet, i, 748-749

55. Adam, S.A., Sheaves, J.K., Wright, N.H., Mosser, G., Harris, R.W. & Vessey, M.P. (1981) A case-control study of the possible association between oral contraceptives and malignant melanoma. Br. J. Cancer, 44, 45-50

56. Bain, C., Hennekens, C.H., Speizer, F.E., Rosner, B., Willett, W. & Belanger, C. (1982) Oral contraceptive use and malignant melanoma. J. natl Cancer Inst., 68, 537-539

57. Holly, E.A., Weiss, N.S. & Liff, J.M. (1983) Cutaneous melanoma in relation to exogenous hormones and reproductive factors. J. natl Cancer Inst., 70, 827-831

58. Helmrich, S.P., Rosenberg, L., Kaufman, D.W., Miller, D.R., Schottenfeld, D., Stolley, P.D. & Shapiro, S. (1984) Lack of an elevated risk of malignant melanoma in relation to oral contraceptive use. J. natl Cancer Inst., 72, 617-620

59. Beral, V., Evans, S., Shaw, H. & Milton, G. (1984) Oral contraceptive use and malignant melanoma in Australia. Br. J. Cancer, 50, 681-685

60. Holman, C.D.J., Armstrong, B.K. & Heenan, P.J. (1984) Cutaneous malignant melanoma in women: exogenous sex hormones and reproductive factors. Br. J. Cancer, 50, 673-780

61. Gallagher, R.P., Elwood, J.M., Hill, G.B., Coldman, A.J., Threlfall, W.J. & Spinelli, J.J. (1985) Reproductive factors, oral contraceptives and risk of malignant melanoma: Western Canada melanoma study. Br. J. Cancer, 52, 901-907

62. Kay, C.R. (1981) Malignant melanoma and oral contraceptives. Br. J. Cancer, 44, 479

63. Ramcharan, S., Pellegrin, F.A., Ray, R. & Hsu, J.-P. (1981) The Walnut Creek Contraceptive Drug Study. A Prospective Study of the Side Effects of Oral Contraceptives (NIH Publ. No. 81-564), Bethesda, MD, National Institutes of Health, pp. 49, 53-55

64. Wingrave, S.J., Kay, C.R. & Vessey, M.P. (1980) Oral contraceptives and pituitary adenomas. Br. med. J., i, 685-686

65. Shy, K.K., McTiernan, A.M., Daling, J.R. & Weiss, N.S. (1983) Oral contraceptive use and the occurrence of pituitary prolactinoma. J. Am. med. Assoc., 249, 2204-2207

66. Berkowitz, R.S., Marean, A.R., Goldstein, D.P. & Bernstein, M.R. (1980) Oral contraceptives and post-molar trophoblastic tumours. Lancet, ii, 752

67. Potter, J.D. & McMichael, A.J. (1983) Large bowel cancer in women in relation to reproductive and hormonal factors: a case-control study. J. natl Cancer Inst., 71, 703-709

68. Weiss, N.S., Daling, J.R. & Chow, W.H. (1981) Incidence of cancer of the large bowel in women in relation to reproductive and hormonal factors. J. natl Cancer Inst., 67, 57-60

69. Brinton, L.A., Vessey, M.P., Flavel, R. & Yeates, D. (1981) Risk factors for benign breast disease. Am. J. Epidemiol., 113, 203-214

70. Pastides, H., Kelsey, J.L., LiVolsi, V.A., Holford, T.R., Fischer, D.B. & Goldenberg, I.S. (1983) Oral contraceptive use and fibrocystic breast disease with special reference to its histopathology. J. natl Cancer Inst., 71, 5-9

71. Hsieh, C.-C., Crosson, A.W., Walker, A.M., Trapido, E.J. & MacMahon, B. (1984) Oral contraceptive use and fibrocystic breast disease of different histologic classifications. J. natl Cancer Inst., 72, 285-290

72. Hislop, T.G. & Threlfall, W.J. (1984) Oral contraceptives and benign breast disease. Am. J. Epidemiol., 120, 273-280

73. Berkowitz, G.S., Kelsey, J.L., LiVolsi, V.A., Holford, T.R., Merino, M.J., Ort, S., O'Connor, T.Z., Goldenberg, I.S. & White, C. (1984) Oral contraceptive use and fibrocystic breast disease among pre- and postmenopausal women. Am. J. Epidemiol., 120, 87-96

74. Ross, R.K., Pike, M.C.,Vessey, M.P., Bull, D., Yeates, D. & Casagrande, J.T. (1986) Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. Br. med. J., 293, 359-362

75. IARC Monographs, 21, 233-255, 257-278, 365-365, 1979

76. IARC Monographs, 21, 233-255, 257-278, 387-395, 1979

77. IARC Monographs, 21, 233-255, 407-415, 1979

78. IARC Monographs, 21, 257-278, 431-439, 1979

79. IARC Monographs, 21, 233-255, 257-278, 441-460, 1979

80. El Etreby, M.F. & Neumann, F. (1980) Influence of sex steroids and steroid antagonists on hormone-dependent tumors in experimental animals. In: Iacobelli, S., King, R.J.B., Lindner, H.R. & Lippman, M.E., eds, Hormones and Cancer, New York, Raven Press, pp. 321-336

81. Higashi, G., Tomita, T., Mizumoto, R. & Nakakuki, K. (1980) Development of hepatoma in rats following oral administration of synthetic oestrogen and progesterone. Gann, 71, 576-577

82. Fitzgerald, J., de la Iglesia, F. & Goldenthal, E.I. (1982) Ten-year oral toxicity study with norlestin in rhesus monkeys. J. Toxicol. environ. Health, 10, 879-896

83. IARC Monographs, 21, 233-255, 461-477, 1979

84. IARC Monographs, 21, 257-278, 479-490, 1979

85. IARC Monographs, 21, 279-326, 491-515, 1979

86. Kwapien, R.P., Giles, R.C., Gell, R.G. & Casey, H.W. (1980) Malignant mammary tumors in beagle dogs dosed with investigational oral contraceptive steroids. J. natl Cancer Inst., 65, 137-144

87. IARC Monographs, Suppl. 6, 444, 1987

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Last updated: 9 February 1998

# ORAL CONTRACEPTIVES, SEQUENTIAL
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 296)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Case reports of endometrial cancer occurring at an unusually young age in users of sequential oral contraceptives provide evidence that these preparations can cause endometrial cancer [ref: 1]. Three case-control studies have provided the following estimates of the relative risk (and 95% confidence intervals) for endometrial cancer in women who had used sequential oral contraceptives: 2.2 (0.6-7.3) [ref: 2], 2.1 (0.8-5.8) [ref: 3] and [1.9 (0.7-5.3)] [ref: 4]. One study [ref: 2] showed a relative risk of 7.3 (1.4-38.8) in users of a preparation that contained a relatively large amount of a potent oestrogen (0.1 mg ethinyloestradiol) and only a weak progestin (25 mg dimethisterone); another [ref: 4] showed a relative risk of 4.6 in users of more than two years' duration. The finding of an increased risk for endometrial cancer in relation to sequential oral contraceptives is in contrast with a reduction in risk for endometrial cancer found in association with the use of combined oral contraceptives.

**B. Evidence for carcinogenicity to animals** (*inadequate* for dimethisterone in combination with ethinyloestradiol)

*Dimethisterone and oestrogen*

When dimethisterone and ethinyloestradiol were given sequentially to female dogs by oral administration, a few palpable mammary nodules were reported to have occurred in treated (4/16) and in untreated animals (2/16) [ref: 5].

**C. Other relevant data**

No adequate data were available on the genetic and related effects of sequential oral contraceptives in humans. See, however, the summaries of data on individual compounds commonly found in sequential oral contraceptives: chlormadinone acetate, dimethistereone, ethinyloestradiol and mestranol.

**Overall evaluation**

Sequential oral contraceptives are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

**References**

1. IARC Monographs, 21, 111-112, 133, 1979

2. Weiss, N.S. & Sayvetz, T.A. (1980) Incidence of endometrial cancer in relation to the use of oral contraceptives. New Engl. J. Med., 302, 551-554

3. Centers for Disease Control Cancer and Steroid Hormone Study (1983) Oral contraceptive use and the risk of endometrial cancer. J. Am. med. Assoc., 249, 1600-1604

4. Henderson, B.E., Casagrande, J.T., Pike, M.C., Mack, T., Rosario, I. & Duke, A. (1983) The epidemiology of endometrial cancer in young women. Br. J. Cancer, 47, 749-756

5. IARC Monographs, 21, 233-255, 377-385, 1979

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Last updated: 10 February 1998

# PHENACETIN
# (Group 2A)
# and ANALGESIC MIXTURES CONTAINING PHENACETIN
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.310)

**Phenacetin**:
**CAS No.**: 62-44-2
**Chem. Abstr. Name**: Acetamide, *N*-(4-ethoxyphenyl)-

**A. Evidence for carcinogenicity to humans** (*limited* for phenacetin; *sufficient* for analgesic mixtures containing phenacetin)

There have been many case reports of renal pelvic and other urothelial tumours in patients who had used large amounts of phenacetin-containing analgesics [ref: 1-13]. Case-control studies have been consistent in showing a positive association between cancer of the renal pelvis and cancer of the bladder and use of phenacetin-containing analgesics, with relative risks varying from 2.4 to over 6; these associations have not been explained by confounding with other causes of urothelial cancer and, where looked for, a positive dose-response relationship has been evident [ref: 14-19]. In one study [ref: 14], use of nonphenacetin-containing analgesics appeared to increase the risk of cancer of the renal pelvis to the same extent as did phenacetin-containing analgesics. This result was not obtained in other studies [ref: 15,17,18].

**B. Evidence for carcinogenicity to animals** (*sufficient* for phenacetin; *limited* for analgesic mixtures containing phenacetin)

Phenacetin given orally induced benign and malignant tumours of the urinary tract in mice [ref: 20] and rats [ref: 1,21] and of the nasal cavity in rats [ref: 1]. When given in combination with aspirin and caffeine to rats or mice, no significant association was found between the administration of the mixture and the incidence of tumours [ref: 1]. In rats, phenacetin alone or in combination with phenazone slightly increased the incidences of renal-cell and renal-pelvic tumours; rats treated with phenacetin, phenazone and caffeine in combination developed hepatomas [ref: 22]. In rats, phenacetin enhanced the incidence of urinary bladder tumours induced by *N*-nitrosobutyl-*N*-(4-hydroxybutyl)amine [ref: 1], and prevented the induction of hepatocellular carcinomas by 2-acetylaminofluorene [ref: 23].

**C. Other relevant data**

No data were available on the genetic and related effects of phenacetin in humans.

The results of studies on the induction of chromosomal aberrations, sister chromatid exchanges and micronuclei in rodents treated with phenacetin *in vivo* were equivocal. Phenacetin induced chromosomal aberrations in Chinese hamster cells *in vitro* but not DNA strand breaks in rat hepatocytes. It did not induce sex-linked recessive lethal mutations in *Drosophila*. Phenacetin was mutagenic to bacteria when tested in the presence of a metabolic system derived from hamster but not mouse or rat liver. The urine from phenacetin-treated Chinese hamsters, but not that from rats, was mutagenic to bacteria [ref: 24].

**Overall evaluation**

Phenacetin is *probably carcinogenic to humans (Group 2A)*.

Analgesic mixtures containing phenacetin are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 13 (1977); Vol. 24 (1980)

**References**


1. *IARC Monographs*, *24*, 135-161, 1980

2. Christensen, T.E. & Ladefoged, J. (1979) Carcinomata in the urinary tract in patients with contracted kidneys and massive abuse of analgesics (phenacetin) (Dan.). *Ugeskr. Laeg.*, *141*, 3522-3524

3. Gonwa, T.A., Corbett, W.T., Schey, H.M. & Bukalew, V.M., Jr (1980) Analgesic-associated nephropathy and transitional cell carcinoma of the urinary tract. *Ann. intern. Med.*, *93*, 249-252

4. Mihatsch, M.J., Manz, T., Knüsli, C., Hofer, H.O., Rist, M., Guetg, R., Rutishauser, G. & Zollinger, H.U. (1980) Phenacetin abuse. III. Malignant urinary tract tumours with phenacetin abuse in Basel, 1963-1977 (Ger.). *Schweiz. med. Wochenschr.*, *110*, 255-264

5. Orell, S.R., Nanra, R.S. & Ferguson, N.W. (1979) Renal pelvic carcinoma in the Hunter Valley. *Med. J. Aust.*, *524*, 555-557

6. Blohmé, I. & Johansson, S. (1981) Renal pelvic neoplasms and atypical urothelium in patients with end-stage analgesic nephropathy. *Kidney int.*, *20*, 671-675

7. Syré, G. & Matejka, M. (1981) Phenacetin abuse and renal pelvis carcinomas (Ger.). *Wien. klin. Wochenschr.*, *93*, 420-423

8. Porpáczy, P. & Schramek, P. (1981) Analgesic nephropathy and phenacetin-induced transitional cell carcinoma - analysis of 300 patients with long-term consumption of phenacetin-containing drugs. *Eur. Urol.*, *7*, 349-354

9. Mihatsch, M.J., Brunner, F.P., Korteweg, E., Rist, M., Dalquen, P. & Thiel, G. (1982) Phenacetin abuse. VII. Tumours of the urinary tract in haemodialysis and kidney transplant patients (Ger.). *Schweiz. med. Wochenschr.*, *112*, 1468-1472

10. Novák, J. & Zidek, I. (1983) Phenacetin as a carcinogen for the renal pelvis (Czech.). *Cas. Lék. ces.*, *122*, 1149-1152

11. Mihatsch, M.J. & Knüsli, C. (1982) Phenacetin abuse and malignant tumors. An autopsy study covering 25 years (1953-1977). *Klin. Wochenschr.*, *60*, 1339-1349

12. Marek, J. & Hradec, E. (1985) Chronic sclerosing ureteritis and nephrogenic adenoma of the ureter in analgesic abuse. *Pathol. Res. Pract.*, *180*, 569-573

13. Kliment, J. (1979) Renal pelvis tumours and abuse of analgesics (Czech.). *Bratisl. lék. Listy*, *72*, 641-764

14. McCredie, M., Ford, J.M., Taylor, J.S. & Stewart, J.H. (1982) Analgesics and cancer of the renal pelvis in New South Wales. *Cancer*, *49*, 2617-2625

15. McCredie, M., Stewart, J.H., Ford, J.M. & MacLennan, R.A. (1983) Phenacetin-containing analgesics and cancer of the bladder or renal pelvis in women. *Br. J. Urol.*, *55*, 220-224

16. McCredie, M., Stewart, J.H. & Ford, J.M. (1983) Analgesics and tobacco as risk factors for cancer of the ureter and renal pelvis. *J. Urol., 130*, 28-30

17. McLaughlin, J.K., Mandel, J.S., Blot, W.J., Schuman, L.M., Mehl, E.S. & Fraumeni, J.F., Jr (1984) A population-based case-control study of renal cell carcinoma. *J. natl Cancer Inst., 72*, 275-284

18. Piper, J.M., Tonascia, J. & Matanoski, G.M. (1985) Heavy phenacetin use and bladder cancer in women aged 20 to 49 years. *New Engl. J. Med., 313*, 292-295

19. Piper, J.M., Matanoski, G.M. & Tonascia, J. (1986) Bladder cancer in young women. *Am. J. Epidemiol., 123*, 1033-1042

20. Nakanishi, K., Kurata, Y., Oshima, M., Fukushima, S. & Ito, N. (1982) Carcinogenicity of phenacetin: long-term feeding study in B6C3$F_1$ mice. *Int. J. Cancer, 29*, 439-444

21. Muradyan, R.Y. (1986) Experimental studies of phenacetin carcinogenicity (Russ.). *Vopr. Onkol., 32*, 63-70

22. Johansson, S.L. (1981) Carcinogenicity of analgesics: Long-term treatment of Sprague-Dawley rats with phenacetin, phenazone, caffeine and paracetamol (acetamidophen). *Int. J. Cancer, 27*, 521-529

23. Yamamoto, R.S., Frankel, H.H. & Weisburger, E.K. (1979) Effect of phenacetin and *N*-alkylacetanilides on *N*-2-fluorenylacetamide hepatocarcinogenesis. *Cancer Lett., 8*, 183-188

24. *IARC Monographs, Suppl. 6*, 448-450, 1987

**Synonyms for Phenacetin**

- 1-Acetamido-4-ethoxybenzene
- Aceto-*para*-phenalide
- *para*-Acetophenetide
- *para*-Acetophenetidide
- Aceto-*para*-phenetidide
- Acetophenetidin
- *para*-Acetophenetidine
- *para*-Acetphenetidin
- Acet-*para*-phenetidin
- Aceto-4-phenetidine
- Acetophenetidine
- Acetophenetin
- Acetphenetidin
- Acetyl-phenetidine
- Acetylphenetidin
- *N*-Acetyl-*para*-phenetidine
- Achrocidin
- Anapac
- APC
- ASA compound
- Bromo Seltzer
- Buff-A-comp
- Citra-fort
- Clistanol
- Codempiral
- Commotional
- Contra-douleur
- Contradol
- Coricidin
- Coriforte

- Coryban-D
- Daprisal
- Darvon compound
- Dasikon
- Dasin
- Dasin CH
- Dolostop
- Dolviran
- Edrisal
- Empiral
- Empirin compound
- Emprazil
- Emprazil-C
- Epragen
- *para*-Ethoxy-acetanilid
- 4'-Ethoxyacetanilide
- *para*-Ethoxyacetanilide
- 4-Ethoxyacetanilide
- Fenacetina
- Fenedina
- Fenidina
- Fenina
- Fiorinal
- Fortacyl
- Gelonida
- Gewodin
- Helvagit
- Hjorton's powder
- Hocophen
- Kafa
- Kalmin
- Malex
- Melabon
- Melaforte
- *N*-*para*-Ethoxyphenylacetamide
- Norgesic
- Pamprin
- Paracetophenetidin
- Paramette
- Paratodol
- Percobarb
- Percodan
- Pertonal
- Phenacet
- Phenacetine
- *para*-Phenacetin
- Phenacetinum
- Phenacitin
- Phenacon
- Phenalgin
- Phenaphen
- Phenaphen plus
- Phenazetin
- Phenazetina
- Phenedina
- Phenidin
- Phenin
- Phenodyne
- Pyrroxate
- Quadronal
- Reformin
- Robaxisal-PH
- Salgydal
- Sanalgine
- Saridon

- Seranex
- Sinedal
- Sinubid
- Sinutab
- Sinutab II
- Soma
- Stellacyl
- Super nahist
- Supralgin
- Synalgos-DC
- Synalogos
- Tacol
- Terracydin
- Tetracydin
- Thephorin A-C
- Treupel
- Veganine
- Viden
- Wigraine
- Xaril
- Zactirin compound-100

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# PHENAZOPYRIDINE HYDROCHLORIDE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 312)

**CAS No.**: 136-40-3
**Chem. Abstr. Name**: 2,6-Pyridinediamine,3-(phenylazo)-,monohydrochloride

**A. Evidence for carcinogenicity to humans** (*inadequate*)

In one limited epidemiological study, no significant excess of any cancer was observed among 2214 patients who received phenazopyridine hydrochloride and were followed for a minimum of three years [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Oral administration of phenazopyridine hydrochloride increased the incidence of hepatocellular adenomas and carcinomas in female mice and induced tumours of the colon and rectum in rats [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of phenazopyridine hydrochloride in humans. It did not induce sex-linked recessive lethal mutations in *Drosophila* and was not mutagenic to bacteria [ref: 2].

**Overall evaluation**

Phenazopyridine hydrochloride is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 8 (1975); Vol. 24 (1980)

**References**

1. IARC Monographs, 24, 175-184, 1980

2. IARC Monographs, Suppl. 6, 451-452, 1987

**Synonyms**

- Azo gantrisin
- Azo gastanol
- Azo-mandelamine
- Azo-standard
- Azo-stat
- Azodine
- Azodium
- Azodyne
- Azotrex
- Baridium

- Bisteril
- Cystamine McClung
- Cystopyrin
- Cystural
- 2,6-Diamino-3-(phenylazo)pyridine monohydrochloride
- 2,6-Diamino-3-phenylazopyridine hydrochloride
- Di-Azo
- Diridone
- Dolonil
- Eucistin
- Giracid
- Mallofeen
- Mallophene
- NC 150
- Nefrecil
- PAP
- Phenazo
- Phenazodine
- Phenazopyridinium chloride
- 3-Phenylazo-2,6-diaminopyridine hydrochloride
- Phenyl-Idium
- Phenyl-Idium 200
- Phenylazo
- Phenylazodiaminopyridine HCl
- β-Phenylazo-α,α'-diaminopyridine hydrochloride
- Phenylazopyridine HCl
- Pirid
- Piridacil
- Pyrazodine
- Pyrazofen
- Pyredal
- Pyridacil
- Pyridenal
- Pyridene
- Pyridiate
- Pyridium
- Pyridivite
- Pyripyridium
- Pyrizin
- Sedural
- Sulodyne
- Thiosulfil-A forte
- Urazium
- Uridinal
- Uriplex
- Urobiotic-250
- Urodine
- Urofeen
- Uromide
- Urophenyl
- Uropyridin
- Uropyrine
- Utostan
- Vestin
- W 1655

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Last updated: 3 March 1998

# PHENELZINE SULPHATE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 312)

**CAS No.**: 156-51-4
**Chem. Abstr. Name**: Hydrazine(2-phenylethyl)-, sulfate(1:1)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

A liver angiosarcoma was reported in one person who had taken phenelzine sulphate for six years preceding tumour diagnosis [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

Phenelzine sulphate was administered to mice in drinking-water for life. Incidences of lung and blood-vessel tumours were significantly increased in female but not in male mice [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of phenelzine sulphate in humans. It did not induce DNA strand breaks in mice treated *in vivo*. In bacteria, it was mutagenic and induced DNA damage [ref: 2].

**Overall evaluation**

Phenelzine sulphate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 24 (1980)

**References**

1. IARC Monographs, 24, 175-184, 1980

2. IARC Monographs, Suppl. 6, 453-454, 1987

**Synonyms**

- Alazin
- Estinerval
- Fenelzin
- Fenelzine
- 1-Hydrazino-2-phenylethane hydrogen sulfate
- Phenalzine dihydrogen sulfate
- Phenalzine hydrogen sulfate
- Phenelzine bisulfate
- Phenethylhydrazine sulfate(1:1)
- Phenethylhydrazine sulfate
- Phenodyn
- Phenylethylhydrazine dihydrogen sulfate

- 2-Phenylethylhydrazine dihydrogen sulfate
- β-Phenylethylhydrazine dihydrogen sulfate
- 2-Phenylethylhydrazine hydrogen sulfate
- β-Phenylethylhydrazine hydrogen sulfate
- Phenylethylhydrazine sulfate
- 2-Phenylethylhydrazine sulfate
- β-Phenylethylhydrazine sulfate
- Kalgan
- Mao-rem
- Monofen
- Nardelzine
- Nardil
- Stinerval

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Last updated: 11 March 1998

# PHENOBARBITAL
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 313)

**CAS No.**: 50-06-6
**Chem. Abstr. Name**: 5-Ethyl-5-phenyl-2,4,6-(1*H*,3*H*,5*H*)pyrimidinetrione

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Phenobarbital has been associated with increased frequencies of several cancers [ref: 1]. Excesses of brain tumours have been reported in studies of epileptics, most of whom were treated with phenobarbital, often in combination with other drugs [ref: 2,3]. The role of anticonvulsant therapy in the origin of these brain tumours is not clear, however, since the tumours may have been the precipitating cause of the epilepsy. In the largest study [ref: 2,4], there was an almost 12-fold excess of brain tumours in the first ten years of follow-up (45 observed, 3.8 expected) but this decreased with duration of follow-up to 1.3 (2 observed, 1.5 expected) 30 or more years following admission. A case-control study involving 84 children with brain tumours [ref: 5] showed a two-fold increase in the incidence of these tumours associated with prenatal or childhood exposure to barbiturates (mostly phenobarbital [ref: 6]). In a study of 11 169 matched case-control pairs of childhood cancers and controls, epilepsy was reported by 39 mothers of cases and 22 mothers of controls (20 and 12, respectively, having used phenobarbital). The number of brain tumours among the 39 cancers was not reported [ref: 7].

Lung cancer was reported in excess in 5834 members of a prepaid health plan prescribed phenobarbital during 1969-1973 and followed to 1976. The standardized mortality ratio (SMR) was 1.5 [95% confidence interval, 1.1-1.9]. Excesses were also found in users of pentobarbital sodium and secobarbital sodium. When users of the three drugs were considered together, the excess of lung cancer was found in both men and women, appeared to be accounted for only partly by cigarette smoking and persisted when cases diagnosed during the first two years of follow-up were excluded. There was no apparent relation with duration of use [ref: 8]. Small increases in lung cancer incidence were also observed in two cohort studies of epileptics [ref: 3,4], 'largely ascribable to tobacco' in one study [ref: 4], although the effects of smoking were not studied. In the larger of the two [ref: 4], the SMR was 1.3 [1.0-1.6]; in the other [ref: 3], it was 1.4 (0.9-2.1).

Liver cancer occurred in excess in the larger cohort study of epileptics [ref: 4] (SMR, 3.8 [2.7-4.9]). However, ten of the 13 observed cancers occurred in individuals exposed to thorotrast. Histology was available for nine of these: two were reported to be haemangiosarcomas, four, cholangiocarcinomas, one, a hepatocellular carcinoma, and two, adenocarcinomas [ref: 2]. In the other cohort study with data available [ref: 3], no primary liver tumour was observed although 0.6 cases of cancer of the liver and gall-bladder were expected.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Phenobarbital produced benign and malignant hepatocellular tumours in mice and hepatocellular tumours in rats after its oral administration [ref: 1,9,10]. Experiments with mice and rats in which phenobarbital was studied for its promoting activity included comparison groups given phenobarbital alone. Oral administration of phenobarbital enhanced the incidence of liver tumours in mice by *N*-nitrosodimethylamine [ref: 11] or *N*-methyl-*N*-nitrosourea [ref: 12] and of benign or malignant liver tumours induced in rats by 2-acetylaminofluorene [ref: 13-16], *N*-nitrosodiethylamine [ref: 17,18], 2-methyl-*N*,*N*-dimethyl-4-aminoazobenzene [ref: 19], benzo[*a*]pyrene [ref: 20], cycasin [ref: 21], *N*-hydroxy-*N*-formyl- or -acetylaminobiphenyl [ref: 22], *N*-nitroso-*N*-(4-hydroxybutyl) butylamine [ref: 16] or *N*-nitrosomorpholine [ref: 23]. In rats, oral administration of phenobarbital in combination with DDT resulted in a high incidence of liver tumours [ref: 24]. Phenobarbital enhanced the development of thyroid tumours [ref: 25,26] and of liver foci [ref: 26] induced in rats by *N*-nitrosodi(2-hydroxypropyl)amine and enhanced the incidences of liver foci, thyroid adenocarcinomas and forestomach carcinomas induced in rats by *N*-methyl-*N*-nitrosourea [ref: 27].

## C. Other relevant data

No data were available on the genetic and related effects of phenobarbital in humans.

Neither phenobarbital nor its sodium salt induced sister chromatid exchanges, chromosomal aberrations, micronuclei or sperm abnormalities in mice treated *in vivo*. Phenobarbital induced chromosomal aberrations and mutation but not sister chromatid exchanges in cultured human cells. Both positive and negative results were obtained for transformation in rodent cells *in vitro*. Phenobarbital enhanced transformation of virus-infected rat embryo cells initiated with 3-methylcholanthrene in a two-stage transformation assay. It induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells, but not in cultured rat liver cells; micronuclei and aneuploidy were not induced in Chinese hamster cells. Phenobarbital induced mutation in Chinese hamster cells, but conflicting or negative results were obtained in other rodent cells. Phenobarbital and its sodium salt did not induce DNA strand breaks, and phenobarbital did not induce unscheduled DNA synthesis, in cultured rodent cells. Phenobarbital inhibited intercellular communication in human hepatoma cells and both phenobarbital and its sodium salt did so in rodent systems. Phenobarbital induced neither somatic mutation nor recombination in *Drosophila*; the sodium salt did not induce sex-linked recessive lethal mutations. Phenobarbital induced aneuploidy but not mutation or gene conversion in fungi. Conflicting results were obtained concerning the mutagenicity of these compounds in bacteria [ref: 28].

## Overall evaluation

Phenobarbital is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001) **Also see previous evaluation**: Vol. 13 (1977)

## References


1. IARC Monographs, 13, 157-181, 1977

2. Clemmesen, J. & Hjalgrim-Jensen, S. (1978) Is phenobarbital carcinogenic? A follow-up of 8078 epileptics. Ecotoxicol. environ. Saf., 1, 457-470

3. White, S.J., McLean, A.E.M. & Howland, C. (1979) Anticonvulsant drugs and cancer. A cohort study in patients with severe epilepsy. Lancet, ii, 458-461

4. Clemmesen, J. & Hjalgrim-Jensen, S. (1981) Does phenobarbital cause intracranial tumors? A follow-up through 35 years. Ecotoxicol. environ. Saf., 5, 255-260

5. Gold, E., Gordis, L., Tonascia, J. & Szklo, M. (1978) Increased risk of brain tumors in children exposed to barbiturates. J. natl Cancer Inst., 61, 1031-1034

6. Gold, E.B., Gordis, L., Tonascia, J.A. & Szklo, M. (1979) Brain tumors in children exposed to barbiturates. J. natl Cancer Inst., 63, 3-4

7. Sanders, B.M. & Draper, G.J. (1979) Childhood cancer and drugs in pregnancy. Br. med. J., i, 717-718

8. Friedman, G.D. (1981) Barbiturates and lung cancer in humans. J. natl Cancer Inst., 67, 291-295

9. Feldman, D., Swarm, R.L. & Becker, J. (1981) Ultrastructural study of rat liver and liver neoplasms after long-term treatment with phenobarbital. Cancer Res., 41, 2151-2162

10. Ward, J.M. (1983) Increased susceptibility of livers of aged F344/NCr rats to the effects of phenobarbital on the incidence, morphology, and histochemistry of hepatocellular foci and neoplasms. J. natl Cancer Inst., 71, 815-823

11. Uchida, E. & Hirono, I. (1979) Effect of phenobarbital on induction of liver and lung tumors by dimethylnitrosamine in newborn mice. Gann, 70, 639-644

12. Pereira, M.A., Knutsen, G.L. & Herren-Freund, S.L. (1985) Effect of subsequent treatment of chloroform or phenobarbital on the incidence of liver and lung tumors initiated by ethylnitrosourea in 15 day old mice. Carcinogenesis, 6, 203-207

13. Watanabe, K. & Williams, G.M. (1978) Enhancement of rat hepatocellular-altered foci by the liver tumor promoter phenobarbital: evidence that foci are precursors of neoplasms and that the promoter acts on carcinogenic-induced lesions. J. natl Cancer Inst., 61, 1311-1314

14. Peraino, C., Staffeldt, E.F., Haugen, D.A., Lombard, L.S., Stevens, F.J. & Fry, R.J.M. (1980) Effects of varying the dietary concentration of phenobarbital on its enhancement of 2-acetylaminofluorene-induced hepatic tumorigenesis. Cancer Res., 40, 3268-3273

15. Takano, T., Tatematsu, M., Hasegawa, R., Imaida, K. & Ito, N. (1980) Dose-response relationship for the promoting effect of phenobarbital on the induction of liver hyperplastic nodules in rats exposed to 2-fluorenylacetamide and carbon tetrachloride. Gann, 71, 580-581

16. Nakanishi, K., Fukushima, S., Hagiwara, A., Tamano, S. & Ito, N. (1982) Organ-specific promoting effects of phenobarbital sodium and sodium saccharin in the induction of liver and urinary bladder tumors in male F344 rats. J. natl Cancer Inst., 68, 497-500

17. Farwell, D.C., Nolan, C.E. & Herbst, E.J. (1978) Liver ornithine decarboxylase during phenobarbital promotion of nitrosamine carcinogenesis. Cancer Lett., 5, 139-144

18. Nishizumi, M. (1979) Effect of phenobarbital, dichlorodiphenyltrichloroethane, and polychlorinated biphenyls on diethylnitrosamine-induced hepatocarcinogenesis. Gann, 70, 835-837

19. Kitagawa, T., Pitot, H.C., Miller, E.C. & Miller, J.A. (1979) Promotion by dietary phenobarbital of hepatocarcinogenesis by 2-methyl-*N*,*N*-dimethyl-4-aminoazobenzene in the rat. Cancer Res., 39, 112-115

20. Kitagawa, T., Hirakawa, T., Ishikawa, T., Nemoto, N. & Takayama, S. (1980) Induction of hepatocellular carcinoma in rat liver by initial treatment with benzo[*a*]pyrene after partial hepatectomy and promotion by phenobarbital. Toxicol. Lett., 6, 167-171

21. Uchida, E. & Hirono, I. (1981) Effect of phenobarbital on the development of neoplastic lesions in the liver of cycasin-treated rats. J. Cancer Res. clin. Oncol., 100, 231-238

22. Shirai, T., Lee, M.-S., Wang, C.Y. & King, C.M. (1981) Effects of partial hepatectomy and dietary phenobarbital in liver and mammary tumorigenesis by two *N*-hydroxy-*N*-acylaminobiphenyls in female CD rats. Cancer Res., 41, 2450-2456

23. Moore, M.A., Hacker, H.-J., Kunz, H.W. & Bannasch, P. (1983) Enhancement of NNM-induced carcinogenesis in the rat liver by phenobarbital: a combined morphological and enzyme histochemical approach. Carcinogenesis, 4, 473-479

24. Barbieri, O., Rossi, L., Cabral, J.R.P. & Santi, L. (1983) Carcinogenic effects induced in Wistar rats by combined treatment with technical-grade dichlorodiphenyltrichloroethane and sodium phenobarbital. Cancer Lett., 20, 223-229

25. Hiasa, Y., Kitahori, Y., Ohshima, M., Fujita, T., Yuasa, T., Konishi, N. & Miyashiro, A. (1982) Promoting effects of phenobarbital and barbital on development of thyroid tumors in rats treated with *N*-bis(2-hydroxypropyl)nitrosamine. Carcinogenesis, 3, 1187-1190

26. Moore, M.A., Thamavit, W., Tsuda, H. & Ito, N. (1986) The influence of subsequent dehydroepiandrosterone, diaminopropane, phenobarbital, butylated hydroxyanisole and butylated hydroxytoluene treatment on the development of preneoplastic and neoplastic lesions in the rat initiated with di-hydroxy-di-*N*-propyl nitrosamine. Cancer Lett., 30, 153-160

27. Tsuda, H., Sakata, T., Shirai, T., Kurata, Y., Tamano, S. & Ito, N. (1984) Modification of *N*-methyl-*N*-nitrosourea initiated carcinogenesis in the rat by subsequent treatment with antioxidants, phenobarbital and ethinyl estradiol. Cancer Lett., 24, 19-27

28. IARC Monographs, Suppl. 6, 455-458, 1987

**Synonyms**

- Adonal
- Aephenal
- Agrypnal
- Amylofene
- Aphenylbarbit
- Aphenyletten
- Austrominal
- Barbapil
- Barbellen
- Barbellon
- Barbenyl
- Barbilettae
- Barbinal
- Barbiphen
- Barbiphenyl
- Barbipil
- Barbita
- Barbivis
- Barbonal
- Barbophen
- Bardorm
- Bartol
- Bialminal
- Blu-phen
- Cabronal
- Calmetten
- Calminal
- Cardenal
- Cemalonal
- Codibarbital
- Coronaletta
- Damoral
- Dezibarbitur
- Dormina
- Dormiral
- Doscalun
- Duneryl
- Ensobarb
- Ensodorm
- Epanal
- Epidorm
- Epilol
- Episedal
- Epsylone
- Eskabarb
- 5-Ethyl-5-phenylbarbituric acid

- Etilfen
- Euneryl
- Fenbital
- Fenemal
- Fenobarbital
- Fenosed
- Fenylettae
- Gardenal
- Gardepanyl
- Glysoletten
- Haplopan
- Haplos
- Helional
- Hennoletten
- Hypnaletten
- Hypno-tablinetten
- Hypnogen
- Hypnolone
- Hypnotal
- Hysteps
- Lefebar
- Leonal
- Lephebar
- Lepinal
- Linasen
- Liquital
- Lixophen
- Lubergal
- Lukrokol
- Lumen
- Lumesettes
- Lumesyn
- Luminal
- Lumofridetten
- Luphenil
- Luramin
- Molinal
- Neurobarb
- Nirvonal
- Noptil
- Nova-Pheno
- Numol
- Nunol
- Parkotal
- PEBA
- Pharmetten
- Phen-Bar
- Phenaemal
- Phenemal
- Phenobal
- Phenobarbitone
- Phenobarbituric acid
- Phenobarbyl
- Phenoluric
- Phenonyl
- Phenoturic
- Phenylbarbital
- Phenylethylbarbiturate
- 5-Phenyl-5-ethylbarbituric acid
- Phenylethylbarbituric acid
- Phenylethylmalonylurea
- Phenyletten
- Phenyral
- Phob
- Polcominal
- Promptonal

- Seda-tablinen
- Sedabar
- Sedicat
- Sedizorin
- Sedlyn
- Sedofen
- Sedonal
- Sedonettes
- Sevenal
- Sombutol
- Somnolens
- Somnoletten
- Somnosan
- Somonal
- Spasepilin
- Starifen
- Starilettae
- Stental extentabs
- Teolaxin
- Thenobarbital
- Triarbarb
- Tridezibarbitur
- Triphenatol
- Versomnal
- Zadoletten
- Zadonal

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Last updated: 3 March 1998

# PHENYLBUTAZONE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 316)

**CAS No.**: 50-33-9
**Chem. Abstr. Name**: 4-Butyl-1,2-diphenyl-3,5-pyrazolidinedione

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Cases of leukaemia have been reported in patients following phenylbutazone therapy [ref: 1,2], but their significance cannot be evaluated, given the widespread use of phenylbutazone [ref: 1]. No significant excess of leukaemia or other malignancy was observed during 1969-1976 among 3660 members of a prepaid health plan prescribed phenylbutazone during 1969-1973 [ref: 3]. In a case-control study of 409 patients with leukaemia or lymphoma and a subset of 127 patients with myelocytic leukaemia, who were compared with equal numbers of hospital controls and with a second control series of members of a prepaid health plan, prior use of phenylbutazone was more frequent in cases than in members of the health plan (relative risk, 1.26; 95% confidence interval, 0.86-1.86). This appeared to be explained by an association of musculo-skeletal disease with these cancers. There was no clear association between the amount or duration of phenylbutazone therapy and risk of leukaemia [ref: 4]. In a cohort study of 489 patients with rheumatoid arthritis, followed for an average of 12.2 years, seven patients developed non-Hodgkin's lymphoma compared to 0.29 expected from regional rates (relative risk, 24.1 [20.4-27.9]), two developed Hodgkin's disease, one, a chronic lymphatic leukaemia and one, an acute myeloid leukaemia. A study of hospital charts indicated that 60% of those with malignancies had received phenylbutazone compared to 3% of the whole cohort; however, the author considered it likely that far more than 3% of the whole cohort had received phenylbutazone. Those patients with malignancies had also received other drugs: 40% had received gold, 20%, steroids and 10%, chloroquine, but none had received cytotoxic agents or radiotherapy. Further, 30% were believed not to have received any of these agents (including phenylbutazone) [ref: 5]. Lymphoproliferative malignancies have been recognized as a complication of other immune disorders, and it is possible that phenylbutazone therapy did not play a causal role in this study.

**B. Evidence for carcinogenicity to animals**

No data were available to the Working Group.

**C. Other relevant data**

In one study of patients given high doses of phenylbutazone, no chromosomal aberration was found in bone-marrow cells [ref: 6].

Phenylbutazone did not induce dominant lethality or micronuclei or chromosomal anomalies in bone-marrow cells of mice treated *in vivo*. It induced chromosomal aberrations in cultured Chinese hamster fibroblasts, but did not induce sister chromatid exchanges or chromosomal aberrations in cultured human cells. Phenylbutazone was not mutagenic to bacteria [ref: 6].

Phenylbutazone is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 13 (1977)

**References**

1. IARC Monographs, 13, 183-199, 1977

2. Mitarnun, W. & Peerabool, R. (1983) Blood dyscrasia evolving into acute lymphoblastic leukemia following ingestion of phenylbutazone, indomethacin, dexamethasone and prednisolone. J. med. Assoc. Thailand, 66, 649-654

3. Friedman, G.D. & Ury, H.K. (1980) Initial screening for carcinogenicity of commonly used drugs. J. natl Cancer Inst., 65, 723-733

4. Friedman, G.D. (1982) Phenylbutazone, musculoskeletal disease, and leukemia. J. chron. Dis., 35, 233-243

5. Symmons, D.P.M. (1985) Neoplasms of the immune system in rheumatoid arthritis. Am. J. Med., 78 (Suppl. 1A), 22-28

6. IARC Monographs, Suppl. 6, 459-460, 1987

**Synonyms**

- Alindor
- Alkabutazona
- Alqoverin
- Anerval
- Anpuzone
- Antadol
- Anuspiramin
- Arthrizin
- Artrizin
- Artrizone
- Artropan
- Azdid
- Azobutil
- Benzone
- Betazed
- Bizolin 200
- B.T.Z.
- Butacote
- Butacompren
- Butadion
- Butadiona
- Butadione
- Butagesic
- Butalgina
- Butalan
- Butalidon
- Butaluy
- Butaphen
- Buta-Phen
- Butapirazol
- Butapyrazole
- Butarecbon
- Butartril
- Butartrina
- Butazina
- Butazolidin
- Butazolidine
- Butazona
- Butazone
- Butidiona
- Butiwas-simple

- Butone
- Butoz
- 4-Butyl-1,2-diphenyl-3,5-dioxopyrazolidine
- 4-Butyl-1,2-diphenyl-pyrazolidine-3,5-dione
- Butylpyrin
- Buvetzone
- Buzon
- Chembutazone
- Digibutina
- Diossidone
- 3,5-Dioxo-1,2-diphenyl-4-n-butylpyrazolidine
- Diozol
- Diphebuzol
- Diphenylbutazone
- 1,2-Diphenyl-4-butyl-3,5-pyrazolidinedione
- 1,2-Diphenyl-3,5-dioxo-4-butylpyrazolidine
- 1,2-Diphenyl-3,5-dioxo-4-*n*-butylpyrazolidine
- 1,2-Diphenyl-2,3-dioxo-4-*n*-butylpyrazolidine
- Ecobutazone
- Elmedal
- Equi Bute
- Eributazone
- Esteve
- Febuzina
- Fenartil
- Fenibutasan
- Fenibutazona
- Fenilbutazona
- Fenylbutazon
- Fenilbutina
- Fenilbutine
- Fenibutol
- Fenilidina
- Fenotone
- Flexazone
- G 13,871
- IA-But
- Intalbut
- Intrabutazone
- Ipsoflame
- Kadol
- Lingel
- Malgesic
- Mephabutazone
- Merizone
- Nadazone
- Nadozone
- Neo-Zoline
- Novo-phenyl
- Phebuzin
- Phebuzine
- Phen-Buta-Vet
- Phenbutazol
- Phenopyrine
- Phenylbetazone
- Phenylbutaz
- Phenylbutazonum
- Phenyl-mobuzon
- Pirarreumol B
- Praecirheumin
- Pyrabutol
- Pyrazolidin
- Rectofasa
- Reudo
- Reudox

- Reumasyl
- Reumazin
- Reumazol
- Reumune
- Reupolar
- Robizon-V
- Rubatone
- Scanbutazone
- Schemergin
- Shigrodin
- Tazone
- Tetnor
- Tevcodyne
- Therazone
- Ticinil
- Todalgil
- Uzone
- VAC-10
- Wescozone
- Zolaphen
- Zolidinum

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Last updated: 11 March 1998

# *N*-PHENYL-2-NAPHTHYLAMINE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 318)

**CAS No.**: 135-88-6
**Chem. Abstr. Name**: *N*-Phenyl-2-naphthalenamine

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No excess of bladder tumours was found among men in a rubber processing factory with known exposure to *N*-phenyl-2-naphthylamine (which contained small amounts of 2-naphthylamine); however, a study of rubber workers who were not exposed to 2-naphthylamine did show an increased incidence of bladder tumours. In the latter study, the men were exposed to several compounds, which probably included *N*-phenyl-2-naphthylamine [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

*N*-Phenyl-2-naphthylamine was tested for carcinogenicity by oral administration in mice, rats, hamsters and dogs. No carcinogenicity was reported in most experiments [ref: 1-4]. In one experiment, the total tumour incidence and the incidence of hepatocellular tumours were increased in male mice of one strain [ref: 1]. In another experiment, two rare kidney tumours were seen in female mice [ref: 2]. Subcutaneous administration to mice increased the total tumour incidence [ref: 1] and the incidences of lung [ref: 5] and liver neoplasms [ref: 1]. Repeated subcutaneous injection after previous unilateral nephrectomy in mice resulted in a significant increase in the total tumour incidence and in the incidences of haemangiosarcomas of the kidney and of carcinomas of the lung [ref: 6,7]. Following exposure of mice by inhalation in one study, lung carcinomas were reported [ref: 8].

**C. Other relevant data**

There is some evidence from one study of 19 human volunteers that up to 0.03% of a single 10-mg dose of *N*-phenyl-2-naphthylamine is converted to 2-naphthylamine. Similarly, the urine of workers exposed to *N*-phenyl-2-naphthylamine was found to contain 2-naphthylamine, indicating that *N*-phenyl-2-naphthylamine is dephenylated in the human body [ref:1]. No data were available on the genetic effects of *N*-phenyl-2-naphthylamine in humans. It was reported not to be mutagenic to bacteria [ref: 9].

**Overall evaluation**

*N*-Phenyl-2-naphthylamine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 16 (1978)

**References**

1. IARC Monographs, 16, 325-341, 1978

2. National Toxicology Program (1987) Technical Report on the Toxicology and Carcinogenesis Studies of *N*-Phenyl-2-naphthylamine (CAS No. 135-88-6) in F344/N Rats and B6C3$F_1$ Mice (Feed Studies) (Tech. Rep. No. 333; NIH Publ. No. 87-2589), Research Triangle Park, NC

3. Ketkar, M.B. & Mohr, U. (1982) The chronic effects of magenta, paramagenta and phenyl-β

-naphthylamine in rats after intragastric administration. Cancer Lett., 16, 203-206

4. Green, U., Holste, J. & Spikermann, A.R. (1979) A comparative study of the chronic effects of magenta, paramagenta and phenyl-β-napthylamine in Syrian golden hamsters. J. Cancer Res. clin. Oncol., 95, 51-55

5. Wang, H., Dzeng, R. & Wang, D. (1982) The carcinogenicity of *N*-phenyl-2-naphthylamine in ICR mice (Chin.). Acta biol. exp. sin., 15, 199-207

6. Wang, D., Zeng, R. & Wang, H. (1983) A comparative study on carcinogenic activity of PBNA and PANA in unilaterally nephrectomized TA-1 mice (Chin.). Acta sci. circumst., 3, 262-266

7. Wang, H., Wang, D. & Dzeng, R. (1984) Carcinogenicity of *N*-phenyl-1-naphthylamine and *N*-phenyl-2-naphthylamine in mice. Cancer Res., 44, 3098-3100

8. You, X. & Yao, Y. (1981) Experimental study of inhalation carcinogenesis of *N*-phenyl-2-naphthylamine aerosol on mice (Chin.). Acta biol. exp. sinica, 14, 139-143

9. IARC Monographs, Suppl. 6, 461-462, 1987

**Synonyms**

- Aceto PBN
- Agerite powder
- Age rite powder
- Anilinonaphthalene
- 2-Anilinonaphthalene
- Antioxidant 116
- Antioxidant PBN
- *N*-(2-Naphthyl)aniline
- 2-Naphthylphenylamine
- β-Naphthylphenylamine
- Neosone D
- Neozon D
- Neozone
- Neozone D
- Nilox PBNA
- Nonox D
- PBNA
- 2-Phenylamino-naphthalene
- Phenyl-2-naphthylamine
- Phenyl(β-naphthyl)amine
- Phenyl-β-naphthylamine
- *N*-Phenyl-β-naphthylamine
- Stabilizator AR

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Last updated: 11 March 1998

# POLYBROMINATED BIPHENYLS
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 321)

**Hexabromobiphenyl**
**CAS No.**: 59080-40-9

**Octabromobiphenyl**
**CAS No.**: 27858-07-7

**Decabromobiphenyl**
**CAS No.**: 13654-09-6

**A. Evidence for carcinogenicity to humans** (*inadequate*)

The mortality has been studied of a cohort of over 3500 male workers with potential exposure to several brominated compounds, including polybrominated biphenyls, who were employed between 1935 and 1976 at chemical plants. Due to a lack of quantitative data, potential exposures of workers to polybrominated biphenyls were categorized as 'routine' and 'nonroutine'. Of the 91 workers potentially exposed on a 'routine' basis, none died during the study period; among the 237 'nonroutinely' exposed, two deaths were observed, with 6.4 expected, one of which was due to cancer of the large intestine [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

The carcinogenicity of a commercial preparation of polybrominated biphenyls (FireMaster FF-1, various lots), composed primarily of hexabromobiphenyl with smaller amounts of penta- and heptabrominated isomers, was tested by oral administration in mice and rats. In mice, it produced malignant liver tumours. In five studies in rats, it produced benign and malignant hepatic tumours, including cholangiocarcinomas, depending on the exposure conditions. Oral administration of polybrominated biphenyls enhanced the incidence of liver nodules induced by *N*-nitrosodiethylamine [ref: 2], but cutaneous application did not increase the incidence of skin tumours induced by 2-acetylaminofluorene [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of polybrominated biphenyls in humans.

Polybrominated biphenyls did not induce chromosomal aberrations in bone-marrow cells of rats or mice nor in rat spermatogonia and did not induce micronuclei in mice treated *in vivo*. They did not induce mutation in human or rodent cells *in vitro* or unscheduled DNA synthesis in rodent hepatocytes *in vitro*. Polybrominated biphenyls were not mutagenic to bacteria *in vitro* or in a host-mediated assay [ref: 3].

2,4,5,2',4',5'-Hexabromobiphenyl, 2,3,4,5,2',4',5'-heptabromobiphenyl and 2,3,4,5,2',3',4',5'-octabromobiphenyl inhibited intercellular communication in Chinese hamster V79 cells; other congeners tested were only weakly active or were inactive [ref: 3].

**Overall evaluation**

Polybrominated biphenyls are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 18 (1978); Vol. 41 (1986)

**References**

1. IARC Monographs, 41, 261-292, 1986

2. Jensen, R.K. & Sleight, S.D. (1986) Sequential study on the synergistic effects of 2,2',4,4',5,5'-hexabromobiphenyl and 3,3',4,4',5,5'-hexabromobiphenyl on hepatic tumour promotion. Carcinogenesis, 7, 1771-1774

3. IARC Monographs, Suppl. 6, 466-468, 1987

**Synonym for Hexabromobiphenyl [technical grade]**

- Hexabromodiphenyl

**Synonym for Octabromobiphenyl [technical grade]**

- Bromkal 80

**Synonyms for Decabromobiphenyl [technical grade]**

- Adine 0102
- Berkflam B-10
- Decabromodiphenyl
- Flammex B-10
- Perbromobiphenyl

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Last updated: 3 March 1998

# POLYCHLORINATED BIPHENYLS
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 322)

**CAS No.:** 1336-36-3
**Chem. Abstr. Name:** Polychlorinated Biphenyls

**Biphenyl:**
**CAS No.:** 92-52-4
**Chem. Abstr. Name:** 1,1'-Biphenyl

**2-Chlorobiphenyl:**
**CAS No.:** 2051-60-7
**Chem. Abstr. Name:** 2-Chloro-1,1'-biphenyl

**4-Chlorobiphenyl:**
**CAS No.:** 2051-62-9
**Chem. Abstr. Name:** 4-Chloro-1,1'-biphenyl

**2,2'-Dichlorobiphenyl:**
**CAS No.:** 13029-08-8
**Chem. Abstr. Name:** 2,2'-Dichloro-1,1'-biphenyl

**2,3'-Dichlorobiphenyl:**
**CAS No.:** 25569-80-6
**Chem. Abstr. Name:** 2,3'-Dichloro-1,1'-biphenyl

**2,4'-Dichlorobiphenyl:**
**CAS No.:** 34883-43-7
**Chem. Abstr. Name:** 2,4'-Dichloro-1,1'-biphenyl

**4,4'-Dichlorobiphenyl:**
**CAS No.:** 2050-68-2
**Chem. Abstr. Name:** 4,4'-Dichloro-1,1'-biphenyl

**2,2',3-Trichlorobiphenyl:**
**CAS No.:** 38444-78-9
**Chem. Abstr. Name:** 2,2',3-Trichloro-1,1'-biphenyl

**2,2',5-Trichlorobiphenyl:**
**CAS No.:** 37680-65-2
**Chem. Abstr. Name:** 2,2',5-Trichloro-1,1'-biphenyl

**2,3',4-Trichlorobiphenyl:**
**CAS No.:** none available
**Chem. Abstr. Name:** 2,3',4-Trichloro-1,1'-biphenyl

**2',3,4-Trichlorobiphenyl:**
**CAS No.:** 38444-86-9
**Chem. Abstr. Name:** 2',3,4-Trichloro-1,1'-biphenyl

**2,4,4'-Trichlorobiphenyl:**
**CAS No.:** 7012-37-5

**Chem. Abstr. Name:** 2,4,4'-Trichloro-1,1'-biphenyl

**2,4',5-Trichlorobiphenyl:**
**CAS No.:** 16606-02-3
**Chem. Abstr. Name:** 2,4',5-Trichloro-1,1'-biphenyl

**2,2'3,5'-Tetrachlorobiphenyl:**
**CAS No.:** 41464-39-5
**Chem. Abstr. Name:** 2,2',3,5'-Tetrachloro-1,1'-biphenyl

**2,2',4,5'-Tetrachlorobiphenyl:**
**CAS No.:** 41464-40-8
**Chem. Abstr. Name:** 2,2',4,5'-Tetrachloro-1,1'-biphenyl

**2,2',5,5'-Tetrachlorobiphenyl:**
**CAS No.:** 35693-99-3
**Chem. Abstr. Name:** 2,2',5,5'-Tetrachloro-1,1'-biphenyl

**2,3,4,4'-Tetrachlorobiphenyl:**
**CAS No.:** 33025-41-1
**Chem. Abstr. Name:** 2,3,4,4'-Tetrachloro-1,1'-biphenyl

**2,3',4,4'-Tetrachlorobiphenyl:**
**CAS No.:** 32598-10-0
**Chem. Abstr. Name:** 2,3',4,4'-Tetrachloro-1,1'-biphenyl

**2,3',4',5-Tetrachlorobiphenyl:**
**CAS No.:** 32598-11-1
**Chem. Abstr. Name:** 2,3',4',5-Tetrachloro-1,1'-biphenyl

**3,3',4,4'-Tetrachlorobiphenyl:**
**CAS No.:** 32598-13-3
**Chem. Abstr. Name:** 3,3',4,4'-Tetrachloro-1,1'-biphenyl

**2,2',3,3',6-Pentachlorobiphenyl:**
**CAS No.:**52663-60-2
**Chem. Abstr. Name:** 2,2',3,3',6-Pentachloro-1,1'-biphenyl

**2,2',3,4,5'-Pentachlorobiphenyl:**
**CAS No.:** 38380-02-8
**Chem. Abstr. Name:** 2,2',3,4,5'-Pentachloro-1,1'-biphenyl

**2,2',3',4,5-Pentachlorobiphenyl:**
**CAS No.:** 41464-51-1
**Chem. Abstr. Name:** 2,2',3'4,5-Pentachloro-1,1'-biphenyl

**2,2',3,4',6-Pentachlorobiphenyl:**
**CAS No.:** none available
**Chem. Abstr. Name:** 2,2',3,4',6-Pentachloro-1,1'-biphenyl

**2,2',3,5',6-Pentachlorobiphenyl:**
**CAS No.:** 38379-99-6
**Chem. Abstr. Name:** 2,2',3,5',6-Pentachloro-1,1'-biphenyl

**2,2',4,4',5-Pentachlorobiphenyl:**
**CAS No.:** 38380-01-7
**Chem. Abstr. Name:** 2,2',4,4',5-Pentachloro-1,1'-biphenyl

**2,2',4,5,5'Pentachlorobiphenyl:**
**CAS No.:** 37680-73-2
**Chem. Abstr. Name:** 2,2',4,5,5'-Pentachloro-1,1'-biphenyl

**2,3,3',4,4'-Pentachlorobiphenyl:**
**CAS No.:** 32598-14-4
**Chem. Abstr. Name:** 2,3,3',4,4'-Pentachlorol-1,1'-biphenyl

**2,3,3',4',6-Pentachlorobiphenyl:**
**CAS No.:** 38380-03-9
**Chem. Abstr. Name:** 2,3,3',4',6-Pentachlorol-1,1'-biphenyl

**2,3',4,4',5-Pentachlorobiphenyl:**
**CAS No.:**31508-00-6
**Chem. Abstr. Name:** 2,3',4,4',5-Pentachlorol-1,1'-biphenyl

**2,2',3,3',4,6-Hexachlorobiphenyl:**
**CAS No.:** 38380-05-1
**Chem. Abstr. Name:** 2,2',3,3',4,6-Hexachloro-1,1'-biphenyl

**2,2', 3,3',6,6'-Hexachlorobiphenyl:**
**CAS No.:** 38411-22-2
**Chem. Abstr. Name:** 2,2',3,3',6,6'-Hexachloro-1,1'-biphenyl

**2,2',3,4,4',5-Hexachlorobiphenyl:**
**CAS No.:** 35694-06-5
**Chem. Abstr. Name:** 2,2',3,4,4',5-Hexachloro-1,1'-biphenyl

**2,2',3,4,4',5'-Hexachlorobiphenyl:**
**CAS No.:** 35065-28-2
**Chem. Abstr. Name:** 2,2',3,4,4',5'-Hexachloro-1,1'-biphenyl

**2,2',3',4,5,6'-Hexachlorobiphenyl:**
**CAS No.:** 38380-04-0
**Chem. Abstr. Name:** 2,2',3',4,5,6'-Hexachloro-1,1'-biphenyl

**2,2',4,4',5,5'-Hexachlorobiphenyl:**
**CAS No.:** 35065-27-1
**Chem. Abstr. Name:** 2,2',4,4',5,5'-Hexachloro-1,1'-biphenyl

**2,2',3,3',4,4',5-Heptachlorobiphenyl:**
**CAS No.:** 35065-30-6
**Chem. Abstr. Name:** 2,2',3,3',4,4',5-Heptachloro-1,1'-bipheny

**2,2',3,3',4,5,6'-Heptachlorobiphenyl:**
**CAS No.:** 38441-25-5
**Chem. Abstr. Name:** 2,2',3,3',4,5,6'-Heptachloro-1,1'-biphenyl

**2,2',3,4,4',5,5'-Heptachlorobiphenyl:**
**CAS No.:** 35065-29-3
**Chem. Abstr. Name:** 2,2',3,4,4',5,5'Heptachloro-1,1'-biphenyl

**A. Evidence for carcinogenicity to humans** (*limited*)

Information on the possible carcinogenic risk of human exposure to polychlorinated biphenyls (PCBs) comes from studies of occupational populations and of populations exposed to the compounds

accidentally. PCB mixtures may be contaminated with polychlorinated dibenzofurans and polychlorinated dibenzodioxins.

A slight increase in the incidence of cancer, particularly melanoma of the skin, was reported in a small group of men exposed to Aroclor 1254, a mixture of PCBs [ref: 1]. In a study of over 2500 US workers exposed to a similar mixture of PCBs during the manufacture of electrical capacitors, five deaths due to cancer of the liver and biliary passages were observed, whereas 1.9 would have been expected. This increase was sustained mainly by female workers in one of the two plants in the study (four of the five deaths), and all five had first been employed before the early 1950s [ref: 2,3]. Another study of workers in a capacitor plant was conducted in Italy. Exposure in the early years of production (until 1964) was to PCB mixtures containing 54% chlorine (mainly Aroclor 1254 and Pyralene 1476), which were later replaced by mixtures containing 42% chlorine (mainly Pyralene 3010 and 3011). Early results showed a significant excess of all cancers among male workers, which was due mainly to cancers of the digestive system and of the lymphatic and haematopoietic tissues. Among female workers, a slight increase in mortality from cancer of the lymphatic and haematopoietic tissues was reported [ref: 4]. The study was later enlarged and extended to include 2100 workers and to cover the period 1946-1982. Both male and female workers exhibited significantly increased cancer mortality in comparison with rates for the local population (14 observed, 7.6 expected; and 12 and 5.3, respectively, for men and women). Among male workers, cancers of the gastrointestinal tract (two stomach, two pancreas, one liver and one biliary passages) taken together were significantly increased (6 observed, 2.2 expected). Female workers showed a significant increase in deaths from haematological neoplasms (4 observed, 1.1 expected) [ref: 5]. In Sweden, among 142 male workers employed between 1965 and 1978 in a capacitor manufacturing plant when PCB mixtures containing up to 42% chlorine had been used, no significant excess of cancer deaths was noted. Cancer incidence was also examined: the number of cases observed corresponded well to that expected. One individual in a subgroup with higher exposure developed two relatively rare tumours, both of which occurred ten years after the start of exposure: a slow-growing mesenchymal tumour (desmoid) and a malignant lymphoma [ref: 6].

After contamination of cooking oil with a mixture of PCBs (Kanechlor 400) in Japan in 1968, a large population was intoxicated ('Yusho' disease). An early report on mortality from 1963-1983 showed a significantly increased risk of all cancers, and an almost five-fold significantly elevated risk of primary liver cancer. The edible rice oil had also been contaminated by polychlorinated quaterphenyls and polychlorinated dibenzofurans. Dose-response relationships were not clarified [ref: 7]. A further comprehensive study of 887 male 'Yusho' patients showed statistically significantly increased mortality from all malignancies (33 observed, 15.5 expected), from liver cancer (9 observed, 1.6 expected) and from lung cancer (8 observed, 2.5 expected). Use of local rather than national rates in calculating expected number of deaths decreased the observed:expected ratio for liver cancer from 5.6 to 3.9, which was still statistically significant. A closer look at the geographical distribution of liver cancer cases did not allow exclusion of factors other than PCB poisoning as a possible explanation for this finding. For the 874 female patients examined, none of the noted observed:expected ratios was significant [ref: 8]. In a series of ten autopsies of 'Yusho' patients, two adenocarcinomas of the liver were found, with no indication of a direct association with exposure to PCBs [ref: 9]. Ultrasonic and tumour marker examination of two series of 79 and 125 patients with 'Yusho' disease in 1983 and 1984, respectively, did not reveal any case of hepatic-cell carcinoma [ref: 10]. Two studies of the PCB content of fat tissues and cancer occurrence were available. An association was suggested between PCB concentrations in subcutaneous abdominal adipose tissue and the occurrence of cancers of the stomach, colon, pancreas, ovaries and prostate [ref: 11]. No indication emerged of a relationship between PCB content in extractable breast fat tissue and the occurrence of breast cancer [ref: 12].

The available studies suggest an association between cancer and exposure to PCBs. The increased risk from hepatobiliary cancer emerged consistently in different studies. Since, however, the numbers were small, dose-response relationships could not be evaluated, and the role of compounds other than PCBs could not be excluded, the evidence was considered to be limited.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Certain PCBs (particularly with greater than 50% chlorination) produced benign and malignant liver neoplasms in mice and rats after their oral administration [ref: 1,13,14]. Oral administration of Aroclor 1254 to rats yielded hepatocellular adenomas and carcinomas as well as intestinal metaplasia and a low, not statistically significant incidence of stomach adenocarcinomas [ref: 15].

PCBs were inadequately tested in mice for induction of skin tumours [ref: 16,17]. In several studies, oral or intraperitoneal administration of PCBs enhanced the incidences of preneoplatic lesions [ref: 18-20] and of neoplasms [ref: 21,22] of the liver induced in rats by *N*-nitrosodiethylamine or 2-acetylaminofluorene. In one study, intragastric administration of PCBs to mice increased the incidence of lung tumours induced by intraperitoneal administration of *N*-nitrosodimethylamine [ref: 23].

**C. Other relevant data**

No data were available on the genetic and related effects of PCBs in humans.

Dominant lethal effects were not induced in rats administered PCBs orally, but were produced in rats nursed by females that had received PCBs orally. PCBs did not induce chromosomal aberrations in bone-marrow cells or spermatagonia of rats treated *in vivo*; micronuclei were not induced in bone-marrow cells of mice in one study, while equivocal results were obtained in a second study in which the PCBs were administered in corn oil. They did not transform Syrian hamster embryo cells *in vitro*. PCBs induced DNA strand breaks and unscheduled DNA synthesis in rat hepatocytes *in vitro*. Neither chromosomal breakage nor aneuploidy was induced in *Drosophila*. PCB mixtures did not induce SOS repair and were not mutagenic to bacteria [ref: 24].

2,2',5,5'-Tetrachlorophenyl induced DNA strand breaks in mouse cells *in vitro*. 2,4,5,2',4',5'-Hexachlorobiphenyl but not 3,4,5,3',4',5'-hexachlorobiphenyl inhibited intercellular communication in Chinese hamster V79 cells. Purified 2,4,2',4'-, 2,5,2',5'- and 3,4,3',4'-tetrachloro- and 2,4,6,2',4',6'-hexachlorobiphenyl were not mutagenic to bacteria [ref: 24].

**Overall evaluation**

Polychlorinated biphenyls are *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 7 (1974); Vol. 18 (1978)

**References**

1. IARC Monographs, 18, 43-103, 1978

2. Brown, D.P. & Jones, M. (1981) Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch. environ. Health, 36, 120-129

3. Brown, D.P. (1987) Mortality of workers exposed to polychlorinated biphenyls. An update. Arch. environ. Health (in press)

4. Bertazzi, P.A., Zocchetti, C., Guercilena, S., Della Foglia, M., Pesatori, A. & Riboldi, L. (1982) Mortality study of male and female workers exposed to PCB's. In: Proceedings of the International Symposium on Prevention of Occupational Cancer, Helsinki, 1981, Geneva, International Labour Office, pp. 242-248

5. Bertazzi, P.A., Riboldi, L., Pesatori, A., Radice, L. & Zocchetti, C. (1987) Cancer mortality of capacitor manufacturing workers. Am. J. ind. Med., 11, 165-176

6. Gustavsson, P., Hogstedt, C. & Rappe, C. (1986) Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am. J. ind. Med., 10, 341-344

7. Umeda, G. (1984) Studies on long-term effects of PCBs on human body: mortality from primary

liver cancer and prevalence of ischemic heart disease (Abstract No. 19.8). In: Eustace, I.E., ed., Proceedings of the XXI International Congress on Occupational Health, Dublin, 1984, p. 166

8. Kuratsune, M., Nakamura, Y., Ikeda, M. & Hirohata, T. (1986) Analysis of deaths seen among patients with Yusho (Abstract FL17). In: Dioxin 86. Proceedings of the VI International Symposium on Chlorinated Dioxins and Related Compounds, Fukuoka, Japan, 1986, p. 179

9. Kikuchi, M. (1984) Autopsy of patients with Yusho. Am. J. ind. Med., 5, 19-30

10. Okumura, M. & Sakaguchi, S. (1985) Hepatic cell carcinoma and the patients with Yusho (Jpn.). Fukuoka Igaku Zasshi, 76, 229-232

11. Unger, M., Olsen, J. & Clausen, J. (1982) Organochlorine compounds in the adipose tissue of deceased persons with and without cancer: a statistical survey of some potential confounders. Environ. Res., 29, 371-376

12. Unger, M., Kiaer, H., Blichert-Toft, M., Olsen, J. & Clausen, J. (1984) Organochlorine compounds in human breast fat from deceased persons with and without breast cancer and in a biopsy material from newly diagnosed patients undergoing breast surgery. Environ. Res., 34, 24-28

13. Norback, D.H. & Weltman, R.H. (1985) Polychlorinated biphenyl induction of hepatocellular carcinoma in the Sprague-Dawley rat. Environ. Health Perspect., 60, 97-105

14. Schaeffer, E., Greim, H. & Goessner, W. (1984) Pathology of chronic polychlorinated biphenyl (PCB) feeding in rats. Toxicol. appl. Pharmacol., 75, 278-288

15. Ward, J.M. (1985) Proliferative lesions of the glandular stomach and liver in F344 rats fed diets containing Aroclor 1254. Environ. Health Perspect., 40, 89-95

16. DiGiovanni, J., Viaje, A., Berry, D.L., Slaga, T.J. & Juchau, M.R. (1977) Tumor-initiating ability of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and Aroclor 1254 in the two-stage system of mouse skin carcinogenesis. Bull. environ. Contam. Toxicol., 18, 552-557

17. Hori, M., Fujita, K., Yamashiro, K., Toriyama, F., Hirose, R., Shukuwa, T., Toyoshima, H. & Yoshida, H. (1985) Methylcholanthrene induced mouse skin cancer. Fukuoka Igaku Zasshi, 76, 208-214

18. Pereira, M.A., Herren, S.L., Britt, A.L. & Khoury, M.M. (1982) Promotion by polychlorinated biphenyls of enzyme-altered foci in rat liver. Cancer Lett., 15, 185-190

19. Buchmann, A., Kunz, W., Wolf, C.R., Oesch, F. & Robertson, L.W. (1986) Polychlorinated biphenyls, classified as either phenobarbital or 3-methylcholanthrene-type inducers of cytochrome P-450, are both hepatic tumor promoters in diethylnitrosamine-initiated rats. Cancer Lett., 32, 243-253

20. Tatematsu, M., Nakanishi, K., Murasaki, G., Miyata, Y., Hirose, M. & Ito, N. (1979) Enhancing effect of inducers of liver microsomal enzymes on induction of hyperplastic liver nodules by N-2-fluorenylacetamine in rats. J. natl Cancer Inst., 63, 1411-1416

21. Nishizumi, M. (1979) Effect of phenobarbital, dichlorodiphenyltrichloroethane, and polychlorinated biphenyls on diethylnitrosamine-induced hepatocarcinogenesis. Gann, 70, 835-837

22. Preston, B.D., Van Miller, J.P., Moore, R.W. & Allen, J.R. (1981) Promoting effects of polychlorinated biphenyls (Aroclor 1254) and polychlorinated dibenzofuran-free Aroclor 1254 on diethylnitrosamine-induced tumorigenesis in the rat. J. natl Cancer Inst., 66, 509-515

23. Anderson, L.M., Ward, J.M., Fox, S.D., Isaaq, H.J. & Riggs, C.W. (1986) Effects of a single dose of polychlorinated biphenyls to infant mice on *N*-nitrosodimethylamine-initiated lung and liver tumors. Int. J. Cancer, 38, 109-116

24. IARC Monographs, Suppl. 6, 469-471, 1987

**Synonyms for Polychlorinated biphenyls:**

- Chlorinated biphenyl
- Chlorinated diphenyl
- Chlorobiphenyl
- PCB
- PCBs
- Polychlorinated biphenyl
- Polychlorobiphenyl

**Trade names for Polychlorinated biphenyls (The producing country is given in parentheses):**

- Aroclor (USA)
- Chlorextol (USA)
- Clophen (FRG)
- Dykanol (USA)
- Fenclor (Italy)
- Inerteen (USA)
- Kanechlor (Japan)
- Noflamol (USA)
- Phenoclor (France)
- Pyralene (as formulated, no longer contains PCBs) (France)
- Pyranol (USA)
- Santotherm (Japan)
- Sovol (USSR)
- Therminol (USA)

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Last updated: 11 February 1998

# PREDNISONE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 326)

**CAS No.**: 53-03-2
**Chem. Abstr. Name**: Pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Many case reports of cancer include a mention of previous treatment with prednisone, as would be expected by chance alone in view of the very wide use of this drug in many different disorders. Prednisone is a common drug, prescribed for long periods in the treatment of many chronic conditions [ref: 1]. Patients treated with prednisone for rheumatoid arthritis appear to have, if anything, a lower than expected cancer risk. Over an average follow-up period of 12 years, 11% of 153 deaths that occurred in patients who had received prednisone were due to malignancies, compared to 20% of 74 deaths among patients who had not received prednisone [ref: 2]. The strong link between combination therapy for Hodgkin's disease and subsequent second malignancies (see summary of data on MOPP and other chemotherapy including alkylating agents) is much more plausibly explained on the basis of concurrent administration of clearly carcinogenic agents than of prednisone.

A study of cancers that appeared within four years after documented use of common drugs showed that prednisone was among the 53 (of 95) drugs associated positively with cancer at least once. However, the excess consisted of 12 cases of lung cancer (31 observed, 19 expected), known to be largely related to cigarette smoking (which was not measured) and known to occur after a latent period much longer than the interval under observation. Of more interest is the absence of those neoplasms, such as acute nonlymphocytic leukaemia and non-Hodgkin's lymphoma, which have been linked to chemotherapy and immunosuppression [ref: 3].

Thus, the evidence for a carcinogenic action of prednisone was not compelling. The evidence did not, however, 'suggest lack of carcinogenicity', because there is no well-designed analytical study of prednisone alone.

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Prednisone was tested for carcinogenicity in mice and rats by intraperitoneal administration. A significant increase in the total number of tumours was reported in female rats, but the study suffered from limitations in both design and reporting [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of prednisone in humans. It did not induce chromosomal aberrations in bone-marrow cells of rats treated *in vivo*. It was not mutagenic to bacteria [ref: 4].

**Overall evaluation**

Prednisone is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 293-309, 1981

2. Fries, J.F., Bloch, D., Spitz, P. & Mitchell, D.M. (1985) Cancer in rheumatoid arthritis: a prospective long-term study of mortality. Am. J. Med., 78 (Suppl. 1A), 56-59

3. Friedman, G.D. & Ury, H.K. (1980) Initial screening for carcinogenicity of commonly used drugs. J. natl Cancer Inst., 65, 723-733

4. IARC Monographs, Suppl. 6, 472-473, 1987

**Synonyms**

- Adasone
- Alto-pred
- Ancortone
- Ancotone
- Antison
- Benison
- Bicortone
- Bidelta
- Buffacort
- Co-deltra
- Colisone
- Cortancyl
- Cortane
- Cortialer
- Corticor
- Cortidelt
- Cortinter
- Cortiol
- Cortisid
- Dabroson
- Dacortin
- Decortancyl
- Decortin
- Decortisyl
- Decorton
- Dehydrocortisone
- 1-Dehydrocortisone
- 1,2-Dehydrocortisone
- 17,21-Dehydrocortisone
- Deidrocortisone
- Dekortin
- Delco-Cortex
- Delcort
- Delcortin
- δ-Corlin
- δ-Cortelan
- Deltacortene
- Deltacortisone
- δ-Cortisone
- δ1-Cortisone
- Deltacortisyl
- Deltacortone
- δ1-Dehydrocortisone
- δ-Dome
- δ E
- Deltalone
- Deltasone

- Deltasson
- Deltastendiolo
- Deltatrione
- Deltison
- Deltisone
- Deltra
- Di-Adreson
- 17,21-Dihydroxy-pregna-1,4-diene-3,11,20-trione
- 17alpha,21-Dihydroxy-1,4-pregnadiene-3,11,20-trione
- 17,21-Dihydroxypregna-1,4-diene-3,11,20-trione
- 17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione
- 17,21-Dihydroxypregn-1,4-diene-3,11,20-trione
- Dispersona
- Ejizon
- Encorton
- Encortone
- Enkorton
- Erftopred
- Fernisone
- Fernisone buffered
- Fiasone
- Hicorton
- Homozol
- Hostacortin
- Idrosone
- Inocortyl
- In-sone
- Intalsone
- Juvason
- Keteocort
- Keysone
- Kolpisone
- Leocortine-D
- Lisacort
- Marnisonal
- Marsone
- Marvidiene
- Marvisona
- Mediasone
- Me-Korti
- Meprison
- Metacortandracin
- Metacortin
- Metasone
- Meticortem
- Meticorten
- Meticortene
- Metisone
- Metreton
- Neoaltesona
- Nisone
- Nizon
- Novoprednisone
- NSC 10023
- Nurison
- Orasone
- Panafcort
- Paracort
- Parmenison
- Precortal
- Predeltin
- Predni-artrit
- Prednicen-M
- Prednicorm
- Prednifor

- Prednilong
- Prednilonga
- Predniment
- Predniseguer
- Prednisol
- Predni-tablinen
- Prednital
- Prednison
- Predni-wolner
- Prednizon
- Prednovister
- Predorgasona
- Predsol
- Predsone
- 1,4-Pregnadiene-17α,21-diol-3,11,20-trione
- δ-Prenovis
- Presone
- Pronison
- Propred
- Rectodelt
- Retrocortin
- Ropred
- δ-Scheroson
- Servisone
- Solisone
- Sone
- Sterapred
- Supercortil
- Supernisona
- Supopred
- Taracorten
- Ultracorten
- Ultracortene
- Ultrilone
- Urtilone
- Vitazon
- Wescopred
- Winpred
- Xynisone
- Zenidrid

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Last updated: 11 March 1998

# PROCARBAZINE HYDROCHLORIDE
# (Group 2A)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 327)

**CAS No.:** 366-70-1
**Chem. Abstr. Name:** Benzamide, *N*-(1-methylethyl)-4-[(2-methylhydrazino)-methyl]-, monohydrochloride

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of procarbazine as a single agent was available to the Working Group. In various combinations with other chemotherapeutic agents, given for Hodgkin's disease, procarbazine use has repeatedly been shown to lead to the appearance of acute nonlymphocytic leukaemia. These combinations usually also include nitrogen mustard, an alkylating agent which is also a potent animal carcinogen, and these many observations do not permit conclusions about the independent effect of either drug [ref: 1].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Procarbazine hydrochloride administered by repeated intraperitoneal injections produced malignant tumours of the nervous system and haematopoietic system in mice and rats of each sex and adenocarcinomas of the mammary gland in rats only [ref: 1]. Repeated intravenous injections induced malignant tumours in different organs of rats [ref: 1]. Oral administration produced pulmonary tumours and leukaemias in mice [ref: 1,2] and mammary tumours in rats [ref: 1,3]. Leukaemias, haemangioendothelial sarcomas and osteogenic sarcomas were induced in rhesus, cynomolgus and African green monkeys of each sex by intraperitoneal, subcutaneous, intravenous or oral administration of procarbazine hydrochloride [ref: 1,4].

**C. Other relevant data**

Procarbazine generates an alkylating species [ref: 1].

No data were available on the genetic and related effects of procarbazine hydrochloride in humans.

Procarbazine gave positive results for germinal mutation in the mouse specific-locus test and caused mutation in the mouse spot test. It induced micronuclei and structural chromosomal aberrations in mice treated *in vivo*, but conflicting results were obtained in tests for dominant lethal mutations and negative results in the heritable-translocation test. It induced sister chromatid exchanges in mice and Chinese hamsters and caused DNA damage in rodents treated *in vivo*. Procarbazine did not transform Syrian hamster embryo cells. It induced mutation but not sister chromatid exchanges in rodent cells *in vitro*. It induced aneuploidy, dominant lethal mutations, sex-linked recessive lethal mutations and somatic mutation and recombination in *Drosophila*, but did not cause heritable translocations. It induced mutation, gene conversion and mitotic recombination in fungi. Conflicting results were obtained for mutation in bacteria, both *in vitro* and in host-mediated assays; it induced DNA damage in bacteria [ref: 5].

**Overall evaluation**

Procarbazine hydrochloride is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

## References


1. IARC Monographs, 26, 311-339, 1981

2. Bacci, M., Cavaliere, A. & Fratini, D. (1982) Lung carcinogenesis by procarbazine chlorate in BALB/c mice. Carcinogenesis, 3, 71-73

3. Bacci, M., Cavaliere, A. & Amorosi, A. (1984) Procarbazine hydrochlorate carcinogenesis in Osborne-Mendel rats. Oncology, 41, 106-108

4. Adamson, R.H. & Sieber, S.M. (1982) Studies on the oncogenicity of procarbazine and other compounds in nonhuman primates. In: Rosenberg, S. & Kaplan, H., eds, Malignant Lymphomas: Etiology, Immunology, Pathology, Treatment (Bristol-Myers Cancer Symposia Series Vol. 3), Orlando, FL, Academic Press, pp. 239-257

5. IARC Monographs, Suppl. 6, 474-478, 1987


## Synonyms

- Ibenzmethyzin hydrochloride
- Ibenzmethyzine hydrochloride
- IBZ
- *N*-4-Isopropylcarbamoylbenzyl-N'-methylhydrazine hydrochloride
- 2-[*para*-(Isopropylcarbamoyl)benzyl]-1-methylhydrazine hydrochloride
- *N*-Isopropyl-*para*-(2-methyl-hydrazinomethyl)benzamide hydrochloride
- *N*-Isopropyl-α-(2-methylhydrazino)-*para*-toluamide monohydrochloride
- MBH
- *para*-(N1-Methylhydrazino-methyl)-*N*-isopropylbenzamide hydrochloride
- 1-Methyl-2-[*para*-(isopropylcarbamoyl)benzyl]hydrazine hydrochloride
- 1-Methyl-2-*para*-(isopropylcarbamoyl)benzylhydrazine hydrochloride
- MIH
- Matulane
- Natulanar
- Natulan
- NSC 77213
- PRO
- Ro 4-6467
- Ro 46467/1

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Last updated: 11 February 1998

# PROGESTINS
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 289)

**Medroxyprogesterone acetate**

**CAS No.**: 71-58-9
**Chem. Abstr. Name**: (6α)-17-(Acetyloxy)-6-methylpregn-4-ene-3,20-dione

**A. Evidence for carcinogenicity to humans** (*inadequate*)

The results of one cross-sectional study of the development of breast nodules in women given medroxyprogesterone acetate was difficult to interpret because of methodological considerations [ref: 1]. Two small cohort studies in the USA showed relative risks (and 95% confidence limits) of breast cancer in women exposed to medroxyprogesterone acetate of 0.69 (0.3-1.4) [ref: 2] and 1.1 (0.5-2.4) [ref: 3], but both included only women with short-term exposure and limited duration of follow-up. A case-control study of 30 women with breast cancer and 179 controls [ref: 4] yielded a relative risk of 1.0 (no confidence limits given) for use of medroxyprogesterone acetate at some time. Preliminary analyses of a collaborative case-control study in Thailand, Kenya and Mexico sponsored by the World Health Organization [ref: 5], based on 427 cases (39 'ever' users) and 5951 controls (557 'ever' users), provided estimates of relative risk (and 95% confidence limits) for breast cancer of 1.0 (0.7-1.5) in women who 'ever' used medroxyprogesterone acetate, 1.1 (0.7-1.9) for users for 1-12 months, 1.2 (0.7-2.2) for users for 13-36 months and 0.8 (0.4-1.7) for users for 37 months or more.

Medroxyprogesterone acetate causes reversible changes in the endometrium, from proliferative to secretory or suppressed [ref: 4]. In one small cohort study, one case of uterine leiomyosarcoma was found, with 0.83 cancers of the uterine corpus expected, giving a relative risk of 1.2 [0.03-6.7] [ref: 2]. In the collaborative study [ref: 5], the estimated a relative risk for endometrial cancer in 'ever' users of medroxyprogesterone acetate was 0.3 (0.04-2.4), based on 57 cases, only one of which was exposed, and 316 matched controls (30 exposed).

In the small cohort study [ref: 2], one ovarian cancer case occurred in a medroxyprogesterone acetate user, with 1.16 expected, giving a relative risk of 0.86 [0.02-4.6]. Preliminary analysis of data from the collaborative study [ref: 5], based on 105 cases (seven exposed) and 637 matched controls (74 exposed) yielded a relative risk for ovarian cancer of 0.7 (0.3-1.7) in 'ever' users of medroxyprogesterone acetate.

The results of two cohort studies of dysplasia and of carcinoma *in situ* of the uterine cervix in women given medroxyprogesterone acetate were conflicting and difficult to interpret because of methodological problems [ref: 1]. Preliminary results from the collaborative study [ref: 5], based on 920 cases of invasive cervical carcinoma (126 exposed to medroxyprogesterone acetate) and 5833 controls (545 exposed) yielded estimated relative risks of 1.2 (0.9-1.5) in 'ever' users, after controlling for parity, history of vaginal discharge, age at first sexual relationship, number of sexual partners, number of prior Pap smears and use of an intrauterine device and oral contraceptives. Relative risks in users for 1-12, 13-24, 25-60 and 61 months or more were estimated to be 1.4 (1.0-2.0), 1.2 (0.7-2.0), 0.6 (0.4-1.1) and 1.4 (0.9-2.2), respectively.

Preliminary analyses of data from the collaborative study [ref: 5] showed the relative risk for primary liver cancer (all histological types combined) in women who had ever used medroxyprogesterone acetate to be 1.0 (0.4-2.8), based on 57 cases (seven exposed) and 290 controls (34 exposed).

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Medroxyprogesterone acetate was tested by intramuscular injection in dogs and by subcutaneous implantation in mice. It induced adenocarcinomas of the mammary gland in one study in female mice [ref: 6], and produced malignant mammary tumours in dogs [ref: 1]. After four years of intramuscular treatment of dogs with a human contraceptive dose, a dose-related increase in the incidence of mammary nodules was seen; the incidence of mammary-gland nodules at that time was comparable with that seen in dogs given progesterone at 25 times the canine luteal level [ref: 7]. Female dogs treated with medroxyprogesterone acetate for at least one year had a significant increase in the incidence of large and small mammary nodules as compared with control animals in one study [ref: 8], and a dose-related increase in the incidence of large mammary nodules was found in another after intramuscular administration [ref: 9].

**C. Other relevant data**

No data were available on the genetic and related effects of medroxyprogesterone acetate alone in humans. See, however, the summary of data for combined oral contraceptives. Medroxyprogesterone acetate induced sister chromatid exchanges in mouse cells *in vitro*.

**References**

1. IARC Monographs, 21, 417-429, 1979

2. Liang, A.P., Levenson, A.G., Layde, P.M., Shelton, J.D., Hatcher, R.A., Potts, M. & Michelson, M.J. (1983) Risk of breast, uterine corpus, and ovarian cancer in women receiving medroxyprogesterone injections. J. Am. med. Assoc., 249, 2909-2912

3. Danielson, D.A., Jick, H., Hunter, J.R., Stergachis, A. & Madsen, S. (1982) Nonestrogenic drugs and breast cancer. Am. J. Epidemiol., 116, 329-332

4. Greenspan, A.R., Hatcher, R.A., Moore, A., Rosenberg, M.J. & Ory, H.W. (1980) The association of depo-medroxyprogesterone acetate and breast cancer. Contraception, 21, 563-569

5. Special Programme of Research, Development and Research Training in Human Reproduction (1986) Depot-medroxyprogesterone acetate DMPA and cancer. Memorandum from a WHO meeting. WHO Bull., 64, 375-382

6. Lanari, C., Molinolo, A.A. & Pasqualini, C.D. (1986) Induction of mammary adenocarcinomas by medroxyprogesterone acetate in BALB/c female mice. Cancer Lett., 33, 215-223

7. Frank, D.W., Kirton, K.T., Murchison, T.E., Quinlan, W.J., Coleman, M.E., Gilbertson, T.J., Feenstra, E.S. & Kimball, F.A. (1979) Mammary tumors and serum hormones in the bitch treated with medroxyprogesterone acetate or progesterone for four years. Fertil. Steril., 31, 340-346

8. van Os, J.L., van Laar, P.H., Oldenkamp, E.P. & Verschoor, J.S.C. (1981) Oestrus control and the incidence of mammary nodules in bitches, a clinical study with two progestogens. Vet. Q., 3, 46-56

9. Concannon, P.W., Spraker, T.R., Casey, H.W. & Hansel, W. (1981) Gross and histopathologic effects of medroxyprogesterone acetate and progesterone on the mammary glands of adult beagle bitches. Fertil. Steril., 36, 373-387

10. IARC Monographs, Suppl. 6, 359-360, 1987

**Synonyms for Medroxyprogesterone acetate**

- 17α-Acetoxy-6α-methylprogesterone
- Amen
- Clinovir
- Depcorlutin

- Depo-clinovir
- Depomedroxyprogesterone acetate
- Depo-provera
- Deporone
- Farlutal
- Farlutin
- Gesinal
- Gestapuran
- Gestapuron
- 17-Hydroxy-6α-methylpregn-4-ene-3,20-dione acetate
- 17α-Hydroxy-6α-methylprogesterone acetate
- Luteocrin
- Lutopolar
- Lutoral
- MAP
- Metigestrona
- Metilgestene
- Metipregnone
- 6α-Methyl-17-acetoxyprogesterone
- 6α-Methyl-17α-hydroxyprogesterone acetate
- MPA
- Nogest
- Oragest
- Perlutex
- Prodasone
- Progestalfa
- Progevera
- Promone-E
- Provera
- Proverone
- Provest
- Repromix
- Sirprogen
- Sodelut G
- U 8839
- Veramix

**Chlormadinone acetate**

**CAS No.**: 302-22-7
**Chem. Abstr. Name**: 17-(Acetyloxy)-6-chloropregna-4,6-diene-3,20-dione

**A. Evidence for carcinogenicity to animals** (*limited*)

Chlormadinone acetate was tested in mice, rats and dogs by oral administration. In dogs, it produced mammary tumours in one study [ref: 1] and increased the incidence of mammary-gland hyperplasia and mammary nodules in another [ref: 2].

**B. Other relevant data**

No data were available on the genetic and related effects of chlormadinone acetate alone in humans. See, however, the summary of data for combined oral contraceptives. Chlormadinone acetate did not induce chromosomal aberrations in cultured human lymphocytes and was not mutagenic to bacteria [ref: 3].

**References**

1. IARC Monographs, 21, 365-375, 1979

2. El Etreby, M.F. & Gräf, K.-J. (1979) Effect of contraceptive steroids on mammary gland of beagle

dog and its relevance to human carcinogenicity. Pharmacol. Ther., 5, 369-402

3. IARC Monographs, Suppl. 6, 148-149, 1987

**Synonyms for Chlormadinone acetate**

- 17α-Acetoxy-6-chloro-6,7-dehydroprogesterone
- 17α-Acetoxy-6-chloro-4,6-pregnadiene-3,20-dione
- Amenyl
- Ay 13390-6
- Bovisynchron
- CAP
- Cero
- Chlordion
- Chlormadinon acetate
- 6-Chloro-$\Delta^6$-17-acetoxyprogesterone
- 6-Chloro-$\Delta^6$-(17α)acetoxyprogesterone
- 6-Chloro-6-dehydro-17α-acetoxyprogesterone
- 6-Chloro-6-dehydro-17α-hydroxyprogesterone acetate
- 6-Chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate
- Chloromadinone acetate
- Clordion
- C-Quens
- Gestafortin
- Gestogan
- Lormin
- Luteran
- Lutestral
- Lutinyl
- Lutoral
- Matrol
- Menova
- Menstridyl
- Normenen
- Normenon
- Retex
- RS 1280
- Sequens
- Skedule
- Skedule TM
- Synchrosyn
- Synchrosyn P
- Traslan
- Verton

**Dimethisterone**

**CAS No.**: 79-64-1
**Chem. Abstr. Name**: (6α,17β)-17-Hydroxy-6-methyl-17-(1-propynyl)-androst-4-en-3-one

**A. Evidence for carcinogenicity to animals** (*inadequate*)

Dimethisterone was reported to have been tested in monkeys in one study. No increase in tumour incidence was found [ref: 1].

**B. Other relevant data**

No data were available on the genetic and related effects of dimethisterone in humans. It did not induce chromosomal aberrations in cultured human lymphocytes [ref: 2].

**References**

1. Weikel, J.H., Jr & Nelson, L.W. (1977) Problems in evaluating chronic toxicity of contraceptive steroids in dogs. J. Toxicol. environ. Health, 3, 167-177

2. IARC Monographs, Suppl. 6, 260-261, 1987

**Synonyms for Dimethisterone**

- Dimethisteron
- 6α,21-Dimethylethisterone
- 6α,21-Dimethyl-17β-hydroxy-17alpha-pregn-4-en-20-yn-3-one
- 17α-Ethynyl-6α,21-dimethyltestosterone
- 17α-Ethynyl-17-hydroxy-6α,21-dimethylandrost-4-en-3-one
- 17β-Hydroxy-6α-methyl-17-(1-propynyl)-androst-4-en-3-one
- Lutogan
- 6α-Methyl-17α-propynyltestosterone
- 6α-Methyl-17-(1-propynyl)testosterone
- Oracon
- Ovin
- P-5048
- Secrosteron
- Tova

**Ethynodiol diacetate**

**CAS No.**: 297-76-7
**Chem. Abstr. Name**: (3β,17α)-19-Norpregn-4-en-20-yne-3,17-diol diacetate

**A. Evidence for carcinogenicity to animals** (*limited*)

Ethynodiol diacetate was tested in mice and rats by oral administration. It increased the incidence of benign liver tumours in male mice and of mammary tumours in castrated male mice, and produced benign mammary tumours in male rats [ref: 1].

**B. Other relevant data**

No data were available on the genetic and related effects of ethynodiol diacetate alone in humans. See, however, the summary of data for combined oral contraceptives. Ethynodiol diacetate did not induce sex-linked recessive lethal mutations in *Drosophila* [ref: 2].

**References**

1. IARC Monographs, 21, 387-398, 1979

2. IARC Monographs, Suppl. 6, 308-309, 1987

**Synonyms for Ethynodiol diacetate**

- CB 8080
- Cervicundin
- Demulen
- Demulen 28
- Demulen 50
- 3β,17β-Diacetoxy-17α-ethynyl-4-estrene
- 3β,17β-Diacetoxy-17α-ethynyl-4-oestrene

- Ethinodiol diacetate
- Ethynodiol acetate
- β-Ethynodiol diacetate
- Femulen
- Luto-metrodiol
- Metrodiol
- Metrodiol diacetate
- Metrulen
- Metrulene
- 19-Nor-17α-pregn-4-en-20-yne-3β,17-diol diacetate
- Neovulen
- Ovulen
- SC 11800

**17α-Hydroxyprogesterone caproate**

**CAS No.**: 630-56-8
**Chem. Abstr. Name**: 17-[(1-Oxohexyl)oxy]pregn-4-ene-3,20-dione

**A. Evidence for carcinogenicity to animals** (*inadequate*)

17α-Hydroxyprogesterone caproate was tested in rabbits by repeated intramuscular injection, giving inconclusive results [ref: 1]. It was reported to have accelerated the growth of a transplantable cervical tumour line in mice [ref: 2].

**B. Other relevant data**

No data were available to the Working Group.

**References**

1. IARC Monographs, 21, 399-406, 1979

2. Umancheeva, A.F., Novikova, A.I. & Anisomov, V.N. (1981) Stimulating effect of pregnancy on the growth of cervical cancer (Russ.). Akush. Ginekol., 1, 53-55

**Synonyms for 17α-Hydroxyprogesterone caproate**

- Capron
- Corlutin L.A.
- Delalutin
- Depo-proluton
- Duralutin
- Estralutin
- Gesterol L.A.
- 17α-Hexanoyloxypregn-4-ene-3,20-dione
- Hormofort
- HPC
- 17-Hydroxypregn-4-ene-3,20-dione hexanoate
- 17α-Hydroxyprogesterone n-caproate
- 17α-Hydroxyprogesterone hexanoate
- Hylutin
- Hyproval-PA
- Hyroxon
- Idrogestene
- Lutate
- Luteocrin
- Lutopron
- Neolutin

- Pharlon
- Primolut depot
- Progesterone caproate
- Progesterone-retard pharlon
- Proluton depot
- Relutin
- Squibb
- Syngynon
- Teralutil

**Lynoestrenol**

**CAS No.**: 52-76-6
**Chem. Abstr. Name**: (17α)-19-Norpregn-4-en-20-yn-17-ol

**A. Evidence for carcinogenicity to animals** (*inadequate*)

Lynoestrenol was tested by oral administration in mice and rats. It induced a slight increase in the incidence of benign liver-cell tumours in male mice and of malignant mammary tumours in female mice. In female rats, a slight but nonsignificant increase in the incidence of malignant mammary tumours was observed after administration of lynoestrenol [ref: 1].

**B. Other relevant data**

No data were available to the Working Group.

**Reference**

1. IARC Monographs, 21, 407-415, 1979

**Synonyms for Lynoestrenol**

- 3-Desoxynorlutin
- Ethinylestrenol
- $\Delta^4$-17α-Ethinylestren-17β-ol
- 17α-Ethinyl-17β-hydroxyestr-4-ene
- Ethinyloestrenol
- $\Delta^4$-17α-Ethinyloestren-17β-ol
- 17α-Ethinyl-17β-hydroxyoestr-4-ene
- Ethynylestrenol
- 17α-Ethynylestrenol
- 17α-Ethynylestr-4-en-17β-ol
- Ethynyloestrenol
- 17α-Ethynyloestrenol
- 17α-Ethynyloestr-4-en-17β-ol
- Exluten
- Exluton
- Exlutona
- Linestrenol
- Linoestrenol
- Lynenol
- Lynestrenol
- 19-Nor-17α-pregn-4-en-20-yn-17-ol
- Lyndiol
- Minilyn
- Noracycline
- Orgametil
- Orgametril
- Orgametrol

## Megestrol acetate

**CAS No.**: 595-33-5
**Chem. Abstr. Name**: 17α-(Acetyloxy)-6-methylpregna-4,6-diene-3,20-dione

### A. Evidence for carcinogenicity to animals (*limited*)

Megestrol acetate was tested by oral administration in mice, rats, dogs and monkeys. It produced nodular hyperplasia, and benign and malignant mammary tumours in dogs [ref: 1]. No tumour was reported in monkeys [ref: 2].

### B. Other relevant data

No data were available on the genetic and related effects of megestrol acetate alone in humans. See, however, the summary of data for combined oral contraceptives (p. 297). Megestrol acetate did not induce chromosomal aberrations in cultured human lymphocytes [ref: 3].

### References


1. IARC Monographs, 21, 431-439, 1979

2. Weikel, J.H., Jr & Nelson, L.W. (1977) Problems in evaluating chronic toxicity of contraceptive steroids in dogs. J. Toxicol. environ. Health, 3, 167-177

3. IARC Monographs, Suppl. 6, 361-362, 1987


### Synonyms for Megestrol acetate

- 6-Dehydro-6-methyl-17α-acetoxyprogesterone
- 17α-Hydroxy-6-methylpregna-4,6-diene-3,20-dione acetate
- Megestryl acetate
- 6-Methyl-$\Delta^{4,6}$-pregnadien-17α-ol-3,20-dione acetate
- BDH 1298
- Co-Ervonum
- Delpregnin
- DMAP
- Kombiguens
- Magestin
- Megace
- Megage
- Megeron
- Minigest
- Niagestin
- Nuvacon
- Ovaban
- Ovarid
- Ovex
- Planovin
- SC 10363
- Serial 28
- Tri-ervonum
- Volidan
- Volidan 21
- Voplan
- Weradys

## Norethisterone

**CAS No.**: 68-22-4
**Chem. Abstr. Name**: (17α)-17-Hydroxy-19-norpregn-4-en-20-yn-3-one

**Norethisterone acetate**

**CAS No.**: 51-98-9
**Chem. Abstr. Name**: (17α)-17-(Acetyloxy)-19-norpregn-4-en-20-yn-3-one

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Norethisterone and its acetate were tested by oral administration in mice and rats, and by subcutaneous implantation in mice. In mice, norethisterone and its acetate increased the incidence of benign liver-cell tumours in males; norethisterone increased the incidence of pituitary tumours in females and produced granulosa-cell tumours in the ovaries of females. Norethisterone increased the incidence of benign liver-cell tumours and benign and malignant mammary tumours in male rats [ref: 1]. Rats fed 3-4 mg/kg bw per day norethisterone acetate (about 100 times the daily human dose) for two years had an increased incidence of neoplastic nodules of the liver; an increase in the incidence of uterine polyps was seen in females [ref: 2]. In rats given weekly intramuscular injections for 104 weeks of norethisterone enanthate at doses of 10, 30 and 100 mg/kg bw (20, 60 and 200 times the daily human contraceptive dose), there was a dose-related increase in pituitary-gland tumours in males, whereas in females no effect on pituitary glands was observed with the lowest dose and a reduction in pituitary tumours was observed with the highest dose. Benign mammary tumours were observed in males at all doses, but there was little effect in females; the incidence of malignant mammary tumours was greatly increased in both males and females given the two higher dose levels and was dose-related. A dose-related increase in the incidence of liver tumours was also seen in animals of each sex [ref: 3].

**B. Other relevant data**

No data were available on the genetic and related effects of norethisterone alone in humans. See, however, the summary of data for combined oral contraceptives.

Aneuploidy was observed in oocytes of mice treated with high doses of norethisterone acetate. In a test for dominant lethal mutations in which female mice were exposed orally to norethisterone acetate, no increase was seen in one strain of mice, and a second strain showed an increase only when females were mated within two weeks after treatment. The compound did not induce aneuploidy or chromosomal aberrations in cultured human lymphocytes. Neither norethisterone nor its acetate was mutagenic to bacteria [ref: 4].

**References**

1. IARC Monographs, 21, 441-460, 1979

2. Schardein, J.L. (1980) Studies on the components of an oral contraceptive agent in albino rats. II. Progestogenic component and comparison of effects of the components and the combined agent. J. Toxicol. environ. Health, 6, 895-906

3. El Etreby, M.F. & Neumann, F. (1980) Influence of sex steroids and steroid antagonists on hormone-dependent tumors in experimental animals. In: Iacobelli, S., King, R.J.B., Lindner, H.R. & Lippman, M.E., eds, Hormones and Cancer, New York, Raven Press, pp. 321-336

4. IARC Monographs, Suppl. 6, 427-429, 1987

**Synonyms for Norethisterone**

- Anhydroxynorprogesterone

- Anovule
- Brevicon
- Brevicon-28 day
- Conludaf
- Conludag
- 19-Nor-17α-ethynyl-17β-hydroxy-4-androsten-3-one
- 17α-Ethinyl-19-nortestosterone
- Ethinylnortestosterone
- 17α-Ethynyl-19-nortestosterone
- Ethynylnortestosterone
- 19-Nor-17α-ethynyltestosterone
- Gestest
- 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one
- Micronett
- Micronor
- Micronovum
- Mini-Pe
- Modicon
- Modicon 28
- Nor-QD
- Noralutin
- Norethindrone
- Norethisteron
- Norethynodrone
- 19-Norethisterone
- Norfor
- Norgestin
- Noriday
- Norinyl
- Norluten
- Norlutin
- Norluton
- Norpregneninolone
- NSC 9564
- Ortho-novin
- Ortho-novum
- Ovcon-35
- Ovysmen
- Primolut N
- Primolutin
- Proluteasi
- SC 4640

**Synonyms for Norethisterone acetate**

- Anvlar 21
- Controvlar
- 17α-Ethinyl-19-nortestosterone acetate
- 17α-Ethinyl-19-nortestosterone 17β-acetate
- 17α-Ethynyl-19-nortestosterone acetate
- Gynovlar 21
- 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate
- Loestrin
- Loestrin-21
- Minovlar
- Norethindrone acetate
- Norethindrone 17-acetate
- Norethisteron acetate
- 19-Norethisterone acetate
- Norethynyltestosterone acetate
- 19-Norethynyltestosterone acetate
- Norethysterone acetate
- Norlestrin
- Norlutate

- Norlutin-A
- Norlutin acetate
- Orlest 21
- Orlutate
- Ovcon 50
- Primodos
- Primolut-nor
- Primosiston
- Prolestrin
- SH 420
- Zorane

**Norethynodrel**

**CAS No.**: 68-23-5
**Chem. Abstr. Name**: (17α)-17-Hydroxy-19-norpregn-5(10)-en-20-yn-3-one

**A. Evidence for carcinogenicity to animals** (*limited*)

Norethynodrel was tested by oral administration in mice and rats and by subcutaneous implantation in mice. It increased the incidence of pituitary tumours in mice of each sex and that of mammary tumours in castrated males of one strain. It also increased the incidence of benign and malignant liver-cell, pituitary and mammary (benign and malignant) tumours in male rats [ref: 1]. Feeding of norethynodrel to rats following partial hepatectomy and treatment with *N*-nitrosodiethylamine increased the number of γ-glutamyl transpeptidase-positive hepatic foci at four months, but there was no significant difference by nine months [ref: 2].

**B. Other relevant data**

No data were available on the genetic and related effects of norethynodrel alone in humans. See, however, the summary of data for combined oral contraceptives. Norethynodrel did not induce aneuploidy in human cells in culture or unscheduled DNA synthesis in rat hepatocytes *in vitro*. It inhibited intercellular communication in Chinese hamster V79 cells. The compound was not mutagenic to bacteria [ref: 3].

**References**

1. IARC Monographs, 21, 461-477, 1979

2. Yager, J.D. & Yager, R. (1980) Oral contraceptive steroids as promoters of hepatocarcinogenesis in female Sprague-Dawley rats. Cancer Res., 40, 3680-3685

3. IARC Monographs, Suppl. 6, 430-431, 1987

**Synonyms for Norethynodrel**

- Conovid E
- Enavid E
- Enidrel
- Enovid-E
- Enovid-E21
- 17α-Ethynyl-17-hydroxy-5(10)-estren-3-one
- 17α-Ethynyl-17-hydroxy-5(10)-oestren-3-one
- 17-Hydroxy-19-nor-17α-pregn-5(10)-en-20-yn-3-one
- 13-Methyl-17-ethynyl-17-hydroxy-1,2,3,4,6,7,8,9,11,12,13,14,16,17-tetradecahydro-15*H*-cyclopenta[a]phenanthren-3-one
- Previson
- SC 4642

## Norgestrel

**CAS No.**: 797-63-7
**Chem. Abstr. Name**: (17α)(+)-13-Ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one

### A. Evidence for carcinogenicity to animals (*inadequate*)

Norgestrel was tested by oral administration in mice and rats. No increase in the incidence of tumours was observed in either species [ref: 1].

### B. Other relevant data

No data were available of the genetic and related effects of norgestrel alone in humans. See, however, the summary of data for combined oral contraceptives. Norgestrel gave inconclusive results in tests for sex-linked recessive lethal mutations in *Drosophila*. It was not mutagenic to bacteria [ref: 2].

### References

1. IARC Monographs, 21, 479-490, 1979

2. IARC Monographs, Suppl. 6, 432-433, 1987

### Synonyms for Norgestrel

- Levonorgestrel
- Adepal
- Denorgestrel
- 13β-Ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one
- 13-Ethyl-17-hydroxy-18,19-dinor-17alpha-pregn-4-en-20-yn-3-one
- 17α-Ethynyl-18-homo-19-nortestosterone
- 17-Ethynyl-18-methyl-19-nortestosterone
- FH 122-A
- Follistrel
- Lo/Ovral
- Micro-30
- Microgynon 30
- Microlut
- Microluton
- Microval
- Mikro-30
- Minidril
- Monovar
- Neogest
- d-Norgestrel
- Ovral
- Ovran
- Ovranette
- Ovrette
- SH 850
- SH 70850
- Stediril
- TSP-6
- Wy 3707

## Progesterone

**CAS No.**: 57-83-0
**Chem. Abstr. Name**: Pregn-4-ene-3,20-dione

**A. Evidence for carcinogenicity to animals** (*sufficient*)

Progesterone was tested by subcutaneous and by intramuscular injection in mice, rabbits and dogs, and by subcutaneous implantation in mice. It increased the incidences of ovarian, uterine and mammary tumours in mice. Neonatal treatment with progesterone enhanced the occurrence of precancerous and cancerous lesions of the genital tract and increased mammary tumorigenesis in female mice [ref: 1]. Dogs treated with progesterone for four years at one to 25 times the luteal-phase levels for that species developed a dose-related incidence of mammary-gland nodules [ref: 2].

**B. Other relevant data**

No data were available on the genetic and related effects of progesterone in humans.

Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in rats treated *in vivo*. It did not induce chromosomal aberrations or sister chromatid exchanges in cultured human cells, nor chromosomal aberrations or DNA strand breaks in rodent cells. Studies on transformation of rodent cells *in vitro* were inconclusive: a clearly positive result was obtained for rat embryo cells, a weakly positive result for mouse cells and a negative result for Syrian hamster embryo cells. Progesterone was not mutagenic to bacteria [ref: 3].

**References**

1. IARC Monographs, 21, 491-515, 1979

2. Frank, D.W., Kirton, K.T., Murchison, T.E., Quinlan, W.J., Coleman, M.E., Gilbertson, T.J., Feenstra, E.S. & Kimball, F.A. (1979) Mammary tumors and serum hormones in the bitch treated with medroxyprogesterone acetate or progesterone for four years. Fertil. Steril., 31, 340-346

3. IARC Monographs, Suppl. 6, 479-481, 1987

**Synonyms for Progesterone**

- Agolutin
- Bio-luton
- Colprosterone
- Corlutin
- Corlutina
- Corlutone
- Corluvite
- Corporin
- Corpormone
- Corpus luteum hormone
- Cyclogesterin
- Flavolutan
- Fologenon
- Gesterol
- Gestin-E
- Gestone
- Gestormone
- Gestron
- Glanducorpin
- Gynlutin
- Gynolutone
- Hormoflaveine
- Hormoluton

- Lipo-Lutin
- Lucorteum
- Lucorteum sol
- Luteal hormone
- Luteine
- Luteinique
- Luteinol
- Luteocrin normale
- Luteodyn
- Luteogan
- Luteohormone
- Luteol
- Luteopur
- Luteosan
- Luteosid
- Luteostab
- Luteosteron
- Luteovis
- Lutex
- Lutex-leo
- Lutidon
- Lutin
- Lutociclina
- Lutocor
- Lutocyclin
- Lutocyclin M
- Lutocylin
- Lutoform
- Lutogyl
- Lutogynon
- Lutren
- Lutromone
- Nalutron
- Paragest
- Paralut
- Paralut forte
- Percutacrine luteinique
- Piaponon
- $\Delta^4$-Pregnene-3,20-dione
- Primolut
- Profac-O
- Progekan
- Progelan
- Progestasert
- Progeste
- Progesterol
- Progestilin
- Progestin
- Progestine
- Progestogel
- Progestone
- Progestron
- Prolidon
- Prolets
- Prolusteron
- Proluton
- Protormone
- Sistociclina
- Syngesterone
- Syngestrets
- Syntolutan
- Syntolutin

**Overall evaluation**

Progestins are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 6 (1974); Vol. 21 (1979)

**Subsequent evaluation**: Vol. 72 (1999)

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Last updated: 3 March 1998

# PROPYLTHIOURACIL
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 329)

**CAS No.**: 51-52-5

**A. Evidence for carcinogenicity to humans** (*inadequate*)

In one survey of 331 hyperthyroid patients treated with antithyroid drugs, including propylthiouracil, and later with thyroidectomy, four thyroid cancers (an excess of unspecified proportion) were diagnosed more than one year after the beginning of drug therapy [ref: 1]. There has been one case report of acute myeloblastic leukaemia following propylthiouracil treatment [ref: 2].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Propylthiouracil produced thyroid tumours in mice, rats, hamsters and guinea-pigs and pituitary adenomas in mice after its oral administration [ref: 3]. When administered orally to rats with *N*-methyl-*N*-nitrosourea given intravenously [ref: 4] or *N*-nitrosobis(2-hydroxypropyl)amine intraperitoneally [ref: 5], it induced malignant thyroid tumours.

**C. Other relevant data**

No adequate data were available to the Working Group.

**Overall evaluation**

Propylthiouracil is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001)

**Also see previous evaluation**: Vol. 7 (1974)

**References**

1. Dobyns, B.M., Sheline, G.E., Workman, J.B., Tompkins, E.A., McConahey, W.M. & Becker, D.V. (1974) Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy follow-up study. J. clin. Endocrinol. Metab., 38, 976-998

2. Aksoy, M., Erdem, S., Tezel, H. & Tezel, T. (1974) Acute myeloblastic leukaemia after propylthiouracil. Lancet, i, 928-929

3. IARC Monographs, 7, 67-76, 1974

4. Milmore, J.E., Chandrasekaran, V. & Weisburger, J.H. (1982) Effects of hypothyroidism on development of nitrosomethylurea-induced tumors of the mammary gland, thyroid gland, and other tissues. Proc. Soc. exp. Biol. Med., 169, 487-493

5. Kitahori, Y., Hiasa, Y., Konishi, N., Enoki, N., Shimoyama, T. & Miyashiro, A. (1984) Effect of propylthiouracil on the thyroid tumorigenesis induced by *N*-bis(2-hydroxypropyl)nitrosamine in rats. Carcinogenesis, 5, 657-660

**Synonyms**

- 2,3-Dihydro-6-propyl-2-thioxo-4(1*H*)-pyrimidinone
- 2-Mercapto-4-hydroxy-6-n-propylpyrimidine
- 2-Mercapto-6-methyl-4-pyrimidone
- 2-Mercapto-6-methylpyrimid-4-one
- 4-Propyl-2-thiouracil
- 6-n-Propyl-2-thiouracil
- 6-Propyl-2-thio-2,4(1H,3H)-pyrimidinedione
- 6-Propyl-2-thiouracil
- 6-Propylthiouracil
- Procasil
- Propacil
- Propycil
- Propyl-thiorit
- Propyl-Thyracil
- Propylthiouracil
- Prothycil
- Prothyran
- PTU
- 2-Thio-4-oxo-6-propyl-1,3-pyrimidine
- 2-Thio-6-propyl-1,3-pyrimidin-4-one
- 6-Thio-4-propyluracil
- Thyreostat II

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Last updated: 3 March 1998

# PULP AND PAPER MANUFACTURE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 385)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Excess incidences of oral and pharyngeal and/or laryngeal cancers were reported in two studies designed to generate hypotheses. These cancer forms have not been evaluated in independent studies [ref: 1].

Some studies, based on a few cases, suggest that an increased risk of lymphoproliferative neoplasms, particularly Hodgkin's disease, may be linked to employment in the pulp and paper industries [ref: 1-3].

In a prospective cohort study of viscose workers exposed to carbon disulphide, 343 pulp and paper workers served as the reference group. During 15 years of follow-up, nine pulp and paper workers had died of lung cancer, compared with four viscose workers (rate ratio, 2.2; [95% confidence interval, 0.7-6.7]). The pulp and paper workers smoked slightly less than the viscose workers [ref: 4]. When national rates were used as the reference, the standardized mortality ratio (SMR) was 154 (70-292). However, a US proportionate mortality study [ref: 3] comprising 2113 deaths revealed no excess of lung cancer among pulp and paper workers.

A US cohort study of 3572 pulp and paper mill workers employed for at least one year between 1945 and 1955 and followed until 1977 showed statistically nonsignificant excesses of lymphosarcoma and reticulosarcoma (10 cases; SMR, 169; 92-287) and of stomach cancer (17 cases; SMR, 123; 78-185). There was no excess of lung cancer. The excess of lymphosarcoma and reticulosarcoma was present only for men who had worked in sulphate mills (6 observed; SMR, 207; 90-408), whereas the excess of stomach cancer occurred in sulphite mills (11 observed; SMR, 149; 83-246) [ref: 5].

Excesses of cancers at miscellaneous sites have been mentioned in some studies on pulp and paper workers [ref: 1,3,6-8]. The findings may be due to chance, because the cases were generally few and the patterns inconsistent.

A case-control study of the paternal occupations of 692 children who had died of cancer in Massachusetts, USA, showed that paternal employment as a pulp or paper mill worker was associated with tumours of the brain and other parts of the nervous system (six cases observed; relative risk, 2.8); however, as many comparisons were made, this may well be a chance finding [ref: 9].

**B. Other relevant data**

Workers employed for two to 30 years in a paper factory and exposed intermittently to high levels of formaldehyde for short periods showed a significant increase in the incidence of structural chromosomal aberrations associated with mean exposure to formaldehyde; however, no increase in the incidence of sister chromatid exchanges was observed as compared with controls. An increase in the incidence of chromosomal and chromatid-type aberrations was reported among seven workers involved in boiling pulp and handling sulphuric acid in a sulphite factory, as compared to six workers exposed to chlorine during the bleaching of pulp, six workers exposed to dust in a paper mill and 15 control subjects; but the results remain uncertain due to methodological problems [ref: 10].

**Overall evaluation**

Pulp and paper manufacture entails exposures that are *not classifiable as to their carcinogenicity to*

*humans (Group 3).*

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 25 (1981)

**References**


1. IARC Monographs, 25, 157-197, 1981

2. Greene, M.H., Brinton, L.A., Fraumeni, J.F., Jr & D'Amico, R. (1978) Familial and sporadic Hodgkin's disease associated with occupational wood exposure. Lancet, ii, 626-627

3. Milham, S., Jr & Demers, R.Y. (1984) Mortality among pulp and paper workers. J. occup. Med., 26, 844-846

4. Nurminen, M. & Hernberg, S. (1984) Cancer mortality among carbon disulfide-exposed workers. J. occup. Med., 26, 341

5. Robinson, C.F., Waxweiler, R.J. & Fowler, D.P. (1986) Mortality among production workers in pulp and paper mills. Scand. J. Work Environ. Health, 12, 552-560

6. Okubo, T. & Tsuchiya, K. (1974) An epidemiological study on the cancer mortality in various industries in Japan (Jpn.). Jpn. J. ind. Health, 16, 438-452

7. Malker, H.S.R., McLaughlin, J.K., Malker, B.K., Stone, B.J., Weiner, J.A., Erickson, J.L.E. & Blot, W.J. (1986) Biliary tract cancer and occupation in Sweden. Br. J. ind. Med., 43, 257-262

8. Malker, H.S.R., McLaughlin, J.K., Malker, B.K., Stone, B.J., Weiner, J.A., Erickson, J.L.E. & Blot, W.J. (1985) Occupational risks for pleural mesothelioma in Sweden, 1961-79. J. natl Cancer Inst., 74, 61-66

9. Kwa, S.-L. & Fine, L.J. (1980) The association between parental occupation and childhood malignancy. J. occup. Med., 22, 792-794

10. IARC Monographs, Suppl. 6, 573, 1987


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Last updated: 11 March 1998

# RESERPINE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 330)

**CAS No.**: 50-55-5
**Chem. Abstr. Name**: Yohimban-16-carboxylic acid, 11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]-, methyl ester (3β,16β,17α,18β,20α)-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Sixteen case-control and three cohort studies on the relationship between reserpine and breast cancer were available to the Working Group [ref: 1-6]. Between and within studies, estimates of relative risk for different degrees of reserpine use varied from 0.6 to over 3. Many of the positive findings were not coherent with one another; and the studies considered to be most satisfactory methodologically showed little or no evidence of increased risk. However, a recent, large case-control study of breast screening participants showed that, although use of rauwolfia (reserpine) was not significantly associated with an overall increase in risk (odds ratio, 1.2; 95% confidence interval, 0.9-1.8), users for ten years or more had a risk ratio of 4.5 [2.3-11.6] [ref: 7]. A study of prolactin levels in 15 women who had taken reserpine for five years or longer showed only 50% greater elevation of levels than in 15 women taking non-reserpine-containing medications and in 15 women taking no hypertensive medication. Elevated prolactin levels have been postulated as the mechanism for increased breast cancer risk following reserpine use, and the authors postulated that the increase in prolactin observed would probably cause only small increases in breast cancer risk [ref: 8].

**B. Evidence for carcinogenicity to animals** (*limited*)

Reserpine was tested for carcinogenicity in three experiments in mice by oral administration; in two experiments, it induced malignant mammary tumours in females, and in one experiment it induced carcinomas of the seminal vesicles in males [ref: 1,9]. It was tested in four experiments in rats by oral administration; in two, it increased the incidence of phaeochromocytomas [ref: 1,9]. An increase in tumour incidence was observed after repeated subcutaneous injections to mice and rats [ref: 9].

When reserpine was administered either prior to and concurrently with or following treatment with 3-methylcholanthrene orally, it had a protective effect against the induction of mammary tumours in rats [ref: 10]. Concurrent subcutaneous administration of reserpine reduced mammary tumour multiplicity and increased the percentage of well-differentiated tumours induced in rats by *N*-methyl-*N*-nitrosourea given intravenously [ref: 11]; its intravenous administration decreased skin tumour growth in 3-methylcholanthrene-treated mice [ref: 12].

**C. Other relevant data**

No data were available on the genetic and related effects of reserpine in humans.

Reserpine did not induce dominant lethal mutations in mice *in vivo*. In human cells *in vitro*, it did not induce chromosomal aberrations or sister chromatid exchanges. It did not induce chromosomal aberrations in cultured rodent cells or unscheduled DNA synthesis in rat hepatocytes. Reserpine was not mutagenic to bacteria [ref: 13].

**Overall evaluation**

Reserpine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 10 (1976); Vol. 24 (1980)

**References**


1. IARC Monographs, 24, 211-241, 1980

2. Labarthe, D.R. & O'Fallon, W.M. (1980) Reserpine and breast cancer. A community-based longitudinal study of 2000 hypertensive women. J. Am. med. Assoc., 243, 2304-2310

3. Kewitz, H., Jesdinksy, H.-J., Kreutz, G. & Schulz, R. (1980) Reserpine and breast cancer. Arch. int. Pharmacodynam. Ther., Suppl., 22-24

4. Danielson, D.A., Jick, H., Hunter, J.R., Stergachis, A. & Madsen, S. (1982) Nonestrogenic drugs and breast cancer. Am. J. Epidemiol., 116, 329-332

5. Curb, J.D., Hardy, R.J., Labarthe, D.R., Borhani, N.O. & Taylor, J.O. (1982) Reserpine and breast cancer in the hypertension detection and follow-up program. Hypertension, 4, 307-311

6. Horwitz, R.I. & Feinstein, A.R. (1985) Exclusion bias and the false relationship of reserpine and breast cancer. Arch. intern. Med., 145, 1873-1875

7. Stanford, J.L., Martin, E.J., Brinton, L.A. & Hoover, R.N. (1986) Rauwolfia use and breast cancer: a case-control study. J. natl Cancer Inst., 76, 817-822

8. Ross, R.K., Paganini-Hill, A., Krailo, M.D., Gerkins, V.R., Henderson, B.E. & Pike, M.C. (1984) Effects of reserpine on prolactin levels and incidence of breast cancer in postmenopausal women. Cancer Res., 44, 3106-3108

9. Muradyan, R.Y. (1986) A study of possible carcinogenicity of reserpine (Russ.). Vopr. Onkol., 32, 76-81

10. Gerard, S.S., Gardner, B., Patti, J., Husain, V., Shouten, J. & Alfonso, A.E. (1980) Effects of triiodothyronine and reserpine on induction and growth of mammary tumors in rats by 3-methylcholanthrene. J. surg. Oncol., 14, 213-218

11. Verdeal, K., Ertürk, E. & Rose, D.P. (1983) Effects of reserpine administration on rat mammary tumors and uterine disease induced by N-nitrosomethylurea. Eur. J. Cancer clin. Oncol., 19, 825-834

12. Lupulescu, A. (1983) Reserpine and carcinogenesis: inhibition of carcinoma formation in mice. J. natl Cancer Inst., 71, 1077-1083

13. IARC Monographs, Suppl. 6, 485-487, 1987


**Synonyms**

- Abesta
- Abicol
- Adelfan
- Adelphane
- Adelphin
- Adelphin-esidrex-K
- Alkarau
- Alkaserp

- Alserin
- Anquil
- Apoplon
- Apresoline
- Apsical
- Arcum R-S
- Ascoserp
- Austrapine
- Banasil
- Banisil
- Bendigon
- Bioserpine
- Brinderdin
- Briserine
- Broserpine
- Butiserpazide-25
- Butiserpazide-50
- Butiserpine
- Cardioserpin
- Carditivo
- Carrserp
- Crystoserpine
- Darebon
- Deserpine
- 11,17α-Dimethoxy-18β[(3,4,5-trimethoxybenzoyl)oxy]-3β, 20α-yohimban-16β-carboxylic acid methyl ester
- Diutensen-R
- Drenusil-R
- Dypertane compound
- Ebserpine
- Elfanex
- Elserpine
- ENT 50146
- Eserpine
- Diupres
- Eskaserp
- Gamaserpin
- Gilucard
- Hexaplin
- Hiposerpil
- Hiserpia
- Hydromox R
- Hydropres
- Hydropres KA
- 18β-Hydroxy-11,17α-dimethoxy-3β, 20α-yohimban-16β-carboxylic acid methyl ester 3,4,5-trimethoxybenzoate (ester)
- Hygroton-reserpine
- Hypercal B
- Hypertane forte
- Hypertensan
- Idoserp
- Interpina
- Key-Serpine
- Kitine
- Klimanosid
- Lemiserp
- Loweserp
- Marnitension simple
- Maviserpin
- Mayserpine
- Mephaserpin
- Metatensin
- Mio-pressin
- Modenol
- Methyl-1α,2α,3α,4,4aα,5,7,8,13,13bβ,14,14aβ-dodecahydro-2α,11-dimethoxy-3β-(3,4,5-

trimethoxybenzoyloxy)benz[g]indolo(2,3α)quinolizine-1β-carboxylate
- Methyl reserpate 3,4,5-trimethoxybenzoic acid ester
- Methyl 11, 17alpha-dimethoxy-18β(3,4,5-trimethoxy-benzoyloxy)-3β,20α-yohimbane-16β-carboxylate
- Naquival
- Nembu-Serpin
- Neo-antitersol
- Neo-serfin
- Neo-Serp
- Neoslowten
- Ondasil
- Orthoserpina
- Perskleran
- Pressimedin
- Purserpine
- Quiescin
- Raucap
- Raudixin
- Raudixoid
- Raugal
- Raulen
- Rauloycin
- Rauloydin
- Raunervil
- Raunormin 'orzan'
- Raupasil
- Raurine
- Rausan
- Rau-Sed
- Rausedan
- Rausedil
- Rausedyl
- Rauserpen-alk
- Rauserpin
- Rausingle
- Rautrin
- Rauvilid
- Rauwasedin
- Rauwilid
- Rauwiloid
- Rauwiloid +
- Rauwipur
- Rauwita
- Rauwoleaf
- Rauwopur 'byk'
- Recipin
- Regroton
- Renese R
- Resaltex
- Resedrex
- Resedril
- Rese-lar
- Reser-ar
- Reserbal
- Resercaps
- Resercen
- Resercrine
- Reserfia
- Reserjen
- Reserlor
- Reserpamed
- Reserpanca
- Reserpene
- Reserpex
- Reserpidefe

- Reserpil
- Reserpin
- Reserpka
- Reserpoid
- Reserpur
- Reserp 'wander'
- Resersana
- Reserutin
- Resiatric
- Resine
- Resocalm
- Resomine
- Respital
- Restran
- Rezerpin
- Riserpa
- Rivased
- Rivasin
- Rolserp
- Roxel
- Roxinoid
- Salupres
- Salutensin
- Sandril
- Sarpagen
- Sedaraupin
- Seda-recipin
- Seda-salurepin
- Sedserp
- Seominal
- Serfin
- Serolfia
- Serp
- Serp-AFD
- Serpalan
- Serpaloid
- Serpanray
- Serpasil
- Serpasil Apresoline
- Serpasil-Esidrex
- Serpasil-Esidrex No. 1
- Serpasil-Esidrex No. 2
- Serpasil-Esidrex K
- Serpasil premix
- Serpasol
- Serpate
- Serpatone
- Serpax
- Serpedin
- Serpen
- Serpena
- Serpentil
- Serpentina
- Serpentine 'pharbil'
- Serpicon
- Serpiloid
- Serpilum
- Serpine
- Serpipur
- Serpivite
- Serplex K
- Serpoid
- Serpone
- Serpresan
- Serpyrit

- Sertabs
- Sertens
- Sertensin
- Sertina
- Sinesalin composition
- Solfo serpine
- Supergan
- Temposerpine
- Tendoscen-compr.
- Tensanyl
- Tenserlix
- Tenserp
- Tenserpine 'assia
- Tensional
- Tensionorme
- Terbolan
- Transerpin
- 3,4,5-Trimethoxybenzoic acid ester with methyl 18β-hydroxy-11,17α-dimethoxy-3β,20α-yohimban-16β-carboxylate
- 3,4,5-Trimethoxybenzoyl methyl reserpate
- Triserpin
- T-Serp
- Tylandril
- Unilord
- Unitensen
- Vio-serpine
- Vioserpine
- Veriloid
- V-Serp
- Yohimban-16-carboxylic acid derivative of benz[g]indolo(2,3α)quinolizine
- 3β,16β,17α,18β,20α-Yohimban-16-carboxylic acid-11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy] methyl ester

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Last updated: 11 March 1998

# THE RUBBER INDUSTRY
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.332)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

A large number of studies have been conducted on the rubber industries in Canada, China, Finland, Norway, Sweden, Switzerland, the UK and the USA [ref: 1-19]. Workers employed in the industry before 1950 have a high risk of bladder cancer, probably associated with exposure to aromatic amines. Leukaemias have been associated with exposure to solvents and with employment in back processing, tyre curing, synthetic rubber production and vulcanization. Excess mortality from lymphomas has been noted among workers exposed to solvents in such departments as footwear and in tyre plants [ref: 20]. Other cancers, including those of the lung, renal tract, stomach, pancreas, oesophagus, liver, skin, colon, larynx and brain, have been reported as occurring in excess in various product areas and departments, but no consistent excess of any of these cancers is seen across the various studies.

**B. Evidence for carcinogenicity to animals** (*inadequate*)

In one inadequately reported experiment, three groups of rats were kept either in the compounding room, in the mixing area of a Banbury mill or in the mastication area of a Banbury mill at a tyre factory. Increased incidences of respiratory and digestive carcinomas were found in rats maintained for two years at the latter two locations when compared with control rats maintained in the institute laboratory [ref: 17].

**C. Other relevant data**

No increase in the incidence of chromosomal aberrations was observed among 55 rubber workers as compared to 35 control subjects, with the exception of a small group of nonsmokers involved in weighing rubber chemicals. Increased frequencies of sister chromatid exchanges were observed both in smoking and nonsmoking weighers and in mixers who smoked, compared with unexposed controls; the frequency of sister chromatid exchanges in vulcanizers was not statistically significantly increased. Negative results for chromosomal aberrations and sister chromatid exchanges were also obtained in another study of vulcanizers [ref: 21].

Urine samples from 55 workers in two rubber factories and from 35 controls were analysed for mutagenicity in bacteria in the presence of an exogenous metabolic system. Mutagenic activity was observed in the urine of workers involved in weighing and mixing rubber components and in the urine of some vulcanizers (Sorsa et al., 1983b). Similar results were reported by Falck (1983) in an extension of this study. No increase in bacterial mutagenicity was observed in urine samples from 72 tyre builders in a rubber factory and from 23 controls [ref: 21].

**Overall evaluation**

Working in the Rubber industry *entails exposures that are carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 28 (1982)

**References**

1. IARC Monographs, 28, 1982

2. Delzell, E. & Monson, R.R. (1981) Mortality among rubber workers. IV. General mortality patterns. J. occup. Med., 23, 850-856

3. Delzell, E. & Monson, R.R. (1982) Mortality among rubber workers. V. Processing workers. J. occup. Med., 24, 539-545

4. Delzell, E. & Monson, R.R. (1982) Mortality among rubber workers. VI. Men with potential exposure to acrylonitrile. J. occup. Med., 24, 767-769

5. Delzell, E. & Monson, R.R. (1984) Mortality among rubber workers. VIII. Industrial products workers. Am. J. ind. Med., 6, 273-279

6. Delzell, E. & Monson, R.R. (1985) Mortality among rubber workers. IX. Curing workers. Am. J. ind. Med., 8, 537-544

7. Delzell, E. & Monson, R.R. (1985) Mortality among rubber workers. X. Reclaim workers. Am. J. ind. Med., 7, 307-313

8. Delzell, E., Andjelkovich, D. & Tyroler, H.A. (1982) A case-control study of employment experience and lung cancer among rubber workers. Am. J. ind. Med., 3, 393-404

9. Holmberg, B., Westerholm, P., Maasing, R., Kestrup, L., Gumaelius, K., Holmlund, L. & Englund, A. (1983) Retrospective cohort study of two plants in the Swedish rubber industry. Scand. J. work Environ. Health, 9 (Suppl. 2), 59-68

10. Holmes, T.M., Buffler, P.A., Holguin, A.H. & Hsi, B.P. (1986) A mortality study of employees at a synthetic rubber manufacturing plant. Am. J. ind. Med., 9, 355-362

11. Kilpikari, I. (1982) Mortality among male rubber workers in Finland. Arch. environ. Health, 37, 295-299

12. Kilpikari, I., Pukkala, E., Lehtonen, M. & Hakama, M. (1982) Cancer incidence among Finnish rubber workers. Int. Arch. occup. environ. Health, 51, 65-71

13. Meinhardt, T.J., Lemen, R.A., Crandall, M.S. & Young, R.J. (1982) Environmental epidemiologic investigation of the styrene-butadiene rubber industry. Scand. J. Work Environ. Health, 8, 250-259

14. Norell, S., Ahlbom, A., Lipping, H. & Osterblom, L. (1983) Oesophageal cancer and vulcanisation work. Lancet, i, 462-463

15. Norseth, T., Andersen, A. & Giltvedt, J. (1983) Cancer incidence in the rubber industry in Norway. Scand. J. Work Environ. Health, 9 (Suppl. 2), 69-71

16. Wilcosky, T.C., Checkoway, H., Marshall, E.G. & Tyroler, H.A. (1984) Cancer mortality and solvent exposures in the rubber industry. Am. ind. Hyg. Assoc. J., 45, 809-811

17. Wang, H.-W., You, X.-J., Qu, Y.-H., Wang, W.-F., Long, Y.-M. & Ni, J.A. (1984) Investigation of cancer epidemiology and study of carcinogenic agents in the Shanghai rubber industry. Cancer Res., 44, 3101-3105

18. Arp, E.W., Jr, Wolf, P.H. & Checkoway, H. (1983) Lymphocytic leukemia and exposures to benzene and other solvents in the rubber industry. J. occup. Med., 25, 598-602

19. Gustavsson, P., Hogstedt, C. & Holmberg, B. (1986) Mortality and incidence of cancer among Swedish rubber workers. Scand. J. Work Environ. Health, 12, 538-544

20. Veys, C. (1982) The rubber industry: reflections on health risks. In: Gardner, A.W., ed., Current Approaches to Occupational Health, Vol. 2, Bristol, Wright PSG, pp. 1-29

21. IARC Monographs, Suppl. 6, 488, 1987

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Last updated: 10 February 1998

# SACCHARIN
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 334)

**Saccharin**
**CAS No.**: 81-07-2
**Chem. Abstr. Name**: 1,2-Benzisothiazo1-3(2*H*)-one, l,l-dioxide

**Sodium Saccharin**
**CAS No.**: 128-44-9
**Chem. Abstr. Name**: 1,2-Benzisothiazo1-3(2*H*)-one, 1,1-dioxide, sodium salt

**Calcium Saccharin**
**CAS No.**: 6485-34-3
**Chem. Abstr. Name**: 1,2-Benzisothiazo1-3(2*H*)-one, 1,1-dioxide, calcium salt

***ortho*-Toluenesulphonamide**
**CAS No.**: 88-19-7
**Chem. Abstr. Name**: 2-Methylbenzenesulfonamide

**A. Evidence for carcinogenicity to humans** (*inadequate*)

The evidence that the risk of cancer is increased among users of artificial sweeteners is inconsistent [ref: 1]. Since the positive report of Howe *et al.* [ref: 2], reports have become available on seven case-control studies and on one population study of bladder cancer.

The largest was a population-based study in ten areas of the USA, with 3010 bladder cancer cases and 5783 controls. The relative risk for bladder cancer associated with use of artificial sweeteners was 1.0 (95% confidence interval, 0.9-1.1) among men and 1.1 (0.9-1.3) among women. Significant trends of increasing risk with increasing average daily consumption were found in certain subgroups examined *a priori* on the basis of the results of animal experiments; these subgroups were female nonsmokers and male heavy smokers [ref: 3]. Subsequent, independent re-analysis of the same data by a different statistical technique (multiple logistic regression) confirmed the original findings overall but cast doubt on the significance of the findings in the two subgroups because of inconsistent dose-response trends, especially among the male heavy smokers [ref: 4]. In response, the original investigators noted that the inconsistency derived from the development of risk scores which, in their opinion, were not correctly derived, as two relevant variables had been omitted [ref: 5]. In a subsequent report on data from one of the areas participating in this study, the use of hospital and population controls was compared. A higher proportion of hospital controls was found to have used artificial sweeteners than population controls [ref: 6]. This had been postulated earlier [ref: 2] as a possible reason for the negative findings of a hospital-based case-control study [ref: 7]. Bias resulting from use of prevalent rather than incident cases [ref: 8] has been suggested as a possible reason for the negative findings of another hospital-based case-control study [ref: 9].

Three other case-control studies have also shown increased risks among subgroups. In one, conducted simultaneously in Japan, the UK and the USA, the relative risks among women in the US component of the study associated with 'any' use of diet drinks and of sugar substitutes were 1.6 and 1.5, respectively, and 2.6 and 2.1, respectively, for nonsmokers [ref: 10]. In the other two areas, however, a history of the use of sugar substitutes, primarily saccharin, was not associated with an elevated bladder cancer risk [ref: 11]. In a second study, conducted in West Yorkshire, UK, elevated risks were found for saccharin takers who were nonsmokers. In men, the relative risk was 2.2 (95% confidence interval, 1.3-3.8); that in women was 1.6 (0.8-3.2) [ref: 12]. In a third study, conducted in a rural district of Denmark, a relative risk of 2.5 (1.0-6.6) was reported for saccharin consumption in men and women combined. This risk was not reduced after controlling for tobacco use and industrial work [ref: 13].

Two studies in Denmark [ref: 14,15], one in the USA [ref: 16] and a further case-control study in Canada [ref: 17], however, gave negative results. In one of the Danish studies, incidence of bladder cancer at ages 20-34 among people born 1941-1945 (when use of saccharin was high in Denmark) was compared with that among those born 1931-1940. The risk for men was 1.0 (0.7-1.6) and that for women 0.3 (0.1-1.0). This study indirectly assessed intrauterine exposure to saccharin [ref: 14]. The other two studies were population-based case-control studies of bladder cancer. In Denmark, the relative risk for people of the two sexes combined was 0.8 (0.6-1.1) [ref: 15]. In a study in the USA of bladder cancer in women aged 20-49, the odds ratio for regular use of artificially sweetened beverages, table-top sweetener or both was 1.0 (0.7-1.7) [ref: 16]. In Canada, the odds ratio for use of saccharin was 1.0 (0.9-1.2) in men and 1.0 (0.8-1.2) in women [ref: 17]. The increased risks seen in subgroups in other studies were not replicated in either study.

In the USA, in a study of 1862 patients hospitalized for cancer and of 10 874 control patients, a greater proportion of artificial sweetener users was found among women with cancer of the stomach. Little information was available on urinary-tract cancer. No overall association was found between artificial sweetener use and cancer [ref: 18].

**B. Evidence for carcinogenicity to animals** (*sufficient*

Saccharin (unspecified or commercial) has been tested for carcinogenicity by oral administration to mice, rats and hamsters. In mice, saccharin produced no difference in tumour incidence between treated and control animals in one single and in one multigeneration study. Two further studies by oral administration in mice and three in rats were considered to be inadequate for evaluation. A study in hamsters by oral administration and one study in mice by skin application could not be evaluated. A study in mice by bladder insertion provided evidence for the induction of bladder carcinomas [ref: 1]. Oral administration to mice produced thyroid tumours [ref: 19].

Sodium saccharin has been tested for carcinogenicity by oral administration to mice, rats and monkeys. One study in mice was inadequate for evaluation [ref: 1]. One single-generation study in rats showed an increased incidence of bladder tumours in males; two further studies showed a few bladder tumours; another study showed no difference in tumour incidence between treated and control animals; and two others were inadequate for evaluation [ref: 1]. In four two-generation studies in rats, sodium saccharin produced a statistically significant increase in the incidence of bladder tumours in $F_1$ males fed either 5% or 7.5% sodium saccharin [ref: 1,20]. In a further two-generation study of rats, a dose-related increase in the incidences of benign, malignant and/or combined bladder neoplasms was observed in males treated with doses ranging from 4-7.5% in the diet, while no tumorigenic effect was observed with 1% [ref: 21,22]. Transplacental exposure of rats to sodium saccharin and to saccharin (commercial) did not produce any treatment-related neoplasm [ref: 21,23]. Sodium saccharin has also been tested in mice by bladder insertion: it increased the incidence of bladder carcinomas. Expreiments in which it was tested by oral administration to monkeys and by intraperitoneal administration to mice were considered to be inadequate for evaluation [ref: 1].

The combination of sodium saccharin with sodium cyclamate in a ratio of 1:10 has been tested by oral administration in a multigeneration experiment in mice and in single experiments in rats. In one study in rats, transitional-cell carcinomas in the bladder were produced in male animals given the highest dose; in two further studies in rats and in the study in mice, there was no difference in tumour incidence between treated and control animals [ref: 1,24]. Another study in rats was inadequate for evaluation [ref: 1].

Pretreatment with a single instillation into the bladder of a low dose of *N*-methyl-*N*-nitrosourea or feeding of *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide and subsequent oral administration of sodium saccharin for long periods increased the incidence of bladder neoplasms in rats over than induced by the nitrosourea or the amide alone [ref: 1]. Simultaneous administration of *N*-nitroso-*N*-(4-hydroxybutyl)butylamine and sodium saccharin significantly enhanced the induction of bladder papillomas compared to treatment with the nitrosamine alone [ref: 25]. Commercial saccharin preparations enhanced lung tumour induction in mice when given before or during intraperitoneal urethane administration [ref: 26]. In rats, oral administration sodium saccharin significantly increased the incidence of bladder neoplasms induced by ulceration of bladder mucosa [ref: 27,28]. Other studies of simultaneous or consecutive treatment with saccharin and known carcinogens were inadequate for evaluation [ref: 1].

*ortho*-Toluenesulphonamide was tested for carcinogenicity by oral administration in rats in a two-generation study: no increase in bladder tumour incidence was noted in animals of either generation. In one of two single-generation studies in rats, benign and malignant bladder tumours were found [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of saccharin, sodium saccharin or *ortho*-toluenesulphonamide in humans [ref: 29].

It should be noted that many studies do not differentiate between saccharin ('insoluble' form) and sodium saccharin. Additionally, when it is reported that 'saccharin' (presumably sodium saccharin) causes a positive response, primarily in assays for chromosomal effects, the effect is seen only with very high concentrations, at which simple salts also give responses [ref: 29].

Treatment of mice with saccharin did not induce micronuclei or chromosomal aberrations in bone-marrow cells or spermatocytes; conflicting results were obtained for the induction of dominant lethal mutations. A commercial preparation (of unknown purity) caused somatic mutations in the mouse spot test. Injection of radioactive saccharin into rats revealed no DNA binding in the liver or bladder, nor did treatment of rats result in DNA damage in bladder tissue. Saccharin did not induce sister chromatid exchanges in cultured human lymphocytes. Negative results were obtained in assays for transformation in cultured rodent cells, but saccharin enhanced transformation of virus-infected rat embryo cells and of C3H 10T1/2 mouse embryo cells initiated with 3-methylcholanthrene in two-stage transformation assays. Results obtained with rodent cell systems were inconclusive with regard to inhibition of intercellular communication. It caused DNA strand breaks in rat hepatocytes but no chromosomal aberration in Chinese hamster cells. Saccharin induced aneuploidy but not recombination or gene conversion in yeast. It was not mutagenic and did not induce prophage in bacteria [ref: 29].

Treatment of mice with sodium saccharin did not induce micronuclei, somatic mutations (in the spot test) or sperm abnormalities. Treatment of Chinese hamsters did not induce chromosomal aberrations in bone-marrow cells or spermatogonia but induced sister chromatid exchanges in bone-marrow cells. Treatment of mice with commercial sodium saccharin resulted in the induction of dominant lethal mutations, but treatment with a preparation 'purified' by undefined criteria did not. Sodium saccharin induced chromosomal aberrations and sister chromatid exchanges in cultured human lymphocytes and induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells but no mutation in mouse lymphoma cells. It did not induce tranformation of BALB/c 3T3 cells. Contradictory results have been reported concerning the ability of sodium saccharin to induce sex-linked recessive lethal mutations in *Drosophila*, and it did not cause a significant increase in heritable translocations. Sodium saccharin induced mutation, gene conversion and recombination in yeast, but was not mutagenic to bacteria [ref: 29].

*ortho*-Toluenesulphonamide did not induce micronuclei or somatic mutation (in the spot test) in mice treated *in vivo*. Contradictory results have been obtained for the induction of sex-linked recessive lethal mutations in *Drosophila*. It was not mutagenic to bacteria [ref: 29].

**Overall evaluation**

Saccharin is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 73 (1999)

**Also see previous evaluation**: Vol. 22 (1980)

**References**

1. IARC Monographs, 22, 55-109, 171-185, 1980

2. Howe, G.R., Burch, J.D., Miller, A.B., Cook, G.M., Estève, J., Morrison, B., Gordon, P., Chambers, L.W., Fodor, G. & Winsor, G.M. (1980) Tobacco use, occupation, coffee, various nutrients and bladder cancer. J. natl Cancer Inst., 64, 701-713

3. Hoover, R.M. & Strasser, P.H. (1980) Artificial sweeteners and human bladder cancer. Preliminary results. Lancet, i, 837-840

4. Walker, A.M., Dreyer, N.A., Friedlander, E., Loughlin, J., Rothman, K.J. & Kohn, H.I. (1982) An independent analysis of the National Cancer Institute study on non-nutritive sweeteners and bladder cancer. Am. J. publ. Health, 72, 376-381

5. Hoover, R. & Hartge, P. (1982) Non-nutritive sweeteners and bladder cancer. Am. J. publ. Health, 72, 382-383

6. Silverman, D.T., Hoover, R.N. & Swanson, G.M. (1983) Artificial sweeteners and lower urinary tract cancer: hospital vs. population controls. Am. J. Epidemiol., 117, 326-334

7. Wynder, E.L. & Stellman, S.D. (1980) Artificial sweetener use and bladder cancer: a case-control study. Science, 207, 1214-1216

8. Goldsmith, D.F. (1982) Calculation of potential bias in the odds ratio illustrated by a study of saccharin use and bladder cancer. Environ. Res., 27, 298-306

9. Kessler, I.I. & Clark, J.P. (1978) Saccharin, cyclamate, and human bladder cancer. No evidence of an association. J. Am. med. Assoc., 240, 349-355

10. Morrison, A.S. & Buring, J.E. (1980) Artificial sweeteners and cancer of the lower urinary tract. New Engl. J. Med., 302, 537-541

11. Morrison, A.S., Verhoek, W.G., Leck, I., Aoki, K., Ohno, Y. & Obata, K. (1982) Artificial sweeteners and bladder cancer in Manchester, UK, and Nagoya, Japan. Br. J. Cancer, 45, 332-336

12. Cartwright, R.A., Adib, R., Glashan, R. & Gray, B.K. (1981) The epidemiology of bladder cancer in West Yorkshire. A preliminary report on non-occupational aetiologies. Carcinogenesis, 2, 343-347

13. Mommsen, S., Aagaard, J. & Sell, A. (1983) An epidemiological study of bladder cancer in a predominantly rural district. Scand. J. Urol. Nephrol., 17, 307-312

14. Jensen, O.M. & Kamby, C. (1982) Intra-uterine exposure to saccharin and risk of bladder cancer in man. Int. J. Cancer, 29, 507-509

15. Møller-Jensen, O., Knudsen, J.B., Sørensen, B.L. & Clemmesen, J. (1983) Artificial sweeteners and absence of bladder cancer risk in Copenhagen. Int. J. Cancer, 32, 557-582

16. Piper, J.M., Matanoski, G.M. & Tonascia, J. (1986) Bladder cancer in young women. Am. J. Epidemiol., 123, 1033-1042

17. Risch, H.A., Burch, J.D., Miller, A.B., Hill, G.B., Steele, R. & Howe, G.R. (1987) Dietary factors and the incidence of cancer of the urinary bladder. Am. J. Epidemiol. (in press)

18. Morrison, A.S. (1979) Use of artificial sweeteners by cancer patients. J. natl Cancer Inst., 62, 1397-1399

19. Prasad, O. & Rai, G. (1986) Induction of papillary adenocarcinoma of thyroid in albino mice by saccharin feeding. Indian J. exp. Biol., 24, 197-199

20. Taylor, J.M., Weinberger, M.A. & Friedman, L. (1980) Chronic toxicity and carcinogenicity of the urinary bladder of sodium saccharin in the in utero-exposed rat. Toxicol. appl. Pharmacol., 54, 57-75

21. Schoenig, G.P., Goldenthal, E.I., Geil, R.G., Frith, C.H., Richter, W.R. & Carlborg, F.W. (1985) Evaluation of the dose response and in utero exposure to saccharin in the rat. Food chem. Toxicol., 23, 475-490

22. Squire, R.A. (1985) Histopathological evaluation of rat urinary bladders from the IRDC two-generation bioassay of sodium saccharin. Food chem. Toxicol., 23, 491-497

23. Schmähl, D. & Habs, M. (1980) Absence of a carcinogenic response to cyclamate and saccharin in Sprague-Dawley rats after transplacental application. Arzneimittelforsch., 30, 1905-1906

24. Schmähl, D. & Habs, M. (1984) Investigations on the carcinogenicity of the artificial sweeteners sodium cyclamate and sodium saccharin in rats in a two-generation experiment. Arzneimittelforsch., 34, 604-606

25. Nakanishi, K., Hirose, M., Ogiso, T., Hasegawa, R., Arai, M. & Ito, N. (1980) Effects of sodium saccharin and caffeine on the urinary bladder of rats treated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. Gann, 71, 490-500

26. Theiss, J.C., Arnold, L.J. & Shimkin, M.B. (1980) Effect of commercial saccharin preparations on urethan-induced lung tumorigenesis in strain A mice. Cancer Res., 40, 4322-4324

27. Cohen, S.M., Murasaki, G., Fukushima, S. & Greenfield, R.E. (1982) Effect of regenerative hyperplasia on the urinary bladder: carcinogenicity of sodium saccharin and *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide. Cancer Res., 42, 65-71

28. Hasegawa, R., Greenfield, R.E., Murasaki, G., Suzuki, T. & Cohen, S.M. (1985) Initiation of urinary bladder carcinogenesis in rats by freeze ulceration with sodium saccharin promotion. Cancer Res., 45, 1469-1473

29. IARC Monographs, Suppl. 6, 488-493, 520-522, 1987

**Synonyms for Saccharin**

- Anhydro-o-sulphaminebenzoic acid
- Assugrin vollsuss [also contains sodium cyclamate]
- 3-Benzisothiazolinone 1,1-dioxide
- 1,2-Benzisothiazolin-3-one, 1,1-dioxide
- 1,2-Benzisothiazolinone, 1,1-dioxide
- Benzoic sulphimide
- *o*-Benzoic sulphimide
- Benzoic sulphinide
- Benzosulphimide
- Benzo-2-sulphimide
- *o*-Benzosulphimide
- *o*-Benzoyl sulphimide
- Benzo-sulphinide
- 1,2-Dihydro-2-ketobenzisosulphonazole
- 2,3-Dihydro-3-oxobenzisosulphonazole
- Edulcor
- Garantose
- Glucid

- Gluside
- Hermesetas
- 3-Hydroxybenzisothiazole-S,S-dioxide
- Insoluble saccharin
- Kandiset
- Natreen [also contains sodium cyclamate]
- Sacarina
- Saccharimide
- Saccharin acid
- Saccharin insoluble
- Saccharina
- Saccharine
- Saccharinol
- Saccharinose
- Saccharol
- Saxin
- Sucre
- Sucrette
- *o*-Sulphobenzimide
- *o*-Sulphobenzoic acid imide
- 2-Sulphobenzoic imide
- Sykose
- Zaharina

**Synonyms for Sodium saccharin**

- 1,2-Benzisothiazolin-3-one,l,l-dioxide, sodium salt
- Cristallose
- Crystallose
- Dagutan
- Kristallose
- ODA
- Saccharinriatrium
- Saccharin sodium
- Saccharin soluble
- Saccharoidum Natricum
- Saxin
- Sodium benzosulphimide
- Sodium 2-benzosulphimide
- Sodium *ortho*-benzosulphimide
- Sodium saccharide
- Sodium saccharinate
- Sodium saccharine
- Soluble saccharin
- Soluble Gluside
- Succaril (also contains sodium cyclamate)
- Sucra
- 2-Sulphobenzoic imide, sodium salt
- Sweeta
- Sykose
- Willosetten

**Synonyms for Calcium saccharin**

- 1,2-Benzisothiazolin-3-one,l,l-dioxide, calcium salt
- Calcium benzosulphimide
- Calcium 2-benzosulphimide
- Calcium-*ortho*-benzosulphimide
- Calcium saccharina
- Calcium saccharinate
- Calcium saccharine
- Daramin
- Saccharin calcium

- 2-Sulphobenzoic imide, calcium salt

**Synonym for *ortho*-Toluenesulphonamide**

- 2-Methylbenzenesulfonamide

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Last updated: 30 September 1999

# SHALE-OILS
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 339)

**CAS No.:** 68308-34-9

**A. Evidence for carcinogenicity to humans** (*sufficient*)

The association between shale-oils and skin cancers, particularly of the scrotum, was demonstrated by analyses of 65 cases of skin cancer, including 31 of the scrotum, from the Scottish shale-oil industry. In the UK, over 2000 cases of skin cancer ('mule-spinners' cancer') were recorded among cotton-textile workers and others exposed to lubricating oils (many of which are believed to have been shale-derived). The occupational etiology of these cases is supported by occupational mortality statistics for the UK and by an occupational comparison with fatal cases of penile cancer. In contrast, one study showed very few scrotal cancers among US cotton-textile workers employed in mills where shale-derived lubricants were not used. A cohort study of shale-oil workers in western USA showed statistically significant excesses of all cancers and of colon cancer, although data on duration and time since first exposure were not available. A cohort study of shale-oil workers in Estonia showed a significant excess of skin cancer but not of cancers at other sites [ref: 1]. A follow-up of 6064 men who had worked in the Scottish oil-shale industry between 1950 and 1962 showed a significant excess of skin cancer [ref: 2]. A case-control study of lung cancer in the shale area showed no association with work in the shale industry [ref: 2].

Two basal- and two squamous-cell carcinomas were found among 325 workers employed at an oil-shale demonstration facility during 1948-1969 in Utah, USA. The incidence was about that expected [ref: 3].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Inhalation of either raw oil shale or spent oil shale produced lung tumours in rats. Application of an extract of spent oil shale produced skin tumours in mice [ref: 1].

Skin application of crude oils from both low- and high-temperature retorting induced skin tumours in mice and rabbits; the high-temperature retorted oils had greater carcinogenic activity. A low-temperature crude oil produced lung tumours in mice after intratracheal instillation [ref: 1].

Various fractions of shale-oils were carcinogenic when applied to the skin of mice and rabbits [ref: 1].

Shale-oil distillates, residues, blends, and commercial products of the oil-shale industry were tested in mice by skin application, producing skin tumours. Distillation fractions from less highly refined shale-oils were more carcinogenic than the more highly refined products [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of shale-oils in humans.

All shale-derived materials assayed in tests for genetic and related effects came from sources in the USA and were therefore all produced by low-temperature processes [ref: 4].

Chromosomal aberrations were induced in bone-marrow cells of rats following administration by gavage of a suspension of raw oil-shale. In-vitro tests of extracts of raw oil-shale in cultured rodent cells, yeast and bacteria gave negative results [ref: 4].

Preparations of spent oil-shale yielded negative results in an assay for chromosomal aberrations *in vivo* and in mutation assays with eukaryotic cells *in vitro*; contradictory results were obtained in bacterial mutation assays [ref: 4].

Preparations of shale-derived crude oils from various sources and retort processes gave both positive and negative results in assays for chromosomal effects in rodents *in vivo*. Two crude shale-oil preparations induced sister chromatid exchanges in cultured human lymphocytes; three others did not induce mitotic gene conversion in yeast. Shale-derived crude oils were mutagenic to cultured rodent cells, yeast and bacteria following metabolic or photoinduced activation [ref: 4].

As compared with the corresponding crude shale-oils, preparations of hydrotreated oils showed less activity or gave negative results in various short-term tests [ref: 4].

Oil-shale retort process-waters induced chromosomal aberrations, but not sister chromatid exchanges, in cells of mice treated *in vivo*, chromosomal aberrations in cultured rodent cells and mutation and DNA damage in cultured rodent cells and bacteria following metabolic activation or photoactivation [ref: 4].

Extracts of oil-shale ash were not mutagenic to fungi but were mutagenic to bacteria in the absence of a metabolic system [ref: 4].

**Overall evaluation**

Shale-oils are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 35 (1985)

**References**

1. IARC Monographs, 35, 161-217, 243-247, 1985

2. Miller, B.G., Cowie, H.A., Middleton, W.G. & Seaton, A. (1986) Epidemiologic studies of Scottish oil shale workers. III. Causes of death. Am. J. ind. med., 9, 433-446

3. Rom, W.N., Krueger, G., Zone, J., Attfield, M.D., Costello, J., Burkart, J. & Turner, E.R. (1985) Morbidity survey of US oil shale workers employed during 1948-1969. Arch. environ. Health, 40, 58-62

4. IARC Monographs, Suppl. 6, 494, 1987

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Last updated: 10 February 1998

# SODIUM *ortho*-PHENYLPHENATE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 392)

**CAS No.**: 132-27-4
**Chem. Abstr. Name**: (1,1'-Biphenyl)-2-ol, sodium salt

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Sodium *ortho*-phenylphenate produced urinary bladder carcinomas in rats following its oral administration [ref: 1-3]. It increased the incidences of haemangiosarcomas of the liver and of hepatocellular carcinomas in male mice after its oral administration [ref: 4]. When given in the diet to rats, it enhanced the incidence of bladder cancer induced by oral administration of *N*-nitroso-*N*-(4-hydroxybutyl)-*N*-butylamine [ref: 5].

**Overall evaluation**

Sodium *ortho*-phenylphenate is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 73 (1999)

**Also see previous evaluation**: Vol. 30 (1983)

**References**

1. IARC Monographs, 30, 329-344, 1983

2. Fujii, T. & Hiraga, K. (1985) Carcinogenicity testing of sodium *ortho*-phenylphenate in F344 rats (Jpn.). J. Saitama med. School,12, 277-287

3. Fujii, T., Mikuriya, H., Kamiya, N. & Hiraga, K. (1986) Enhancing effect of thiabendazole on urinary bladder carcinogenesis induced by sodium *o*-phenylphenate in F344 rats. Foodchem. Toxicol., 24, 207-211

4. Hagiwara, A., Shibata, M., Hirose, M., Fukushima, S. & Ito, N. (1984) Long-term toxicity and carcinogenicity study of sodium *o*-phenylphenate in B6C3$F_1$ mice. Food chem. Toxicol., 22, 809-814

5. Fukushima, S., Kurata, Y., Shibata, M., Ikawa, E. & Ito, N. (1983) Promoting effect of sodium *o*-phenylphenate and *o*-phenylphenol on two-stage urinary bladder carcinogenesis in rats. Gann, 74, 625-632

**Synonyms**

- 2-Biphenylol, sodium salt
- Biphenyl-2-ol, sodium salt
- Dowicide
- Dowicide A & A flakes
- Dowizid A
- 2-Hydroxybiphenyl sodium salt

- 2-Hydroxydiphenyl sodium
- Mystox WFA
- Natriphene
- 2-Phenylphenol sodium salt
- *ortho*-Phenylphenol sodium salt
- Preventol ON & ON extra
- Sodium [1,1'-biphenyl]-2-olate
- Sodium 2-biphenylolate
- Sodium 2-hydroxydiphenyl
- Sodium 2-phenylphenate
- Sodium *ortho*-phenylphenol
- Sodium *ortho*-phenylphenolate
- Sodium *ortho*-phenylphenoxide
- Sodium *ortho*-phenylphenylolate
- Sodium phenylphenate
- SOPP
- Stopmold B
- Topane

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Last updated: 30 September 1999

# SOOTS
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.343)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

The carcinogenicity of soot is demonstrated by numerous case reports, dating back over 200 years, of skin cancer, particularly of the scrotum, among chimney-sweeps. More recent cohort studies of mortality among chimney-sweeps in Sweden and Denmark have shown a significantly increased risk of lung cancer. Supporting evidence for an association with lung cancer was provided by two earlier epidemiological studies in the German Democratic Republic and the UK. The potentially confounding and interactive effects of smoking could not be evaluated; however, cigarette smoking is not believed to have seriously biased these estimates. In addition to lung cancer, statistically significant excess mortality from oesophageal cancer, primary liver cancer and leukaemia was found among chimney-sweeps in one study [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate* for soots; *sufficient* for soot extracts)

Coal soot was tested in two experiments in mice by whole-body exposure, but the studies were inadequate for evaluation. Coal-soot extracts applied to the skin of mice produced skin tumours in two studies. A wood-soot extract applied to the skin of mice was inadequately tested. In limited studies, subcutaneous implants of wood soot in female rats produced a few local sarcomas; similar implants in the scrotal sac of rats did not. An extract of fuel-oil soot was inadequately tested by application to the skin of mice. Extracts of soot from the combustion of oil shale produced skin tumours in mice after dermal application and lung tumours in rats after intratracheal instillation. Extracts of soot from the combustion of a heating oil produced from shale-oil produced skin tumours in mice in two experiments when applied to the skin [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of soots in humans.

Extracts of soot samples from domestic sources were mutagenic to *Salmonella typhimurium* both in the presence and absence of an exogenous metabolic system. Extracts of experimentally-derived soots were mutagenic in forward mutation assays in *S. typhimurium* and in cultured human lymphoblasts in the presence of an exogenous metabolic system. Extracts of particulate emissions from wood combustion were shown to induce sister chromatid exchanges in Chinese hamster ovary cells, transformation of Syrian hamster embryo cells and mutation in *S. typhimurium*. An experimentally-derived, intact particulate soot and an extract of this material were mutagenic in a human lymphoblastoid cell line [ref: 2].

**Overall evaluation**

Soots are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 35 (1985)

**References**

1. IARC Monographs, 35, 219-246, 1985

2. IARC Monographs, Suppl. 6, 497, 1987

**Synonym**

- Primary carbonaceous particulate emissions

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Last updated: 10 February 1998

# SPIRONOLACTONE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 344)

**CAS No.**: 52-01-7
**Chem. Abstr. Name**: Pregn-4-ene-21-carboxylic acid,7-(acetylthio)-17-hydroxy-3-oxo-, γ-lactone,(7α, 17α)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Cases of breast cancer have been reported in women who had used spironolactone. Four analytical studies, however, showed no consistent evidence of an assocation [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

Spironolactone was tested by oral administration in two experiments in rats. Increased incidences of thyroid and testicular tumours were reported in one experiment but not in another experiment of longer duration with lower doses [ref: 1].

**C. Other relevant data**

No data were available to the Working Group.

**Overall evaluation**

Spironolactone is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001)

**Also see previous evaluation**: Vol. 24 (1980)

**Reference**

1. IARC Monographs, 24, 259-273, 1980

**Synonyms**

- 7α-Acetylthio-17β-hydroxy-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone
- 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone
- 7α-Acetylthio-3-oxo-17β-pregn-4-ene-21, 17β-carbolactone
- Aldactazide
- Aldactide
- Aldactone
- Aldactone A
- β-(7α-Acetylthio-17β-hydroxy)-3-oxoandrost-4-en-17α-yl)propionic acid, lactone
- 17-Hydroxy-7α-mercapto-3-oxo-17α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid γ-lactone 7-acetate
- 3-(3-Keto-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl) propionic acid lactone

- Osiren
- Osyrol
- 3'-(3-Oxo-7α-acetylthio-17β-hydroxyandrost-4-en-17β-yl)propionic acid lactone
- 3-(3-Oxo-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl)propionic acid gamma-lactone
- S-Ester with 17-hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone
- SC 15983
- SC 9420
- Spiresis
- Spiridon
- Spiro[17*H*-cyclopenta[a]phenanthrene-17,2'(5'*H*)furan], pregn-4-ene-21-carboxylic acid deriv.
- Spiroctanie
- Spirolactone
- Spirolakton
- Spirolang
- Spirone
- Spironolactone A
- Uractone
- Verospiron
- Verospirone

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Last updated: 11 March 1998

# SULFAFURAZOLE (SULPHISOXAZOLE)
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 347)

**CAS No.**: 127-69-5

**Chem. Abstr. Name**: Benzenesulfonamide, 4-amino-*N*-(3,4-dimethyl-5-isoxazolyl)-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No significant association with cancer at any site was oberved during 1969-1976 among 11 659 members of a prepaid health plan prescribed sulfafurazole during 1969-1973 [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Sulfafurazole was tested in mice and rats by oral administration; no increase in tumour incidence was observed [ref: 2].

**C. Other relevant data**

No data were available to the Working Group.

**Overall evaluation**

Sulfafurazole (sulphisoxazole) is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 24 (1980)

**References**

1. Friedman, G.D. & Ury, H.K. (1980) Initial screening for carcinogenicity of commonly used drugs. J. natl Cancer Inst., 65, 723-733

2. IARC Monographs, 24, 275-285, 1980

**Synonyms**

- Accuzole
- Alphazole
- Amidoxal
- 5-(*p*-Aminobenzenesulphonamide)-3,4-dimethylisoxazole
- 4-Amino-*N*-(3,4-dimethyl-5-isoxazolyl)benzenesulphonamide
- 5-(4-Aminophenylsulphonamido)-3,4-dimethylisoxazole
- Astrazolo
- Azo gantrisin
- Azosulfizin
- Bactesulf
- Barazae

- Chemouag
- 3,4-Dimethylisoxazole-5-sulphanilamide
- N'-(3,4)Dimethylisoxazol-5-yl-sulphanilamide
- $N_1$-(3,4-Dimethyl-5-isoxazolyl)sulphanilamide
- 3,4-Dimethyl-5-sulphanilamidoisoxazole
- 3,4-Dimethyl-5-sulphonamidoisoxazole
- Dorsulfan
- Entusil
- Entusul
- Ganda
- Gantrisin
- Gantrisine
- Gantrisona
- Gantrosan
- Isoxamin
- J-Sul
- Koro-Sulf
- Neazolin
- Neoxazol
- Norilgan-S
- Novazolo
- Novosaxazole
- NU 445
- Pancid
- Renosulfan
- Resoxol
- Roxosul
- Roxoxol
- Saxosozine
- Sodizole
- Sosol
- Soxamide
- SK-soxazole
- Soxisol
- Soxitabs
- Soxo
- Soxomide
- Stansin
- Sulbio
- Sulfagan
- Sulfagen
- Sulfalar
- Sulfapolar
- Sulfasan
- Sulfasol
- Sulfazin
- Sulfazole
- Sulfisin
- Sulfizin
- Sulfizol
- Sulfizole
- Sulfoxol
- Suloxsol
- Sulphadimethylisoxazole
- Sulphafuraz
- Sulphafurazol
- Sulphafurazole
- Sulphafurazolum
- Sulphaisoxazole
- 5-Sulphanilamido-3,4-dimethyl-isoxazole
- Sulphisoxazol
- Sulphisoxazole
- Sulphofurazole
- Sulsoxin
- Thiasin

- TL-azole
- Unisulf
- Urisoxin
- Uritrisin
- Urogan
- U.S.-67
- Vagilia
- V-Sul

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Last updated: 11 March 1998

# SULFAMETHOXAZOLE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 348)

**CAS No.**: 723-46-6
**Chem. Abstr. Name**: Benzenesulfonamide, 4-amino-*N*-(5-methyl-3-isoxazolyl)-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Although no increase in the incidence of cancer at all sites combined was noted during 1969-1976 among 1709 members of a prepaid health plan prescribed sulfamethoxazole during 1969-1973, significant increases in the incidence of nasopharyngeal carcinoma (3 observed, 0.1 expected; relative risk, 30.0 [95% confidence interval, 23.7-36.3]) and of cancer of the cervix after a two-year lag period (7 observed, 2.2 expected; relative risk, 3.2 [1.8-4.5]) were observed. However, a significant deficit of colon cancer was also seen (none observed, 4.7 expected) [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

Sulfamethoxazole produced thyroid tumours in rats following its oral administration; no information on other tumour types was reported [ref: 2].

**C. Other relevant data**

In a single study, sulfamethoxazole did not induce chromosomal aberrations in human lymphocytes *in vivo* or *in vitro*. It was not mutagenic to bacteria [ref: 3].

**Overall evaluation**

Sulfamethoxazole is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Subsequent evaluation**: Vol. 79 (2001)

**Also see previous evaluation**: Vol. 24 (1980)

**References**

1. Friedman, G.D. & Ury, H.K. (1980) Initial screening for carcinogenicity of commonly used drugs. J. natl Cancer Inst., 65, 723-733

2. IARC Monographs, 24, 285-295, 1980

3. IARC Monographs, Suppl. 6, 502-503, 1987

**Synonyms**

- N1-(5-Methylisoxazol-3-yl)sulphanilamide
- 3-*p*-Aminobenzenesulphonamido-5-methylisoxazole

- 4-Amino-*N*-(5-methyl-3-isoxazolyl)benzene sulphonamide
- 3-(*p*-Aminophenylsulphonamido)-5-methylisoxazole
- Azo-gantanol
- Bactrim
- Co-trimoxazole
- Eusaprim
- Fectrim
- Gantanol
- Metoxal
- $N_1$-(5-Methyl-3-isoxazolyl)sulphanilamide
- 5-Methyl-3-sulphanilamidoisoxazole
- MS 53
- Radonil
- Ro 4-2130
- Septra
- Septran
- Septrin
- Sinomin
- Sulphamethalazole
- Sulphamethoxazol
- Sulphamethoxazole
- Sulphamethoxizole
- Sulphamethylisoxazole
- 3-Sulphanilamido-5-methylisoxazole
- Sulphisomezole
- Trib
- Trimetoprim-sulfa

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Last updated: 11 March 1998

# TALC NOT CONTAINING ASBESTIFORM FIBRES
# (Group 3)

# TALC CONTAINING ASBESTIFORM FIBRES
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.349)

**Talc**
**CAS No.:** 14807-96-6

**A. Evidence for carcinogenicity to humans** (*inadequate* for talc not containing asbestiform fibres; *sufficient* for talc containing asbestiform fibres)

Evaluation of the effects of talc is confused by the fact that talc deposits may be contaminated with various other minerals, including carbonates, quartz, serpentines and amphiboles (asbestiform and nonasbestiform) [ref: 1].

Case studies have suggested an association between mesothelioma and exposure to talc containing asbestiform fibres [ref: 1].

A proportionate mortality study of miners and millers of talc containing asbestiform tremolite has shown an excess of lung cancer and one case of mesothelioma. Another cohort study of workers mining and milling talc containing tremolite, anthophyllite and serpentine minerals revealed significant excess mortality from lung cancer and from nonmalignant respiratory disease. Mortality from lung cancer increased with latency [ref: 1].

Several mortality studies have assessed cancer risk among miners and millers of talc that was reported to contain no more than trace amounts of asbestos. A cohort mortality study of talc miners and millers showed an excess of lung cancer among underground miners but not among millers; a contributory etiological role of radon daughters to the lung cancer risk in miners could not be excluded. The three other studies published suffered from methodological limitations and could not be interpreted [ref: 1].

A cohort study of pottery workers exposed to silica and talc showed an excess risk of lung cancer (standardized mortality ratio [SMR], 143; 52 observed, 36.3 expected). Among those exposed to high levels of silica, an SMR of 254 (21 observed, 8.3 expected; $p < 0.05$) occurred among those with exposure to nonfibrous talc in contrast to an SMR of 137 (18 observed, 13.2 expected; $p > 0.05$) among those without talc exposure. Mortality from lung cancer increased with duration of exposure to talc (SMR, 364 for those with 15 years or more of exposure), but not with duration of exposure to silica [ref: 2].

A case-control study has suggested an approximate doubling in relative risk for ovarian cancer among women with perineal use of talc, but the possibility of recall bias cannot be ruled out [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*; for talc not containing asbestiform fibres and for talc containing asbestiform fibres)

Talc of different grades was tested in mice, rats and hamsters by various routes of administration, including intraperitoneal, intrathoracic and intrapleural routes. Most of these studies were inadequate. No tumour was induced in rats following either a single intrapleural administration or four intraperitoneal injections of talc, or following administration of talc in the diet. No local tumour developed in mice following a single subcutaneous injection of talc [ref: 1].

### C. Other relevant data

No data were available on the genetic and related effects of talc in humans.

Talc did not induce dominant lethal mutations or chromosomal aberrations in bone-marrow cells of rats treated *in vivo*, or chromosomal aberrations in human cells *in vitro*. Talc was not mutagenic to yeast or to bacteria in a host-mediated assay [ref: 3].

### Overall evaluation

Talc not containing asbestiform fibres is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Talc containing asbestiform fibres is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 42 (1987)

### References

1. IARC Monographs, 42, 185-224, 1987

2. Thomas, T.L. & Stewart, P.A. (1987) Mortality from lung cancer and respiratory disease among pottery workers exposed to silica and talc. Am. J. Epidemiol., 125, 35-43

3. IARC Monographs, Suppl. 6, 504-5-5, 1987

### Synonyms for Talc

- Agalite
- Asbestine
- B9 finntalc P40
- B13
- Beaver white 200
- CP 10-40
- CP 38-33
- Crystalite
- CR 6002
- Desertalc 57
- Emtal 500
- Emtal 549
- Emtal 596
- Emtal 599
- Fibrene C 400
- French chalk
- FW-XO
- HSDB 830
- IT Extra
- LMR 100
- Microneeca K 1
- Micro white 5000A
- Microtalco IT extra
- Mistron
- MP 25-38
- MP 40-27
- MP 45-26

- MST
- MT 12-50
- Mussolinite
- NCI CO6018
- Nytal 200
- Nytal 400
- Pk-C
- Pk-N
- Polytal 4641
- Polytal 4725
- Potstone
- Snowgoose
- Soapstone
- Steatite
- Steawhite
- Supreme
- Supreme dense
- Talcan PK-P
- Talcron CP 44-31
- Talcum

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Last updated: 10 February 1998

# TOBACCO PRODUCTS, SMOKELESS
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 357)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

In North America and western Europe, case reports indicate an association between tobacco chewing and oral cancer at the site where the quid was placed habitually. In those case-control studies in which an association between tobacco chewing and cancer of the oral cavity, pharynx and larynx has been observed, confounding by tobacco smoking or alcohol consumption could not be excluded. A slight increase in the incidence of oesophageal cancer related to tobacco chewing has been seen in four case-control studies [ref: 1].

Case reports indicate an association between oral use of snuff and oral cancer. Four case-control studies imply a causal association between snuff use and oral, and possibly pharyngeal, cancer. That oral use of snuff increases the risk of nasal-sinus cancer was suggested in one case-control study [ref: 1].

Three case series also show a high relative frequency of smokeless-tobacco use (chewing tobacco or oral snuff, unspecified) among oral cancer patients. Four case-control studies have shown the association between smokeless-tobacco use and the risk of oral cancer. Two cohort mortality studies provide evidence of a positive association with oesophageal cancer, and one suggests an increased risk for oral and pharyngeal cancer [ref: 1].

Two large case-control studies from Pakistan and India reported substantial increases in the risk for oral cancer related to tobacco-lime (*khaini*) chewing [ref: 1]. In addition, evidence is available from various studies in which cancer risks were studied in relation to unspecified habits of betel-tobacco-lime chewing [ref: 2].

Case series have indicated an association between use of *shammah* and *nass* and oral cancer. Oral cancer was found to develop at the site at which *nass* was placed habitually. Two case-control studies showed substantial increases in the risk of oral cancer associated with *nass* use and one with *naswar* use; however, in these studies positive confounding by smoking and other factors could not be excluded. Oral cancer in users of *mishri* and *gudakhu* was studied in a prevalence survey; no case was found [ref: 1]. A study of 64 patients with squamous-cell carcinoma of the head and neck in Saudi Arabia showed that 81% were *alshammah users* and 34% were *alqat* users, but only 14% were cigarette smokers; none used alcohol to excess [ref: 3].

No association has been seen between nasal use of snuff and oral cancer. In two case-control studies, an association between snuff inhaling and nasal-sinus cancer has been reported. One case-control study reported snuff inhaling to be more common among patients with cancers of the oesophagus, hypopharynx or oropharynx than among controls [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

Various chewing tobaccos and unburnt cigarette tobaccos and their extracts were tested for carcinogenicity by oral administration in mice, by topical application to the oral mucosa of mice, rats and hamsters, and by subcutaneous administration, skin application, inhalation, intravesicular implantation and intravaginal application to mice. All of these studies suffered from certain deficiencies [ref: 1].

In a two-stage mouse-skin assay, applications of tobacco extract followed by treatment with croton oil induced papillomas and squamous-cell carcinomas of the skin. In further two-stage mouse-skin assays, application of tobacco extracts following initiation by 7,12-dimethylbenz[*a*]anthracene

resulted in papillomas [ref: 1].

A commercial Swedish snuff was tested for carcinogenicity in rats by topical administration in a surgically-created oral canal, alone or in combination with herpes simplex type 1 infection. Two squamous-cell carcinomas of the oral cavity were observed in the group receiving both treatments, but this result was not statistically significant [ref: 1]. A commercial North American snuff was tested in rats by the same route. One squamous-cell carcinoma and two papillomas of the oral cavity were found, but this result was not statistically significant [ref: 4].

An aqueous extract of a commercial North American snuff was also tested by topical application to the oral mucosa in rats, alone or enriched with the tobacco-specific nitrosamines, *N*'-nitrosonornicotine and 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone. Some papillomas of the oral cavity were observed in rats treated with the enriched snuff extract, but this result was not statistically significant [ref: 4].

Snuff was tested by oral administration in hamsters, alone and in combination with calcium hydroxide, but the data were insufficient for evaluation. Several studies in hamsters in which snuff was administered as single or repeated applications into the cheek pouch or fed in the diet yielded insufficient data for evaluation. Subcutaneous injection of ethanol extracts of snuff to rats did not produce an increase in tumour incidence [ref: 1].

*Nass* was tested for carcinogenicity in hamsters by administration into the cheek pouch or by skin application. No tumour was found at the site of application. Although *nass* administration was associated with an apparent excess of liver tumours in various groups receiving cheek-pouch administration, which may be indicative of carcinogenicity, deficiencies in reporting do not allow an evaluation to be made [ref: 1].

**C. Other relevant data**

An increased incidence of micronuclei was observed in exfoliated epithelial cells from users of *khaini* and *nass*. Saliva collected from chewers of Indian tobacco induced chromosomal aberrations in Chinese hamster ovary cells *in vitro* [ref: 5].

Ethanol extracts of Indian chewing tobacco induced micronuclei in bone-marrow cells of Swiss mice treated *in vivo* and were mutagenic to Chinese hamster V79 cells *in vitro*, both in the presence and absence of an exogenous metabolic system, and to *Salmonella typhimurium*. Both ethanol and ethyl acetate extracts of Sri Lankan chewing tobacco induced transformation of Syrian hamster embryo cells. Ethyl acetate extracts induced sister chromatid exchanges in cultured human cells, but not mutation in Chinese hamster V79 cells when tested in the absence of an exogenous metabolic system [ref: 5].

Aqueous extracts of *nass* and *khaini* induced chromosomal aberrations in Chinese hamster ovary cells. Powdered tobacco fed to larvae of *Drosophila* did not induce sex-linked recessivel lethal mutations, autosomal translocations or sex-chromosome loss [ref: 5].

Chloroform extracts of *shammah* induced transformation in mouse C3H 10T1/2 cells. The same extracts also induced aberrant colonies and gene conversion in yeast and were mutagenic to *S. typhimurium*, both in the presence and absence of an exogenous metabolic system [ref: 5].

Extracts of North American oral snuff (at pH 3.0) and extracts of North American chewing tobacco treated with sodium nitrite under acidic conditions were mutagenic to *S. typhimurium* in the presence and absence of a metabolic system. Organic solvent extracts of snuff induced a dose-related increase in the frequency of sister chromatid exchanges in human peripheral lymphocytes *in vitro* in the absence of a metabolic system [ref: 5].

**Overall evaluation**

Smokeless tobacco products are *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 37 (1985)

**References**

1. IARC Monographs, 37, 37-136, 1985

2. IARC Monographs, 37, 141-209, 1985

3. Ibrahim, E.M., Satti, M.B., Al Idrissi, H.Y., Higazi, M.M., Magbool, G.M. & Al Quorain, A. (1986) Oral cancer in Saudi Arabia: The role of alqat and alshammah. Cancer Detect. Prev., 9, 215-218

4. Hecht, S.S., Rivenson, A., Braley, J., DiBello, J., Adams, J.D. & Hoffmann, D. (1986) Induction of oral cavity tumors in F344 rats by tobacco-specific nitrosamines and snuff. Cancer Res., 46, 4162-4166

5. IARC Monographs, Suppl. 6, 519, 1987

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Last updated: 10 February 1998

# TOBACCO SMOKE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p.359)

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Cigarette smoking has been shown to cause lung cancer, bladder cancer, cancer of the renal pelvis (and possibly renal adenocarcinoma), cancer of the lip, and oropharyngeal, hypopharyngeal, laryngeal, oesophageal and pancreatic cancers. In some studies, increased risks of cancers of the stomach, liver and cervix have been noted, but the data were inadequate to decide whether the association is causal or not. The risk for lung cancer due to cigarette smoking is substantially increased in conjunction with exposure to radon daughters or asbestos. An increase in the incidence of lung cancer also results from smoking other forms of tobacco, i.e., pipe, cigars and *bidis*. Pipe and cigar smoking probably increase the risk of bladder cancer, but at lower levels than that caused by cigarette smoking. They also increase the risks of oral, oropharyngeal, hypopharyngeal, laryngeal and oesophageal cancers to approximately the same extent as cigarette smoking, and, as with cigarette smoking, the risk is substantially augmented in conjunction with high-dose exposure to alcohol [ref: 1].

Tobacco smoke affects not only people who smoke but also those who are exposed to the combustion products of other people's tobacco (passive smokers). The most numerous observations hitherto available concern lung cancer, and the results of most of the 13 main epidemiological studies [ref: 2] carried out so far are compatible with either an increased risk from passive smoking or an absence of risk. However, the aggregate evidence from these studies, taken together with knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during passive smoking and of the quantitative relationships between dose and effect that are commonly observed after exposure to carcinogens, leads to the conclusion that passive smoking does carry some risk for lung cancer.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Cigarette smoke has been tested for carcinogenicity by inhalation in mice, rats, hamsters and dogs. Exposure of hamsters and rats to whole smoke produced malignant respiratory-tract tumours [ref: 1]. In mice, inhalation of whole tobacco smoke resulted in a slightly increased incidence of alveologenic lung tumours, but this was not statistically significant in some of the studies [ref: 1,3]. An increased incidence of lung tumours has also been reported in dogs exposed to cigarette smoke, but the data were insufficient for evaluation. More tumours of the respiratory tract occurred in rodents exposed to both cigarette smoke and 7,12-dimethylbenz[*a*]anthracene than to either one alone; the same is true for concomitant exposure to benzo[*a*]pyrene or radon daughters [ref: 1].

Cigarette-smoke condensate induced benign and malignant skin tumours in mice and rabbits after application to the skin. Following its topical administration to oral mucosa, it resulted in an increased incidence of lung tumours and tumours of other organs, primarily lymphomas, in one strain of mice. In rats, cigarette-smoke condensate produced lung cancer after intrapulmonary injection. In two-stage mouse-skin assays, a single topical administration of cigarette-smoke condensate induced changes resulting in benign and malignant skin tumours after additional application of croton oil. Skin tumours were also produced when cigarette-smoke condensate was applied chronically subsequent to a single treatment with other agents, such as 7,12-dimethylbenz[a]anthracene [ref: 1].

**C. Other relevant data**

Structural chromosomal aberrations, sister chromatid exchanges and micronuclei have been observed in peripheral blood lymphocytes of tobacco smokers. Although in some studies there was no increase in the incidence of sister chromatid exchanges, in several others a dose-response relationship was reported between the amount and duration of cigarette smoking and the frequency

of sister chromatid exchange. Long-term heavy smokers generally also had higher frequencies of chromosomal aberrations in peripheral blood lymphocytes. In a large study, a significant dose-response relationship was found between the frequency of structural chromosomal aberrations and the estimated daily uptake of condensate. In a single study, it was reported that DNA adducts associated with cigarette smoke were detected in the bronchus of one smoker and in the larynx of another, but not in the bronchus of a nonsmoker. In another study, one of several DNA adducts detected in 16/17 placentas from smokers and 3/14 placentas from nonsmokers was claimed to be related to maternal smoking. Antigenicity against polycyclic aromatic hydrocarbon DNA adducts has been demonstrated in peripheral lymphocytes and lung samples from cigarette smokers, although the occurrence of these adducts could not be correlated with cigarette smoking [ref: 4].

Extracts of urine from smokers induced chromosomal aberrations in Chinese hamster ovary cells and were mutagenic to bacteria in the presence of an exogenous metabolic system. Passive exposure to tobacco smoke has also been reported to increase urinary mutagenicity. In studies of amniotic fluid samples from smoking and nonsmoking mothers, more mutagenicity to *Salmonella typhimurium* was reported in samples taken at term from heavy smokers as compared to nonsmokers, but not in samples taken at 16 weeks by amniocentesis. One study of the mutagenicity of cervical mucus from smoking and nonsmoking women was difficult to interpret due to inadequate reporting [ref: 4].

Tobacco smoke inhibited DNA repair capacity in mice and increased the frequency of sister chromatid exchanges in bone-marrow cells of mice exposed *in vivo* and in human lymphocytes in vitro; it also induced single-strand breaks in cultured human cells. It induced sex-linked recessive lethal mutations in *Drosophila* and mitotic recombination, gene conversion and mutation in yeast. The urine of rats and baboons exposed to cigarette smoke was mutagenic to bacteria [ref: 4].

Tobacco smoke and extracts of particulate matter collected on filters in rooms containing cigarette smoke were mutagenic to bacteria. The extracts also induced sister chromatid exchanges in cultured Chinese hamster ovary cells [ref: 4].

Tobacco condensates induced mutation, sister chromatid exchanges and transformation in rodent cells in culture, sex-linked recessive lethal mutations in *Drosophila* and mutation and gene conversion in fungi. Tobacco-smoke condensate inhibited intercellular communication of Chinese hamster V79 cells. All tobacco-smoke condensates tested were mutagenic to bacteria [ref: 4].

**Overall evaluation**

Tobacco smoke is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 38 (1986)

**References**

1. IARC Monographs, 38, 1986

2. Wald, N.J., Nanchahal, K., Thompson, S.G. & Cuckle, H.S. (1986) Does breathing other people's tobacco smoke cause lung cancer? Br. med. J., 293, 1217-1222

3. Henry, C.J. & Kouri, R.E. (1986) Chronic inhalation studies in mice. II. Effects of long-term exposure to 2R1 cigarette smoke on (C57BL/Cum x C3H/AnfCum)$F_1$ mice. J. natl Cancer Inst., 77, 203-212

4. IARC Monographs, Suppl. 6, 519-520, 1987

Last updated: 9 February 1998

# *ortho*-TOLUIDINE
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 362)

**CAS No.**: 95-53-4
**Chem. Abstr. Name**: Benzenamine, 2-methyl-

**A. Evidence for carcinogenicity to humans** (*inadequate*)

There are numerous studies of dyestuffs workers, dating back to the classical cohort studies in 1954. Although an excess of bladder tumours has often been found in workers exposed to varying combinations of dyestuffs and dyestuff intermediates, no population of workers exposed to *ortho*-toluidine alone has been described [ref: 1]. Occasional cases of bladder tumours have been reported in workers classified as being exposed primarily to *ortho*-toluidine, but either insufficient data or insufficient follow-up time have prevented a clear association being made with the exposure. An excess of bladder tumours was noted in workers exposed to toluene, *ortho*-nitrotoluene, *ortho*-toluidine and 4,4'-methylene bis(2-methylaniline) during the manufacture of new fuchsin ('new' magenta) and safranine-T [ref: 1,2].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

*ortho*-Toluidine hydrochloride was tested for carcinogenicity in mice and rats by oral administration, producing neoplasms at various sites in both species; in particular, vascular tumours were induced, including tumours of the spleen and other abdominal haemangiosarcomas [ref: 1,3]. Following subcutaneous injection in a limited study in hamsters, no treatment-related neoplasm was observed [ref: 4]. Experiments in rabbits and guinea-pigs by subcutaneous administration were inadequate for evaluation [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of *ortho*-toluidine in humans.

*ortho*-Toluidine did not induce micronuclei in mice treated *in vivo*; equivocal results were obtained for sister chromatid exchanges in Chinese hamsters. It induced sister chromatid exchanges, mutation and unscheduled DNA synthesis in human cells *in vitro*. It induced transformation, aneuploidy and chromosomal aberrations in cultured rodent cells; conflicting results were obtained for sister chromatid exchanges, mutation and DNA damage. *ortho*-Toluidine caused somatic mutation in *Drosophila*. Conflicting results were obtained for mutagenicity to yeast; it induced aneuploidy, but not mitotic recombination. *ortho*-Toluidine was mutagenic to bacteria when higher amounts of an exogenous metabolic system were used than in the standard assay [ref: 5].

**Overall evaluation**

*ortho*-Toluidine is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 16 (1978); Vol. 27 (1982); Vol. 77 (2000)

**References**

1. IARC Monographs, 27, 155-175, 1982

2. Rubino, G.F., Scansetti, G., Piolatto, G. & Pira, E. (1982) The carcinogenic effect of aromatic amines: an epidemiological study of the role of *o*-toluidine and 4,4'-methylene bis(2-methylaniline) in inducing bladder cancer in man. Environ. Res., 27, 241-254

3. Hecht, S.S., El-Bayoumy, K., Rivenson, A. & Fiala, E. (1982) Comparative carcinogenicity of *o*-toluidine hydrochloride and *o*-nitrosotoluene in F-344 rats. Cancer Lett., 16, 103-108

4. Hecht, S.S., El-Bayoumy, K., Rivenson, A. & Fiala, E.S. (1983) Bioassay for carcinogenicity of 3,2'-dimethyl-4-nitrosobiphenyl, *o*-nitrosotoluene, nitrosobenzene and the corresponding amines in Syrian golden hamsters. Cancer Lett., 20, 349-354

5. IARC Monographs, Suppl. 6, 523-527, 1987

**Synonyms**

- 1-Amino-2-methylbenzene
- 2-Amino-1-methylbenzene
- 2-Aminotoluene
- *o*-Aminotoluene
- Azoic brown 29 [component]
- 1-Methyl-2-aminobenzene
- 2-Methyl-1-aminobenzene
- *o*-Methylaniline
- 2-Methylaniline
- 2-Methylbenzenamine
- *o*-Methylbenzenamine
- 2-Toluidine
- *o*-Toluidin
- *o*-Tolylamine

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Last updated: 3 March 1998

# TREOSULPHAN
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 363)

**CAS No.:** 299-75-2
**Chem. Abstr. Name**: 1,2,3,4-Butanetetrol, 1,4-dimethanesulfonate, [S-(R*,R*)]-

**A. Evidence for carcinogenicity to humans** (*sufficient*)

In one epidemiological study of 553 patients with ovarian cancer treated only with treosulphan and followed for nine years (over 1700 person-years) after treatment, 13 patients developed acute nonlymphocytic leukaemia, mostly within five years after the start of chemotherapy; the expected number of cases among the patients was less than 0.1, giving a relative risk in excess of 100. There was a significant correlation between cumulative dose of treosulphan and risk of leukaemia [ref: 1,2].

**B. Evidence for carcinogenicity to animals**

No data were available to the Working Group.

**C. Other relevant data**

Treosulphan is a bifunctional alkylating agent. No data were available on the genetic and related effects of this compound in humans. It induced chromosomal aberrations in plant cells [ref: 3].

**Overall evaluation**

Treosulphan is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 341-349, 1981

2. Pedersen-Bjergaard, J., Ersböll, J., Sorensen, H.M., Keiding, N., Larsen, S.O., Philip, P., Larsen, M.S., Schultz, H. & Nissen, N.I. (1985) Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. Comparison with results obtained in patients treated for Hodgkin's disease and ovarian carcinoma with other alkylating agents. Ann. intern. Med., 103, 195-200

3. IARC Monographs, Suppl. 6, 528-529, 1987

**Synonyms**

- 1,4-Bis-O-methanesulphonyl-L-threitol
- Dihydroxybusulphan
- 1,4-Di-O-methanesulfonylbutan-1,2,3,4-tetrole

- 1,4-Dimethanesulphonate-(L-threitol)
- NSC 39069
- 1-Threitol-1,4-bis(methanesulphonate
- (2S,3S)-Threitol 1,4-bismethanesulphonate
- L-Threitol 1,4-dimethanesulfonate
- L-(+)Threitol 1,4-dimethanesulphonate
- L-Threitol dimethanesulphonate
- Treosulfan
- Tresulphan
- Treosulphan leo

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Last updated: 10 February 1998

# 4,5',8-TRIMETHYLPSORALEN
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 366)

**CAS No.**: 3902-71-4
**Chem. Abstr. Name**: 2,5,9-Trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one

**A. Evidence for carcinogenicity to humans** (*inadequate*)

Malignant melanoma was diagnosed in a 30-year-old male shortly after commencement of treatment with 4,5',8-trimethylpsoralen for vitiligo. No skin cancer was observed during two to 14 months of follow-up in 57 patients with psoriasis treated for one to 23 months with 4,5',8-trimethylpsoralen [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

No skin tumour was observed in mice given thrice-weekly skin applications of 4,5',8-trimethylpsoralen followed by low doses of ultraviolet A irradiation for nine months [ref: 1,2].

**C. Other relevant data**

No data were available on the genetic and related effects of 4,5',8-trimethylpsoralen in humans.

In combination with ultra-violet A radiation, 4,5',8-trimethylpsoralen bound covalently to DNA in guinea-pig skin *in vivo*. It induced sister chromatid exchanges and unscheduled DNA synthesis in human cells *in vitro*, and DNA cross-links in human and rodent cells *in vitro*. It induced mutation in yeast and DNA damage in bacteria. Results on the induction of mutation in bacteria were inconclusive [ref: 3].

In the absence of ultra-violet A radiation, 4,5',8-trimethylpsoralen did not induce sister chromatid exchanges in human lymphocytes *in vitro*; results for induction of unscheduled DNA synthesis were equivocal. Mutagenicity studies in bacteria were inconclusive [ref: 3].

4,5,8'-Trimethylpsoralen is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 40 (1986)

**References**

1. IARC Monographs, 40, 357-371, 1986

2. Hannuksela, M., Stenbäck, F. & Lahti, A. (1986) The carcinogenic properties of topical PUVA. A lifelong study in mice. Arch. Dermatol. Res., 278, 347-351

3. IARC Monographs, Suppl. 6, 541-544, 1987

**Synonyms**

- 6-Hydroxy-β,2,7-trimethyl-5-benzofuranacrylic acid, δ-lactone
- NSC 71047
- TMP
- Trimethylpsoralen
- 2',4,8-Trimethylpsoralen
- Trioxalen
- Trioxsalen
- Trioxysalen
- Trisoralen

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Last updated: 11 March 1998

# TRIS(AZIRIDINYL)-*para*-BENZOQUINONE (TRIAZIQUONE) (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 367)

**CAS No.**: 68-76-8
**Chem. Abstr. Name**: 2,3,5-Tris(1-aziridinyl)-2,5-cyclohexadiene-1,4-dione

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of triaziquone as a single agent was available to the Working Group. Occasional case reports of exposure to triaziquone, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1].

**B. Evidence for carcinogenicity to animals** (*limited*)

Triaziquone produced a small number of different types of malignant tumours in rats after repeated intravenous injections or after repeated intravenous injections followed by repeated intraperitoneal injections [ref: 1].

**C. Other relevant data**

Triaziquone is an alkylating agent [ref: 2]. No data were available on its genetic and related effects in humans.

Triaziquone induced dominant lethal mutations, heritable translocations, chromosomal aberrations and micronuclei in bone-marrow cells of mice and chromosomal aberrations in oocytes of mice and hamsters treated *in vivo*. In human cells *in vitro*, it induced chromosomal aberrations and sister chromatid exchanges. In Chinese hamster cells *in vitro*, triaziquone induced chromosomal aberrations, micronuclei and sister chromatid exchanges; it induced unscheduled DNA synthesis in mouse testicular cells. It induced aneuploidy, chromosomal aberrations and sex-linked recessive lethal mutations in *Drosophila*, mutation in plant cells, gene conversion in yeast and mutation and DNA damage in bacteria [ref: 2].

Tris(aziridinyl)-*para*-benzoquinone (triaziquone) is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 9 (1975)

**References**

1. IARC Monographs, 9, 67-73, 1975

2. IARC Monographs, Suppl. 6, 545-548, 1987

**Synonyms**

- Bayer 3231
- 1,1'1''-(3,6-Dioxo-1,4-cyclohexadiene-1,2,4-triyl)trisaziridine

- Oncovedex
- Prenimon
- Riker 601
- TEIB
- Trenimon
- Triaziquinone
- Triaziquone
- Triethyleneiminobenzoquinone
- Triethyleniminobenzoquinone
- 2,3,5-Triethylenimino-1,4-benzoquinone
- 2,3,5-Tris(aziridino)-1,4-benzoquinone
- 2,3,5-Tris(aziridinyl)-1,4-benzoquinone
- 2,3,5-Tris(1-aziridinyl)-*p*-benzoquinone
- Tris-(ethyleneimino)benzoquinone
- 2,3,5-Trisethyleneiminobenzoquinone
- Trisethyleneiminoquinone
- 2,3,5-Tris(ethylenimino)benzoquinone
- 2,3,5-Tris(ethylenimino)-1,4-benzoquinone
- 2,3,5-Tris(ethylenimino)-*p*-benzoquinone

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Last updated: 11 March 1998

# URACIL MUSTARD
# (Group 2B)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 370)

**CAS No.**: 66-75-1
**Chem. Abstr. Name**: 5-[Bis(2-chloroethyl)amino]-2,4(1H,3H)pyrimidinedione

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of uracil mustard as a single agent was available to the Working Group. Occasional case reports of treatment with uracil mustard, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1-5].

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Intraperitoneal administration of uracil mustard to mice of three strains induced lung adenomas and adenocarcinomas in a dose-dependent incidence; in one of the strains, liver, ovarian and lymphatic tumours were also observed. In rats, intraperitoneal administration induced peritoneal sarcomas and lymphomas and tumours in the pancreas, ovary and mammary gland [ref: 6].

**C. Other relevant data**

Uracil mustard is an alkylating agent [ref: 7]. No data were available on its genetic and related effects in humans.

Uracil mustard did not induce dominant lethal mutations in mice in one study using low doses. It induced mutation in mouse lymphoma cells *in vitro*, aneuploidy and sex-linked recessive lethal mutations in *Drosophila* and mitotic recombination in yeast. It caused DNA damage and was mutagenic in bacteria [ref: 7].

**Overall evaluation**

Uracil mustard is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 9 (1975)

**References**

1. Reimer, R.R., Hoover, R., Fraumeni, J.F., Jr & Young, R.C. (1977) Acute leukemia after alkylating-agent therapy of ovarian cancer. New Engl. J. Med., 297, 177-181

2. Zarrabi, M.H. & Rosner, F. (1979) Acute myeloblastic leukemia following treatment for non-hematopoietic cancers. Report of 19 cases and review of the literature. Am. J. Hematol., 7, 357-367

3. McKenna, R.W., Parkin, J.L., Foucar, K. & Brunning, R.D. (1981) Ultrastructural characteristics of therapy-related acute nonlymphocytic leukemia: evidence for a panmyelosis. Cancer, 48, 725-737

4. Rosner, F. (1976) Acute leukemia as a delayed consequence of cancer chemotherapy. Cancer, 37, 1033-1036

5. Zarrabi, M.H. (1980) Association of non-Hodgkin's lymphoma (NHL) and second neoplasms. Semin. Oncol., 7, 340-351

6. IARC Monographs, 9, 235-241, 1975

7. IARC Monographs, Suppl. 6, 558-560, 1987

**Synonyms**

- 5-Aminouracil mustard
- 5-[Bis(2-chloroethyl)amino]uracil
- 5-*N*,*N*-Bis(2-chloroethyl)aminouracil
- CB 4835
- Demethyldopan
- Desmethyldopan
- 5-[Di(β-chloroethyl)amino]uracil
- 2,6-Dihydroxy-5-bis(2-chloroethyl)aminopyrimidine
- ENT 50439
- NSC 34462
- SK 19849
- U-8344
- Uramustine

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Last updated: 3 March 1998

# VINBLASTINE SULPHATE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 371)

**CAS No.**: 143-67-9
**Chem. Abstr. Name**: Vincaleukoblastine, sulfate (1:1) (salt)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of vinblastine sulphate as a single agent was available to the Working Group. Occasional case reports of exposure to vinblastine sulphate, especially in the presence of concurrent therapy with other putative carcinogens, such as ionizing radiation, alkylating agents and other potent oncotherapeutic drugs, do not constitute evidence of carcinogenesis [ref: 1].

In a large systematic follow-up of patients with Hodgkin's disease treated with an intensive chemotherapeutic combination including vinblastine (plus adriamycin, bleomycin and dacarbazine) but no alkylating agent, preliminary evidence suggests no excess of acute nonlymphocytic leukaemia in the first decade after therapy [ref: 2,3].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

No evidence of carcinogenicity was found after intraperitoneal administration of vinblastine sulphate to mice and rats or after its intravenous administration to rats, but it has not been adequately tested at high doses [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of vinblastine sulphate in humans.

Vinblastine sulphate weakly induced micronuclei in a single study using low doses, but it did not induce dominant lethal mutations in mice treated *in vivo*. It induced chromosomal aberrations but not mutation in Chinese hamster cells *in vitro* and was not mutagenic to bacteria [ref: 4].

**Overall evaluation**

Vinblastine sulphate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 349-363, 1981

2. Santoro, A., Viviani, S., Villarreal, C.J.R., Bonfante, V., Delfino, A., Valagussa, P. & Bonadonna, G. (1986) Salvage chemotherapy in Hodgkin's disease irradiation failures: superiority of doxorubicin containing regimens over MOPP. Cancer Treat. Rep., 70, 343-348

3. Valagussa, P., Santoro, A., Fossati Bellani, F., Franchi, F., Banfi, A. & Bonadonna, G. (1982)

Absence of treatment-induced second neoplasms after ABVD in Hodgkin's disease. Blood, 59, 488-494

4. IARC Monographs, Suppl. 6, 561-562, 1987

**Synonyms**

- Exal
- LE 29060
- NSC 49842
- Velban
- Velbe
- Vincaleucoblastine sulfate
- Vincaleukoblastine sulfate
- VLB sulfate

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Last updated: 11 March 1998

# VINCRISTINE SULPHATE
# (Group 3)

For definition of Groups, see Preamble Evaluation.

**Supplement 7**: (1987) (p. 372)

**CAS No.**: 2068-78-2
**Chem. Abstr. Name**: Vincaleukoblastine, 22-oxo, sulfate (1:1) (salt)

**A. Evidence for carcinogenicity to humans** (*inadequate*)

No epidemiological study of vincristine sulphate as a single agent was available to the Working Group. Intensive combination chemotherapy with regimens including vincristine has been shown to result in increased risks for acute nonlymphatic leukaemia (ANLL). (See also the summary of data on MOPP and other combined chemotherapy including alkylating agents) Such combinations usually include procarbazine together with an alkylating agent such as nitrogen mustard (see p. 269), both of which are potent animal carcinogens, suggesting more plausible explanations for the association between combination chemotherapy and ANLL. In the presence of concurrent therapy with other putative carcinogens, including ionizing radiation and other potent drugs, occasional case reports of exposure to vincristine sulphate do not constitute evidence of carcinogenesis [ref: 1].

**B. Evidence for carcinogenicity to animals** (*inadequate*)

In limited studies in mice and rats, no evidence of carcinogenicity was found after intraperitoneal administration of vincristine sulphate [ref: 1].

**C. Other relevant data**

No data were available on the genetic and related effects of vincristine sulphate in humans.

Vincristine sulphate induced micronuclei in bone-marrow cells of mice and hamsters treated *in vivo*. Conflicting results were obtained for induction of sister chromatid exchanges in human lymphocytes *in vitro*. It induced aneuploidy in and transformation of Syrian hamster embryo cells, but it did not transform mouse C3H 10T1/2 cells. It did not induce chromosomal aberrations, sister chromatid exchanges or unscheduled DNA synthesis in rodent cells *in vitro*. It induced mutation in mouse lymphoma cells but not in other rodent cells. It did not induce sex-linked recessive lethal mutations in *Drosophila* and was not mutagenic to bacteria [ref: 2].

**Overall evaluation**

Vincristine sulphate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluation**: Vol. 26 (1981)

**References**

1. IARC Monographs, 26, 365-384, 1981

2. IARC Monographs, Suppl. 6, 563-565, 1987

**Synonyms**

- Des-Na-methyl-Na-formylvinblastine sulfate
- LCR sulfate
- Leurocristine sulfate (1:1) (salt)
- Leurocristine sulfate
- Leurocristine sulfate (1:1) (salt)
- NSC 67574
- Oncovin
- Onkovin
- VCR sulfate
- Vincristin
- Vincrisul

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Last updated: 11 March 1998

# VINYL CHLORIDE
# (Group 1)

For definition of Groups, see Preamble Evaluation.

**Supplement 7:** (1987) (p. 373)

**CAS No.**: 75-01-4
**Chem. Abstr. Name**: Chloroethene

**A. Evidence for carcinogenicity to humans** (*sufficient*)

Vinyl chloride has been associated with tumours of the liver, brain, lung and haematolymphopoietic system [ref: 1]. A large number of epidemiological studies [ref: 2-12] and case reports [ref: 13-25] have substantiated the causal association between vinyl chloride and angiosarcoma of the liver. Several studies also confirm that exposure to vinyl chloride causes other forms of cancer, i.e., hepatocellular carcinoma [ref: 13,19,23,26], brain tumours [ref: 11,27], lung tumours [ref: 12,28-30] and malignancies of the lymphatic and haematopoietic system [ref: 11,29,31]. Exposure to polyvinyl chloride dust was associated with an increased incidence of lung tumours in one study; the authors suggested that trapped vinyl chloride monomer was responsible [ref: 30]. Melanoma occurred in excess in one study [ref: 12] but has not been mentioned in others. Slightly elevated risks for gastric [ref: 29] and gastrointestinal cancer (other than liver cancer) [ref: 32] were indicated in some studies, but these were not confirmed in others.

**B. Evidence for carcinogenicity to animals** (*sufficient*)

Vinyl chloride administered orally or by inhalation to mice, rats and hamsters produced tumours in the mammary gland, lung, Zymbal gland and skin and angiosarcomas of the liver [ref: 1]. Similar findings were made in more recent studies [ref: 33-39]. In one, a combination of oral administration of ethanol and inhalation of vinyl chloride resulted in more liver tumours (including angiosarcomas) than after treatment with vinyl chloride alone [ref: 40].

**C. Other relevant data**

Chromosomal aberrations were induced in peripheral blood lymphocytes of workers exposed to vinyl chloride at levels of 5-500 ppm (13-1300 mg/$m^3$). Two studies reported negative results for sister chromatid exchanges in exposed workers, while in another study a weakly positive response was found [ref: 41].

Vinyl chloride induced chromosomal aberrations, sister chromatid exchanges and micronuclei in rodents exposed *in vivo* but did not induce mutation in the mouse spot test or dominant lethal mutations in rats or mice. It alkylated DNA in several tissues of mice and rats exposed *in vivo*. Vinyl chloride induced sister chromatid exchanges in human lymphocytes *in vitro*. It induced mutation in Chinese hamster cells and unscheduled DNA synthesis in rat hepatocytes *in vitro* and induced transformation in BALB/c 3T3 cells and virus-infected Syrian hamster cells. It induced sex-linked recessive lethal mutations, but not aneuploidy, heritable translocations or dominant lethal mutations in Drosophila. It was mutagenic to plants and to *Schizosaccharomyces pombe* but not to other fungi; it induced gene conversion in yeast. It caused DNA damage and mutation in bacteria. Vinyl chloride bound covalently to isolated DNA in the presence of a metabolic system [ref: 41].

**Overall evaluation**

Vinyl chloride is *carcinogenic to humans (Group 1)*.

For definition of the italicized terms, see Preamble Evaluation.

**Also see previous evaluations**: Vol. 7 (1974); Vol. 19 (1979)

**References**


1. IARC Monographs, 19, 377-438, 1979

2. Baxter, P.J., Anthony, P.P., MacSween, R.N.M. & Scheuer, P.J. (1977) Angiosarcoma of the liver in Great Britain. 1963-73. Br. med. J., ii, 919-921

3. Brady, J., Liberatore, F., Harper, P., Greenwald, P., Burnett, W., Davies, J.N.P., Bishop, M., Polan, A. & Viana, N. (1977) Angiosarcoma of the liver: an epidemiologic survey. J. natl Cancer Inst., 59, 1383-1385

4. Baxter, P.J., Anthony, P.P., MacSween, R.N.M. & Scheuer, P.J. (1980) Angiosarcoma of the liver: annual occurrence and aetiology in Great Britain. Br. J. ind. Med., 37, 213-221

5. Baxter, P.J. (1981) The British hepatic angiosarcoma register. Environ. Health Perspect., 41, 115-116

6. Falk, H., Herbert, J., Crowley, S., Ishak, K.G., Thomas, L.B., Popper, H. & Caldwell, G.G. (1981) Epidemiology of hepatic angiosarcoma in the United States, 1964-1974. Environ. Health Perspect., 41, 107-113

7. Thériault, G. & Allard, P. (1981) Cancer mortality of a group of Canadian workers exposed to vinyl chloride monomer. J. occup. Med., 23, 671-676

8. Vianna, N.J., Brady, J.A. & Cardamone, A.T. (1981) Epidemiology of angiosarcoma of liver in New York State. N.Y. State J. Med., 6, 895-899

9. Weber, H., Reinl, W. & Greiser, E. (1981) German investigations on morbidity and mortality of workers exposed to vinyl chloride. Environ. Health Perspect., 41, 95-99

10. Forman, D., Bennett, B., Stafford, J. & Doll, R. (1985) Exposure to vinyl chloride and angiosarcoma of the liver: a report of the register of cases. Br. J. ind. Med., 42, 750-753

11. von Greiser, E., Reinl, W. & Weber, H. (1982) Vinyl chloride exposure and mortality of German chemical workers in comparison to mortality of non-exposed chemical workers and PVC workers (Ger.). Zbl. Arbeitsmed., 32, 44-62

12. Heldaas, S.S., Langard, S.L. & Andersen, A. (1984) Incidence of cancer among vinyl chloride and polyvinyl chloride workers. Br. J. ind. Med., 41, 25-30

13. Gokel, J.M., Liebezeit, E. & Eder, M. (1976) Hemangiosarcoma and hepatocellular carcinoma of the liver following vinyl chloride exposure. A report of two cases. Virchows Arch. Pathol. Anat. Histol., 372, 195-203

14. Bonneton, G., Champetier, J., Fournet, J., Guidicelli, H., Legrand, J., Dupre, A., Hostein, M., Marty, F. & Pahn, M. (1977) Angiosarcoma of the liver and portal fibrosis in vinyl chloride workers. Two cases (Fr.). Nouv. Presse méd., 6, 735-742

15. Puech, A.-M., Fournet, A., Laulhere, L., Faure, J., Cau, G. & Mallion, J.-M. (1977) Study of hepatic lesions seen in 5 subjects exposed to vinyl chloride, including 3 cases of angiosarcoma of the liver (Fr.). Arch. Mal. prof., 38, 787-795

16. Réty, J., Lambert, R. & Pialat, J. (1981) Medical surveillance of persons exposed to occupational

toxic compounds with late or carcinogenic effects. The 11th French case of angiosarcoma of the liver in a PVC worker (Fr.). Arch. Mal. prof., 42, 405-406

17. Pialat, J., Pasquier, B., Pahn, M. & Kopp, N. (1979) Hepatic lesions cuased by vinyl chloride monomer. Study of eight clinicopathological cases (Fr.). Arch. Anat. Cytol. pathol., 27, 361-375

18. Ghandur-Mnaymneh, L. & Gonzalez, M.S. (1981) Angiosarcoma of the penis with hepatic angiomas in a patient with low vinyl chloride exposure. Cancer, 47, 1318-1324

19. Koischwitz, D., Lelbach, W.K., Lackner, K. & Hermanutz, D. (1981) Angiosarcoma of the liver and hepatocellular carcinomas induced by vinyl chloride (Ger.). Fortschr. Rontgenstr., 134, 283-290

20. Vianna, N.J, Brady, J. & Harper, P. (1981) Angiosarcoma of the liver: a signal lesion of vinyl chloride exposure. Environ. Health Perspect., 41, 207-210

21. Chiappino, G., Bertazzi, P.A., Baroni, M. & Masini, T. (1982) Hepatic angiosarcoma from vinyl chloride. Report of a new Italian case. Med. Lav., 6, 555-563

22. Jones, D.B. & Smith, P.M. (1982) Progression of vinyl chloride induced hepatic fibrosis to angiosarcoma of the liver. Br. J. ind. Med., 39, 306-307

23. Evans, D.M.D., Williams, W.J. & Kung, I.T.M. (1983) Angiosarcoma and hepatocellular carcinoma in vinyl chloride workers. Histopathology, 7, 377-388

24. Maltoni, C., Clini, C., Vicini, F. & Masina, A. (1984) Two cases of liver angiosarcoma among polyvinyl chloride (PVC) extruders of an Italian factory producing PVC bags and other containers. Am. J. ind. Med., 5, 297-302

25. Louagie, Y.A., Gianello, P., Kestens, P.J., Bonbled, F. & Haot, J.G. (1984) Vinyl chloride induced hepatic angiosarcoma. Br. J. Surg., 71, 322-323

26. Langbein, G., Permanetter, W. & Dietz, A. (1983) Hepatocellular carcinoma after vinyl chloride exposure (Ger.). Dtsch. med. Wochenschr., 108, 741-745

27. Cooper, W.C. (1981) Epidemiologic study of vinyl chloride workers: Mortality through December 31, 1972. Environ. Health Perspect., 41, 101-106

28. Buffler, P.A., Wood, S., Eifler, C., Suarez, L. & Kilian, D.J. (1979) Mortality experience of workers in a vinyl chloride monomer production plant. J. occup. Med., 21, 195-203

29. Fedotova, I.V. (1983) The incidence of malignant tumors among workers engaged in the manufacture of vinyl chloride and polyvinyl chloride (Russ.). Gig. Tr. prof. Zabol., 4, 30-32

30. Waxweiler, R.J., Smith, A.H., Falk, H. & Tyroler, H.A. (1981) Excess lung cancer risk in a synthetic chemicals plant. Environ. Health Perspect., 41, 159-165

31. Filatova, V.S., Antonyuzhenko, V.A., Smulevich, V.B., Fedotova, I.V., Kryzhanovskaya, N.A., Bochkareva, T.V., Goryacheva, L.A. & Bulbulyan, N.A. (1982) Blastomogenic hazard of vinyl chloride (clinico-hygienic and epidemiologic study) (Russ.). Gig. Tr. prof. Zabol., 1, 28-31

32. Molina, G., Holmberg, B., Elofsson, S., Holmlund, L., Moosing, R. & Westerholm, P. (1981) Mortality and cancer rates among workers in the Swedish PVC processing industry. Environ. Health Perspect., 41, 145-151

33. Hong, C.B., Winston, J.M., Thornburg, L.P., Lee, C.C. & Woods, J.S. (1981) Follow-up study on

the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: tumor incidence and mortality subsequent to exposure. J. Toxicol. environ. Health, 7, 909-924

34. Feron, V.J., Hendriksen, C.F.M., Speek, A.J., Til, H.P. & Spit, B.J. (1981) Lifespan oral toxicity study of vinyl chloride in rats. Food Cosmet. Toxicol., 19, 317-333

35. Hehir, R.M., McNamara, B.P., McLaughlin, J., Jr, Willigan, D.A., Bierbower, G. & Hardisty, J.F. (1981) Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. Environ. Health Perspect., 41, 63-72

36. Maltoni, C., Lefemine, G., Ciliberti, A., Cotti, G. & Carretti, D. (1981) Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. Environ. Health Perspect., 41, 3-29

37. Drew, R.T., Boorman, G.A., Haseman, J.K., McConnell, E.E., Busey, W.M. & Moore, J.A. (1983) The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice and hamsters. Toxicol. appl. Pharmacol., 68, 120-130

38. Suzuki, Y. (1983) Neoplastic effect of vinyl chloride in mouse lung - lower doses and short-term exposure. Environ. Res., 32, 91-103

39. Groth, D.H., Coate, W.B., Ulland, B.M. & Hornung, R.W. (1981) Effects of aging on the induction of angiosarcoma. Environ. Health Perspect., 41, 53-57

40. Radike, M.J., Stemmer, K.L. & Bingham, E. (1981) Effect of ethanol on vinyl chloride carcinogenesis. Environ. Health Perspect., 44, 59-62

41. IARC Monographs, Suppl. 6, 566-569, 1987

**Synonyms**

- Chloroethylene
- Monochloroethylene
- VC
- VCM
- Vinyl C monomer

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