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TITLE: A REVIEW OF THE CARCINOGEN LITERATURE OF 125 CHEMICALS

AUTHORS: Carl R. McMillin

ABSTRACT: The first task of EPA Contract 68-02-2773 is to identify 20 significant atmospheric carcinogens. Sampling and analytical methodology based on porous polymer sorbants and gas chromatography/mass spectrometry will then be developed for 15 of these chemicals.

In order to identify significant carcinogens, the literature has been reviewed for about 125 chemicals to determine whether they should be considered carcinogens for this project.

Different criteria must be used to define what tests results indicate carcinogenicity depending on the use to which the resulting list is intended. For this program, some chemicals have been included on the possible carcinogen list based on a limited amount of short-term mutagenicity data. If these lists should be used for other purposes, it would be expedient to review the literature cited and draw the appropriate conclusions based on other guidelines.

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Introduction

The first task of EPA Contract 68-02-2773 is to identify 20 significant atmospheric carcinogens. Sampling and analytical methodology based on porous polymer sorbants and gas chromatography/mass spectrometry will then be developed for 15 of these chemicals.

In order to identify significant carcinogens, the literature has been reviewed for about 125 chemicals to determine whether they should be considered carcinogens for this project.

Different criteria must be used to define what test results indicate carcinogenicity depending on the use to which the resulting list is intended. For this program, some chemicals have been included on the possible carcinogen list based on a limited amount of short-term mutagenicity data. If these lists should be used for other purposes, it would be expedient to review the literature cited and draw the appropriate conclusions based on other guidelines.

For this project, a probable carcinogen generally has at least some positive animal data coupled with positive mutagenicity data from at least one well established mutagenicity test or several mutagenicity tests which have not been as extensively validated. The mutagenicity tests which were considered fairly well established include the Ames Salmonella typhimurium test and the enhancement of viral transformation tests (e.g. B. C. Casto), with the E. coli (pol A) differential toxicity and the Drosophila tests also considered important.

Animal carcinogenicity tests were considered less significant if they were conducted more than 5 - 10 years ago, tested by the subcutaneous route of administration demonstrating only local tumors, utilized only a few animals, or reported no concurrent control animals.

Dr. B. C. Casto, BioLabs, Inc. - Northbrook, Illinois, has been a consultant for Monsanto Research Corporation on this EPA contract.

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Acetaldehyde

Acetaldehyde is possibly a carcinogen promoter[1], but no references to it as a carcinogen or mutagen were found in Toxline or Cancerline. Two references by Nakahara and Morl in 1939 and 1940[2] demonstrated no tumors in rats fed acetaldehyde in their food for more than 300 days. It is probably not a carcinogen.

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[1]Davies, J. C., "Co-Carcinogenesis with Respect to the Contents of Cigarette Tobacco", R. Soc. Health J. 93(6), 296-301, 1973.

[2]Hartwell, J. L., "Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Second Edition", National Technical Information Service Number PB 216 478, 1951.

Acetone

Acetone (2-propanone, dimethyl ketone, CAS No. 67-64-1) has been extensively tested for carcinogenic activity both by itself and as a negative solvent control for other chemicals[1]. No significant positive results could be found on Cancerline or Toxline for acetone. It is also negative on most *in vitro* tests and is used as a negative solvent control for many chemicals in these tests.

[1] Survey of Compounds Which Have Been Tested for Carcinogenic Activity, National Cancer Institute, PHS-149, Volumes 1, 2, 3, 4, 5, 6 and 7.

Acetonitrile

The only data suggesting that acetonitrile is a carcinogen is a reference citing equivocal results from a 2-year rat study[1]. It is considered a non-carcinogen for this project.

[1]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Acrolein

Acrolein appears to be toxic and reduces ciliary action of the bronchial epithelium[1,2], but is not mutagenic in S. cerevisiae[3] or dominant lethal mice tests[4]. Acrolein has been found to be a mutagen to the TA1538 and TA98 strains of S. typhimurium[5]. It will be considered to be a possible carcinogen for this project.

Production and Persistance

It is estimated that 6.5×10^6 Kg is emitted per year, primarily associated with acrylic acid manufacture[6]. Other estimates are 4.2×10^5 Kg/yr released from 2.8×10^7 produced[7] and a production of 2.8×10^7 produced in 1974 with a 6.7% growth forecasted through 1979[8]. It has an atmospheric half life estimated at 2.6 hours[9]. Its boiling point is -88°C and it has a vapor pressure of 220 mm at 20°C[10].

---

[1]Shabad, L. M. et al., "The Feasibility of Preventing the Effects of Carcinogens on Man", Kazan Med. Zh (5), 92-93, 1973.

[2]Terrell, J. H. and Schmeltz, I., "Cigarettes: Chemical Effect of Sodium Nitrate Content", Science 160, 1456, 1968.

[3]Izard, C., "Mutagenic Effects of Acrolein and its Two Epoxides, Glycidol and Glycidal, in Saccharomyces Cerevisiae", C. R. Acad. Sci., Ser. D., 276 (23), 3037-3040, 1973.

[4]Epstein, S. S., et al., "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse", Toxicol, Appl. Pharmacal. 23, 288-325, 1972.

[5]Bignami, M. et al., "Relationship Between Chemical Structure and Mutagenic Activity in Some Pesticides: The Use of Salmonella Typhimurium and Aspergillus Nidulans", Mutat. Res. 46 (3), 243-244, 1977.

[6]MRC Source Assessment Data Base, July 1977.

[7]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[8]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[9]Padding, S. R., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[10]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N.Y., 1977.

Acrylonitrile

Positive Ames tests[1] E. coli mutation tests[2] and viral transformation enhancement tests[3] have been reported along with negative recessive lethal Drosophila melanogaster and negative Vicia faba chromosome aberration tests[4]. Human epidemelogical evidence points toward acrylonitrile being a carcinogen[5]. Additionally, one-year interim report from the Manufacturing Chemists' Association of on-going ingestion and inhalation studies of acrylonitrile in laboratory rats report the rats developing a variety of tumors including carcinomas[6]. Based on these findings, acrylonitrile is being placed on the probable carcinogen list for this project.

Production and Persistance

It is estimated that 3.7×10^5 Kg is emitted per year[7]. (Another estimate is 9.6×10^6 Kg per year[8]). Acrylonitrile has a boiling point of 77°C and a vapor pressure of 100 mm at 23°C[9].

---

[1]Milvey, P. and Wolff, M., "Mutagenic Studies with Acrylonitrile", Mut. Res. 48 (3-4), 271-278, 1977.

[2]Venitt, S. et al., "Mutagenicity of Acrylonitrile (Cyanoethylene) in Escherichia Coli", Mut. Res. 45, 283-288, 1977.

[3]Personal communication with B. C. Casto on 9 February 1978.

[4]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[5]"Acrylonitrile Linked to Cancer on Workers", Chem. Eng. News, 55, 6, 1977.

[6]Finklea, J. F., "Acrylonitrile" Am. Ind. Hyg. Assoc. J. 38, 417-422, 1977.

[7]MRC Source Assessment Data Base, July 1977.

[8]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[9]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Aldrin

Aldrin has been found to cause neoplasia in two strains of mice[1] and tumors in weanling rats[2]. Aldrin is converted into dieldrin in the environment[3] and dieldrin is a carcinogen at 0.1 ppm in dietary exposure to mice[4]. Thus the sale and production of aldrin was suspended[5]. Many other animal studies have been conducted with questionable results[6], and some *in vitro* tests have been negative[7]. Since there is enough data to suspend production of aldrin, it will be considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 4.5×10^6 Kg aldrin were produced in 1971[6]. Another production estimate is 1.1×10^7 Kg/year (1976)[8].

---

[1]Song, J. and Harville, W. E., "Carcinogenecity of Aldrin and Dieldrin on Mouse and Rat Liver", Fed. Proc. 23, 336, 1964.

[2]Deichmann, W. B., et al., "Tumorigenicity of Aldrin, Dieldrin, and Endrin in the Albino Rat", Ind. Med. Surg. 39 (10), 426-434, 1950.

[3]Wurster, C. F., "Aldrin and Dieldrin", Environment 13 (8), 33-45, 1971.

[4]Epstein, S. S., "Prevention - Environmental Exposure: An Overview, Including the Role of Pesticides", Third International Symposium on Detection and Prevention of Cancer, 5, 1976.

[5]Epstein, S. S. "Case Study 5: Aldrin and Dieldrin Suspension Based on Experimental Evidence and Evaluation and Societal Needs", Ann. N.Y. Acad. Sci. 271, 187-195, 1976.

[6]"Aldrin", in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 5, 25-38, 1974.

[7]Fahrig, R., "Comparative Mutagenicity Studies with Pesticides", in Chemical Carcinogenesis Essays, IARC Sci. Pub. No. 10, 161-181, 1974.

[8]Fuller, B. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Allyl Chloride

Allyl chloride (3-chloropropene, CAS No. 107-05-1) is on the NIOSH Safety Alert List. No references have been found on the Toxline, Cancerline or the Stanford Research Institute study on hazard priority ranking[1], to indicate that allyl chloride is a carcinogen or mutagen. A recent reference, however, reports that allyl chloride is a mutagen in S. typhimurium, S. cerevisiae, and E. coli test systems[2]. It is therefore classified as a possible carcinogen for this project.

Production and Persistance

It is estimated that 4.2×10^5 Kg is emitted per year from stationary sources[3]. Another estimate is 2×10^6 Kg released from a production of 1.3×10^8 Kg per year[4], and a production estimate of 1.3×10^8 Kg in 1972[5]. It is reported to take 27 minutes for 50% of the allyl chloride in a 1 ppm solution to evaporate at 25°C[6]. It has a half-life with HO radical of 21 hours, with O_3 radicals of 9 hours, and hydrolyzes with a half-life of 7 days[4]. It has a boiling point of 45°C, a vapor pressure of 340 mm at 20°C, and a solubility of 3.3 gm/l[6].

---

[1]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[2]McCoy, E. C., et al., "Genetic Activity of Allyl Chloride", Mutat. Res., 57, 11-15, 1978.

[3]MRC Source Assessment Data Base, July 1977.

[4]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 164, 1975.

[5]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 443, 1976.

[6]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Aniline

The IARC monograph on aniline[1] reports that aniline is probably not a carcinogen and that what early researches believed was cancer from aniline was most likely due to impurities such as benzidene. It has tested negative on a differential growth E. coli test (pol A)[2] and on S. typhimurium strains TA1535, 1537, 100 and 98 with and without microsomes[3]. It has also been reported negative in reversion to prototrophy in Aspergillus nidulans ($meth_3$) and several other tests[3]. It was classified negative/inadequate in one of the latest reviews[3] and will be considered a probable non-carcinogen for this project.

---

[1] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 4, 27-36, 1974.

[2] Fluck, E. R., et al., "Evaluation of a DNA Polymerase-Defecient Mutant of E. Coli for the Rapid Detection of Carcinogens", Chem. Biol. Interact. 15, 219-231, 1976.

[3] Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

Anthracene

Anthracene is on the NIOSH Suspected Carcinogen List because of two 1955 references. In the first reference cited (1), anthracene was found to be non-carcinogenic orally and interperitoneally. But when injected in 550 doses over a two-three year period (6 times/week - total dose 4.5 g/rat) 5 out of 9 rats developed local fibrosarcomas. It is now known that multiple injections can sometimes cause fibrosarcomas. Recent studies (2) have shown anthracene to be a non-carcinogen and it is presently being used as a non-carcinogenic standard on studies to develop short-term assays for carcinogens (3-6).

---

1 Schmall, D., "Prufung von Naphthalin und Anthracen auf Carcerogene Wirking an Ratten", Zeitschrift fur Krebsforschung 60, 697-710, 1955.

2 Stanton, M. F., Miller, E., Wrench, C., and Blackwell, R., J. Natl. Cancer Institute 49 (3), 867-877, 1972.

3 Pienta, R. J. et al., "Morphological Transformation of Early Passage Golden Syrian Hamster Embryo Cells Derived from Cryopreserved Primary Cultures as a Reliable in vitro Bioassay for Identifying Diverse Carcinogens", Int. J. Cancer 19, 642-655, 1977.

4 DiPaolo, J. A. et al., "Quantitation of Chemically Induced Neoplastic Transformation of BALB/3T3 Cloned Cell Lines", Cancer Research 32, 2686-2695, 1972.

5 Purchase, I. F. H., et al., "Evaluation of Six Short Term Tests for Detecting Organic Chemical Carcinogens and Recommendations for Their Use", Nature 264, 624-627, 1976.

6 McCann, J. et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test" Assay of 300 Chemicals", Proc. Natl. Acad. Sci. (USA) 72, 5135-5139, 1975.

Benz(a)Anthracene

Benz(a)anthracene (1,2-benzanthracene, CAS No. 56-55-3) is well known as a carcinogen. It is carcinogenic orally, subcutaneously and topically for mice[1]. It is one of the standard carcinogens used to evaluate the validity of short-term tests and will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that less than 100 kg/year is emitted from carbon black furnaces, the only stationary source cited for this chemical[2]. It is emitted in the exhaust from gasoline engines (61.7 mg/kg exhaust tar) and diesel engines (2.3-15 $\mu g/m^3$ exhaust)[1]. It has been detected in the air, soil, food, and cigarette smoke condensate[1]. It has a boiling point of 400°C.[1]

---

[1] "Benz(a)Anthracene" in IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man, Volume 3, 45-68, 1973.

[2] MRC Source Assessment Data Base, July 1977.

Benzene

Benzene (CAS No. 71-43-2) is one of the industrial substances suspected of carcinogenic potential to man as listed by the American Conference of Governmental Industrial Hygienists[1] and will soon be controlled as a carcinogen. The International Agency for Research on Cancer[2] reports animal data which "do not permit the conclusion that carcinogenic activity has been demonstrated". In human data they support a relationship between exposure to benzene or benzene mixtures and the development of leukemia. Along with some positive studies[3], many references occur in the literature where benzene is a negative solvent control in animal studies[4]. In spite of these references, it is believed that benzene induces chromosomal damage in animals and man[5] and is a known carcinogen. An assessment of the air pollution aspects of benzene has been conducted[6]. Since benzene is being controlled as a carcinogen, it will be considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 1×10^8 kg benzene is emitted per year with solvent evaporation from degreasing operations contributing over 70% of the total[7]. Another estimate is 4×10^7 kg per year released from commercial uses of benzene[3]. It reacts rapidly with HO ($t_{\frac{1}{2}}$ = 3 days) but slowly with RO_2 and O_3 and has a 2.15 log partition coefficient[3]. Its boiling point is 80.1°C and it has a vapor pressure of 76 mm at 20°C[8].

---

[1] "Threshold Limit Values for Chemical Substances in Workroom Air Adopted by ACGIH for 1977", American Conference of Governmental Industrial Hygienists, 1977.

[2] "Benzene", in "IARC Monographs on the Evaluation of Carcinogenic Risk of Chemical to Man", Volume 7, 203-222, 1974.

[3] Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 162, 1975.

[4] Survey of Compounds Which Have Been Tested for Carcinogenic Activity, PHS-149, National Cancer Institute.

[5] Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[6] Walker, P., "Air Pollution [illegible]", National Technical [illegible]

MRC Source Assessment Data Base, July 1977.

Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nortrand Reinhold Co., N. Y., 1977.

Benzidine

Benzidine is reported to be carcinogenic in the mouse, rat, hamster, and possibly in the dog[1]. Given orally, it has produced bladder carcinoma in the dog after a long latent period and liver tumors in the rat and hamster. Benzidine was a carcinogen to mice when given p.o. either by stomach intubation or in food[2]. These references, along with many others in Toxline and Cancerline show that benzidine should be considered a probable carcinogen.

Production and Persistance

It is estimated that 4.7×10^6 Kg is produced per year[3]. A release factor of 0.015 is assumed which would give 7×10^4 Kg released per year. This is probably too high since benzidine is well known as a carcinogen. Perhaps 7×10^3 Kg would be closer to reality. It reacts with OH and O_3 with a t 1/2 of one day[4]. It has a boiling point of 402°C[5] and can be sublimed[1].

---

[1] "Benzidine" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 1, 80-86, 1972.

[2] Vesselinovitch, S. D., et al., "Factors Modulating Benzidine Carcinogenicity Bioassay", Cancer Res. 35 (10), 2814-2819, 1975.

[3] Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[4] Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 163, 1975.

[5] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Benzo(a)Pyrene

Benzo(a)pyrene (3,4-benzpyrene, CAS No. 50-32-8) is a well established carcinogen following many different administrations including oral, skin, subcutaneous and intratracheal routes[1]. Positive results have been reported with mice, rats, guinea pigs, monkeys, newts, hamsters, and ducks[1]. It will be considered a probable carcinogen for this project.

Production and Persistence

Although not manufactured in quantity, it is a by-product of combustion. It is estimated that 8.3×10^5 kg per year is released from stationary sources with 96% of this coming from: 1) coal refuse piles, outcrops and abandoned mines, 2) residential external combustion of bituminous coal, 3) coke manufacture, and 4) residential external combustion of anthracite coal[2]. It has a boiling point of 311°C at 10 mm and 475°C at 760 mm[1].

---

[1]"Benzo(a)Pyrene" in IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemicals to Man, Volume 3, 91-136; 1973.

[2]MRC Source Assessment Data Base, July 1977.

Benzoquinone (Quinone)

1940 and 1941 Japanese references[1] state that 3/87 mice painted with benzoquinone (in benzene) developed skin cancer with 9/87 papillomas after 200 days compared to 0/46 skin cancers and 1/46 papillomas for the benzene control. Skin painting with a benzene solution in 1953 was said to cause 16/80 ear duct carcinomas[2]. In 1954 and 1956, inhalation experiments with a total of 50 treated mice were conducted with negative results[3]. By subcutaneous injection, 24 rats were tested with negative results in 1957[3].

More recent references show that benzoquinone does not decrease hatchability of the Drosophila melanogaster[4], is not mutagenic toward Drosophila or cultured human leukocytes[4], produces no increase in recessive sex-linked lethal mutations in Drosophila and did not significantly alter the rate of chromated translocations or breaks in leukocytes[5]. No other significant data were found in Toxline, Cancerline, or the "Survey of Compounds Which Have Been Tested for Carcinogenic Activity". Benzoquinone is therefore, to be considered a probable non-carcinogen for this project.

---

[1]Takizawa, N., "On the Carcinogenic Action of Certain Quinones", Proc. Imperial Acad. (Tokyo) 16, 309-312, 1940.

[2]Tiedemann, H. Ztschr. Naturforsch. 8b, 49-50, 1953.

[3]"para-Quinone" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 15, 255-264, 1977.

[4]Vogel, E., "Differential Sensitivity of Immature and Mature Oocytes of Drosophila Melanogaster to the Induction of Dominant Lethals Following Treatment of Mono- and Polyfunctional Aziridine Analogues", Mutat. Res. 14, 250-253, 1972.

[5]Lueers, H. and Obe, G., "Possible Mutagenic Activity of P-Benzoquinone", Mutat. Res. 15, 77-80, 1972.

Benzoyl Peroxide

Benzoyl peroxide (CAS No. 94-36-0) was extensively tested in mice and rats between 1962 and 1967 by six authors on more than eleven hundred animals[1]. Benzoyl peroxide is on the NIOSH Suspected Carcinogen list because in one of these studies, 1/30 mice developed a squameous papiloma after application of benzoyl peroxide in benzene to the skin. No recent mutagen or carcinogen references could be found on Toxline or Cancerline. It has been found negative in a dominant lethal mouse test, on an E. Coli(pol A) mutagen test, and a Micrococcus pyogenes test[2]. There is very little doubt that benzoyl peroxide should be considered a non-carcinogen.

[1]Survey of Compounds Which Have Been Tested for Carcinogen Activity, NCI, PHS-149, Volume 1961-1967.

[2]Allport, J. et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

Benzyl Chloride

Benzyl Chloride (α-chlorotoluene, CAS No. 100-44-7) has been found positive on a differential growth E. coli (pol A) mutagen test[1]. It is also positive on a subcutaneous rat test at 2.1 g/kg (51 weeks) in 3/14 rats and at 3.9 g/kg in 6/8 rats[2]. It is weakly mutagenic in S. typhimurium tests at 2 mg/plate[3], and is considered carcinogenic in rats by the IARC[4]. It is considered a probable carcinogen for this project.

Production and Persistence

In 1972 it was estimated that 3.6×10^7 kg was produced with 65-70% of this going towards the manufacture of butyl phthalate and 30-35% towards other organic products[2]. Production has been estimated at 4.5, 3.2 and 4.1×10^7 kg in 1974, 1975 and 1976 and is predicted to grow at 5-7% per year through 1980[4]. It has a boiling point of 179°C and vapor pressure of 1 mm at 22°C[5].

---

[1]Fluck, E. R., et al., "Evaluation of a DNA Polymerase - Deficient Mutant of E. coli for the Rapid Detection of Carcinogens", Chem. Biol. Interact., 15, 219-231, 1976.

[2]"Benzyl Chloride" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 11, 1976.

[3]McCann, J., et al., "Detection of Carcinogens as Mutagens: Bacterial Tester Strains with R Factor Plasmids", Proc. Nat. Acad. Sci., 72, 979-983, 1975.

[4]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[5]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N.Y., 1977.

Biphenyl

There is one reference which shows subcutaneous biphenyl (diphenyl, CAS No. 92-52-4) to induce an excess of tumors in mice[1]. No other references could be found in Cancerline or Toxline which would support that data. Biphenyl is therefore placed on the possible carcinogen list for this project.

Production and Persistance

It is estimated that 9.2×10^4 Kg biphenyl is emitted per year from the manufacture of polychlorinated biphenyls[2]. Since the production of polychlorinated biphenyls has been stopped, this source of biphenyl emissions has probably ceased to exist. It has a boiling point of 254°C[3].

---

[1] "Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", National Technical Information Service Number PB 223 159, 1968.

[2] MRC Source Assessment Data Base, July 1977.

[3] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N.Y., 1977.

Bis (Chloromethyl) Ether

Bis(chloromethyl) ether (BCME, dichloromethylether, CAS No. 542-88-1) is carcinogenic to mice following inhalation, skin application and subcutaneous administration[1]. It is also carcinogenic to rats by inhalation and subcutaneous administration[1]. Epidemilogical data suggests it is also a human carcinogen[1]. It is being regulated as a carcinogen and will be considered a probable carcinogen for this project.

Production and Persistance

It is estimated that less than 100 Kg BCME is emitted per year[2]. A primary source of emissions is in the production of polymethylene polyphenyl isocyanate[2]. Its production in 1974 was estimated to be less than 450 Kg[3]. In water the half life of BCME is 38 seconds and in the air (50% relative humidity) its half life is 25 minutes[3]. It has a boiling point of 104°C[3].

---

[1] "Bis(Chloromethyl) Ether" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 4, 231-238, 1974.

[2] MRC Sourse Assessment Data Base, July 1977.

[3] Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

Butadiene

1,3-Butadiene (CAS No. 106-99-0) has not been estensively tested for mutagenicity or carcinogenicity. No references could be found on Toxline, Cancerline, or in the seven collected volumes of Survey of Compounds Which Have Been Tested for Carcinogenic Activity on tests conducted although there is interest in a possible relationship between styrene-butadiene rubber plants and neoplasms of the lymphatic and hematopietic tissue[1]. Butadiene will be considered a probable non-carcinogen for this project.

[1]Smith, A. H. and Ellis, L., "Styrene Butadiene Rubber Synthetic Plants and Leukemia" (Letter to Editor), J. Occup. Med. 19 (7), 441, 1977.

Captan

Captan has been found to be a potent mutagen, in both prokaryote and enkaryote test systems too numerous to list. It has also been found to produce heptomas in mice[1]. Because of the many positive mutagenicity tests along with a marginally positive mouse carcinogenicity test, Captan has been placed on the probable carcinogen list.

Production and Persistance

It is estimated that less than 100 Kg per year of captan is emitted[2]. (Another estimate is production of 8.1×10^6 Kg per year with 0.01 released or 8×10^4 Kg per year emitted[3].)

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[1] "Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemials", National Technical Information Service Number PB 223 159, 1968.

[2] MRC Source Assessment Data Base, July 1977.

[3] Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Carbon Disulfide

There is nothing in Toxline or Cancerline to indicate that carbon disulfide is a carcinogen or a mutagen. One industrial epidemiological study showed carbon disulfide to have no correlation with incidence of cancer[1].

[1]DiVito, G. and Sommi, G. L., "The Incidence of Infectious Diseases, Hemopathies, and Neoplasms in Workers Exposed to Carbon Disulfide", Folia Med. (Napoli), 46 (11), 972-979, 1963.

Carbon Tetrachloride

Carbon tetrachloride (tetrachloromethane, CAS No. 56-23-5) has been reported to produce liver tumors in the mouse, hamster, and rat following administration by inhalation and oral ingestion[1]. It was not a mutagen as tested by several microbial systems[2]. Carbon tetrachloride is considered a probable carcinogen for this project.

Production and Persistence

It is estimated that 1.2×10^7 kg of carbon tetrachloride is emitted per year[3]. Another estimate is a production of 4.5×10^8 kg with 2.7×10^7 kg released[4]. A document is available on the air pollution assessment of carbon tetrachloride[5]. Estimates of carbon tetrachloride production include 4.5×10^8 kg (1970)[1], 4.8×10^8 kg[6], 7.3×10^8 kg (1974)[7] and 5.3, 4.1, and 3.8×10^8 kg for 1974, 1975, and 1976[2]. It is forecasted that the 1975-1976 decline will continue. The half life of carbon tetrachloride in the water is about 70,000 years[4], and in the troposphere it is about 10 years[7]. It is estimated to have a half life of 10-33 weeks toward atmospheric photodegradation[5]. The boiling point of carbon tetrachloride is 76.7°C and it has a vapor pressure of 90 mm at 20°C[8]. For a review of its production, uses and biological activity, see the Fishbein article[9].

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[1]"Carbon Tetrachloride" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 1, 53-60, 1972.

[2]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[3]MRC Source Assessment Data Base, July 1977.

[4]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[5]Johns, R., "Air Pollution Assessment of Carbon Tetrachloride", National Technical Information Service Number PB 256 732, 1976.

[6]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[7]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[8]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

[9]Fishbein, L., "Industrial Mutagens and Potential Mutagens, I. Halogenated Aliphatic Derivatives", Mutat. Res. 32, 267-308, 1976.

Chloracetic Acid

Chloracetic Acid (monochloroacetic acid, CAS No. 79-11-8) has been reported as being carcinogenic in mice when injected subcutaneously at 100 mg/kg[1]. The primary reference, however, does not report a statistical difference in tumors and reports data with the test chemical not much different than the control mice[2]. In other tests, chloracetic acid was negative when given to 6 rats as 0.005-0.1% of their diet for 208 days[3] and negative when given at 46.4 mg/kg in the water of 72 mice for days 7-28 followed by 149 ppm in their diet for another 17 months[4]. It has also been found non-mutagenic by B. subtilis[5] and S. typhimurium[5-8] tests *in vitro*. All of these demonstrate that chloracetic acid is not a mutagen and is not a carcinogen.

[1]NIOSH Suspected Carcinogens list, 1976.

[2]"Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Volume 1.", National Technical Information Service Number PB 223 159, 1968.

[3]Fuhrman, F. A., et al., Arch. Inst. Pharmacodym., 102, 113-125, 1955.

[4]Innes, J. R. M., et al., J. Nat. Cancer Inst. 42, 1101-1114, 1969.

[5]Elmore, J. D., et al., "Vinyl Chloride Mutagenicity via the Metabolites Chlorooxirane and Chloroacetaldehyde Monomer Hydrate," Biochem. Biophys. Acta 442, 409-419, 1976.

[6]Rannug, U., et al., "The Mutagenicity of Chloroethylene Oxide, Chloroacetaldehyde, 2-Chloroethanol and Chloroacetic Acid, Conceivable Metabolities of Vinyl Chloride," Chem. Biol. Interact. 12 (3-4), 251-263, 1976.

[7]Bartsch, H., et al., "Human, Rat and Mouse-Liver Mediated Mutagenicity of Vinyl Chloride in S. Typhimurium Strains," Int. J. Cancer, 15 (3), 429-437, 1975.

[8]Malaveille, C., et al., "Mutagenicity of Vinyl Chloride, Chloroethyleneoxide, Chloroacetaldehyde and Chloroethanol," Biochem. Biophys. Res. Comm. 63 (2), 363-370, 1975.

Chlordane

Chlordane has been found to be a carcinogen to mice in a study conducted by the National Cancer Institute[1]. It is also a mutagen in tests like the enhancement of viral transformation[2]. It is considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 1.1×10^7 Kg per year of chlordane is produced[3].

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[1] "Bioassay of Chlordane for Possible Carcinogenicity. (CAS No. 57-74-9)", National Technical Information Service Number PB 271 977/ISL.

[2] Personal communication with B. C. Casto on 9 February 1978.

[3] Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Cresols

Cresols (primarily o-cresol) have been shown to be promoters of carcinogenicity when given with initiators such as 3,4-benzpyrene (Kaiser), dimethylbenzanthracene[1] or in complex mixtures[2,3]. On the other hand, normal adults excrete about 30 mg of volatile phenols per day of which 90% is p-cresol[4]. Thus, cresols are probably not carcinogens but could be promoters.

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[1]Bakke, O. M. and Midtvedt, T., "Influence of Germ-Free Status on the Excretion of Simple Phenols of Possible Significance in Tumor Promotion", Experimentia, 26 (5), 519, 1970.

[2]Bock, F. G., et al., "Composition studies on Tobacco. XLIV. Tumor-Promoting Activity of Subfractions of the Weak Acid Fraction of Cigarette Smoke Condensate", J. Nat. Cancer Inst., 47 (2), 429-436, 1971.

[3]Shustova, M. N. and Samiolovich, L. N., "Blastomogenicity of Neutralized Soots from the Sulfate Shop of a Coke Plant", Gig. Sanit., 36 (7), 103-104, 1971.

[4]Bone, E. S., et al., "The Production of Urinary Phenol by Human Gut Bacteria", (Meeting Abstract), J. Med. Microbiol. 9 (2), vi, 1976.

Chlorobenzilate

Chlorobenzilate (CAS No. 510-15-6) has been found to produce heptomas in mice when administered orally[1,3], and is listed by the U. S. Commission on Pesticides and Their Relationship to Environmental Health as a group B chemical (positive results in one or more animal species at 0.01 significance level)[4]. Several short term tests have been negative for Chlorobenzilate[5]. For this project, it is considered a probable carcinogen.

Production and Persistance

A 1976 reference[6] cites a production of 9×10^5 Kg per year and it is said[3] that the 1971 production was 1×10^6 Kg.

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[1] Innes, J. R. M., et al., "Bioassay of Pesticides and Industrial Chemicals for Tumorigencity in Mice. A Preliminary Note", J. Nat. Cancer Inst., 42, 1101, 1969.

[2] "Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", National Technical Information Service Number PB 223 159, 1968.

[3] "Chlorobenzilate" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 5, 75-81, 1974.

[4] Jurek, A., "Carcinogenicity of Pesticides", Roczn. Panstw. Zakl. Hig. 25 (5), 563-576, 1974.

[5] Fahrig, R., "Comparative Mutagenicity Studies with Pesticides", in Chemical Carcinogenesis Essays, IARC Sci. Pub. No. 10, 161-181, 1974.

[6] Fuller, B. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Chloroform

Some of the current literature[1-4] indicates that chloroform is a carcinogen. Even though more data is required before a final determination is made, the positive data on mice and rats suggest that chloroform be placed on the probable carcinogen list for this project.

Production and Persistance

It is estimated that 1 x 10^6 Kg chloroform is emitted per year[5]. Another estimate is 1.7 x 10^7 Kg per year[6] emitted. Production estimates are 1.3 x 10^8 Kg per year[7], 1.1 x 10^8 Kg per year[8], and 1.1 x 10^8 Kg per year[1]. About 96% of production is converted to chlorodifluoromethane. In the troposphere chloroform degrades slowly with a 10 year half life[7]. It reacts with HO radical with a t 1/2 of 13 hours[7] and hydrolyses with a t 1/2 of 3000 years[6,7]. The log partition coeficient is 1.97 for chloroform[6]. It has a vapor pressure of 160 mm at 20°C and a boiling point of 62°C[9]. It takes only 18-25 minutes to evaporate 50% of the chloroform from a 1 ppm solution at 25°C[9].

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[1]IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man, "Chloroform", Volume 1, 61-65, 1972.

[2]Powers, M. B. and Yoelker, R. W., "Evaluation of the Oncogeric Potential of Chloroform by Long-Term Oral Administration in Rodents" (Meeting Abstract), Toxicol. Appl. Pharmacol. 37, 179, 1976.

[3]Renne, R. A. et al., "Pathology of Long-Term Oral Administration of Chloroform in Rodents" (Meeting Abstract), Toxicol. Appl. Pharmacol. 37, 179-180, 1976.

[4]"Chloroform Tagged as Carcinogen in Mice", Chem. Eng. News 54, 6, 1976.

[5]MRC Source Assessment Data Base, July 1977.

[6]Brown, S. L., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 163, 1975.

[7]Radding, S. R., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[8]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[9]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N.Y., 1977.

Chloroprene

Chloroprene (2-chloro-1,3-butadine, CAS No. 126-99-8) although known to be toxic was not considered to be a suspected carcinogen until three Russian papers linked occupational exposure of chloroprene to skin and lung cancers[1-3]. Since that time, a short-term viral enhancement[4] test at 125 μg/ml[5] and S. typhimurium (Ames) tests[6] have been positive, while long-term rat and mouse studies have been negative[7,8]. A review of health records and death certificates for DuPont Corporation employees exposed to chloroprene convinced investigators that no excess of any disease similar to that seen for vinyl chloride had been observed[9]. However, some increase in lung cancer has been seen in this population[9]. It has also been found to accelerate the growth of transplanted Crocker murine sarcoma in the rat[10]. Thus, chloroprene lies on the border between a possible and a probable carcinogen. It will be classifed as a possible carcinogen for this project.

Production and Persistance

It is estimated that 7.5×10^6 Kg chloroprene is emitted per year[11]. Another estimate is 2.7×10^6 Kg/year released[10]. Some estimates of production are about 1.8×10^8 Kg/year[10,12], 1.6×10^8 Kg/year[13], and 1.8×10^8 Kg and 1.6×10 Kg in 1974 and 1975 with 4% annual growth predicted through 1981[14]. Because of its low soluability and high volatility, it will soon migrate to the atmosphere[13]. In the atmosphere it is said to have an atmospheric half life of less than 10 hours because of OH radical reaction[13]. Its boiling point is 59.4°C and it has a vapor pressure of 200 mm at 20°C[15].

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[1]Khachatryan, E. A., "The Role of Chloroprene in the Process of Skin Neoplasm Formation", Gig, Tr. Prof. Zabol. 16, 54-55, 1972.

[2]Khachatryan, E. A., "The Occurrence of Lung Cancer Among People Working with Chloroprene", Problems in Oncology 18, 85, 1972.

[3]Khachatryan, E. A., "Lung Cancer Incidence Among Chloroprene Handling Workers", Yopr. Onkol. 18, 85-86, 1972.

[4]Casto, B. C. et al., "Assay of Industrial Chemicals in Syrian Hamster Cells for Enhancement of Viral Transformation", Proc. Am. Assoc. Cancer Res. 18, 155, 1977.

[5]Personal Communication with B. C. Casto on 9 February 1978.

[6]Bartsch, H., et al., "The Predictive Value of Tissue-Mediated Mutagenicity Assays to Assess the Carcinogenic Risk of Chemicals", IARC Sci. Pub. No. 12, 467-491, 1976.

[7]Zilfyan, Y. N. et al., "Experimental Study of Chloroprene for Carcinogenicity", Yopr. Onkol. 23, 61-65, 1977.

[8]Zilfyan, V. N. et al., "Results of a Study of Chloroprene for Carcinogenicity", Zh. Eksp. Klin. Med. 15, 54-57, 1975.

[9]Lloyd, J. W., "Cancer Risks Among Workers Exposed to Chloroprene", Ann. N. Y. Acad. Sci. 271, 91-93, 1976.

[10]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 164, 1975.

[11]MRC Source Assessment Data Base, July 1977.

[12]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[13]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", NTIS No. PB 267 121, 1977.

[14]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[15]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Chloropropane

No reference to carcinogenic or mutagenic action of chloropropane could be found in Toxline, Cancerline, or any of the other references consulted. It is probably a non-carcinogen and will be considered as such for this project.

Chrysene

Chrysene (benz (a) phenanthrene, CAS No. 218-01-9) is fairly well established as a weak carcinogen. It has produced skin tumors in mice following repeated painting and 2-20 mg injected subcutaneously in mice produced tumors after a long induction period[1]. It is also a mutagen causing 167 revertants per microgram[2]. It is considered a probable carcinogen for this project.

Production and Persistance

Although chrysene is not a manufactured chemical, it is a product of combustion and found widely dispersed in the environment. In one test of automobile exhaust, 12 micrograms were found after one minute of operation[1]. In the atmosphere, 150-490 µg chrysene has been found per gram organic particulate matter[1]. It has a boiling point of 488°C[3].

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[1] "Chrysene" in IARC Monographs on the Evaluation of Carcinogenic Risk of the Chemical to Man, Volume 3, 159-177, 1973.

[2] McCann, J., et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals", Proc. Nat. Acad. Sci., USA, 72 (12), 5135-5139, 1975.

[3] Verschueren, L., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Cumene Hydroperoxide

Cumene hydroperoxide (dimethylbenzyl hydroperoxide) is cited as being a carcinogen but at 34 and 90 mg/kg did not induce statistically significant dominant lethal effects in mice[1,2]. Cumene hydroperoxide is said to cause neoplasims in mice both by inhalation at 304 mg/kg[3] and subcutaneously at 10 g/kg[4]. On the basis of the two animal studies, it is considered a possible carcinogen for this project.

Production and Persistance

It is estimated[5] that the 1974 production was 1.4×10^9 Kg. Another estimate of production[6] is 9.1×10^8 Kg per year with a production loss factor of 0.015 or 1.3×10^7 Kg/year. It has a vapor pressure of 1 mm at 70°C[6]. Because of its low volatility and moderate solubility in water, it is not likely to remain in the atmosphere[5]. Photochemical and HO radical reactions are likely pathways for transformation of peroxides in the atmosphere with a half-life of less than a few hours[5].

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[1]Epstein, S. S. and Shafner, H., "Chemical Mutagens in the Human Environment", Nature 219, 385-387, 1968.

[2]Epstein, S. S., et al., "Detection of Chemical Mutagens by the Dominant Lethal Assay in Mouse", Toxicol. Appl. Pharmacol. 23, 288-325, 1972.

[3]From NIOSH Suspected Carcinogens - Radiation Research Supplement 3, 193, 1963.

[4]From NIOSH Suspected Carcinogens - J. Nat. Cancer Inst. 37, 825, 1966.

[5]Radding, S. B. et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[6]Fuller, B. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

DDT

DDT (1,1,1-trichloro-2,2-di-(4-chlorophenyl) ethane, CAS No. 50-29-3) has both positive and negative in vivo and in vitro data. It was negative in feeding studies of dogs and monkeys[1] and in a differential growth E. coli (pol A) mutagen test[2]. Given orally, it produced liver cell tumors in several strains of mice and some of its metabolites produced lung tumors in mice[2]. It is positive in a recessive lethal Drosophila test[3]. All things considered, it is probably a carcinogen and will be classified as one for this project.

Production and Persistance

In 1971, 2×10^7 Kg was the estimated production[1]. In 1971 it was found in the air in concentrations of 0.1 ng/m^3 to 1.56 µg/m^3. The soil half life is estimated to be 15 years[1]. It has a vapor pressure[1] of 1.9×10^{-7}mm at 20°C and a melting point of 74°C.

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[1] "DDT and Associated Substances" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man", Volume 5, 83-124, 1974.

[2] Fluck, E. R., et al., "Evaluation of a DNA Polymerase-Deficient Mutant of E. Coli for the Rapid Detection of Carcinogens", Chem. Biol. Interact., 15, 219-231, 1976.

[3] Vogel, E., "The Relation Between Mutational Pattern and Concentration by Chemical Mutagens in Drosophila", IARC Sci. Pub. No. 12, 117-137, 1976.

Di-tert-Butyl Peroxide

Di-tert-butyl peroxide (bis(1,1-dimethylethyl) peroxide, CAS No. 110-05-4) has been found to induce malignant lymphomas in 7/35 mice which inhaled 100 mcM of this chemical[1]. Skin applications on mice did not prove to be carcinogenic[2]. (Tert-butyl hydroperoxide has also been found negative by skin application tests on mice[3,4].) Di-tert-butyl peroxide is on a list of "suspected carcinogens" studied for environmental fate[5]. Since the positive mice test results were by the inhalation route which has fewer false positives than injection, di-tert-butyl peroxide will be considered a possible carcinogen for this project. Considering the type and date (1963) of the positive tests, however, negative short term in vitro mutagenicity data would probably change its classification to a probable non-carcinogen by the criteria used for this project.

Production and Persistance

Production is estimated to be 3 million pounds per year[5]. It is only slightly volatile but moderatly soluable in water. Thus most of the di-tert-butyl peroxide will remain in the water system. In the water the presence of >1 ppm Fe^{2+} and Mn^{2+} leads to decomposition to acids and alcohols with $t_{1/2}$ <10 hours[5]. In the atmosphere photochemical and HO radical decomposition lead to a $t_{1/2}$ of 79 hours[5].

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[1]Kotin, P. and Falk, H. L., Radist. Res. (Supp. 3), 193-211, 1963. (From PHS-149; Survey of Compounds Which Have Been Tested for Carcinogenic Activity.)

[2]Saffioti, U. and Shubik, P., Nat. Cancer Inst. Monog., 10, 489-507, 1963. (From PHS-149.)

[3]Hoshing, H., et al., Gann 61 (2), 121-124, 1970. (From PHS-149.)

[4]Van Duaren, B. L., et al., J. Nat. Cancer Inst., 39, 1217-1228, 1967. (From PHS-149.)

[5]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

Di(2-Ethylhexyl)Phthalate

Di(2-ethylhexyl)phthalate (DEHP, dioctyl phthalate, DOP, CAS No. 117-81-7 is a high volume plasticizer which had in the past been considered virtually non-toxic as judged by various acute and chronic tests[1]. Although early animal tests (dog, guinea pig, rat) were negative[2], at least one source[3] now cites neoplastic effects in rats orally given 43.2 g/kg (96 weeks) di(2-ethylhexyl)phthalate. Although this dose is rather high, there are also several references which show this chemical to be both mutagenic and teratogenic[4-12]. It is therefore classed as a possible carcinogen for this project at least until the present carcinogen bioassay being conducted is concluded[13].

Production and Persistance

It is estimated that 2.6×10^5 Kg DEHP is emitted per year from stationary sources[14]. Other estimates are 2.0×10^9 Kg produced and released[15] and 1.8×10^8 Kg produced in 1974[16]. It is said to biodegrade rapidly in water and sludge[17].

In the air it reacts with the HO radical with a half-life of one day[15]. It has a boiling point of 385°C and a vapor pressure of 1.2 mm at 200°C[18].

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[1]Documentation of the Threshold Limit Values for Substances in Workroom Air, American Conference of Governmental Industrial Hygienists, P. 96-97, 1976.

[2]Shubik, P. et al., "Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Supplement I", National Technical Information Service Number PB 216 248, 1957.

[3]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 443, 1976.

[4]Singh, A. R., et al., "Mutagenic and Antifertility Sensitivies of Mice to Di-2-Ethylhexyl Phthalate (DEHP) and Dimethoxyethyl Phthalate (DMEP)," Toxicol. Appl. Pharmacol. 29 (1), 35-46, 1974.

[5]Mathur, S. P., "Respirometric Evidence of the Utilization of DiOctyl and Di-2 Ethylhexyl Phalate Plasticisers", J. Environ. Qual. 3(3), 207-209, 1974.

[6]Peakall, D. B., "Phthalate Esters: Occurrence and Biological Effects", Residue Reviews 54, 1-41, 1975. (177 references).

[7]"Recent Progress in Safety Evaluation Studies on Plasticizers and Plastics and Their Controlled Use in Japan", Environ. Health Perspec. 17, 203-209, 1976.

[8]Singh, A. R., et al., "Mutagenic and Anti Fertility Sensitivities of Mice to Phtholic-Acid Esters", J. Anim. Sci., 38(1), 216, 1974.

[9]Taylor, R. F. and Corcoran, E. F., "Biodegradation of Phthalic Acids and Esters", Contract No. ES-00994-02 from National Inst. of Env. Health Sci., 1975.

[10]Autain, J., "Toxicity and Health Threats of Phthalate Esters" Review of the Literature", Environ. Health Perspec. 4, 3-26, 1973.

[11]Yagi, Y., et al., "Teratogenicity and Mutagenicity of a Phthalate Ester", Teratology 14, 259-260, 1976.

[12]Dillingham, E. O. and Autian, J., "Teratogenicity, Mutagenicity and Cellular Toxicity of Phthalate Esters", Environ. Health Perspec. 3, 81-89, 1973.

[13]Landon, J. C., "Carcinogenesis Bioassay of Di(2-Ethylhexyl) Phthalate", Contract from National Cancer Institute to Tracor Jitco, Inc., 10/76-9/77, 1977.

[14]MRC Source Assessment Data Base, July 1977.

[15]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 163, 1975.

[16]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 444, 1976.

[17]Saeger, V. W. and Tucker, E. S., "Biodegradation of Phthalic Acid Esters in River Water and Activated Sludges", Appl. Environ. Microbiol. 31 (1), 29-34, 1976.

[18]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

2,3-Diaminoanisole

2,4-Diaminoanisole (4-methoxy-m-phenylenediamine) was non-mutagenic in the L51178Y mouse lymphoma cell test[1] and negative on rat skin[2] (in combination with other chemicals) and mouse skin[3] (the sulfate form) carcinogen tests. It did not produce dominant lethal mutations in rats[4].

It has been shown to be mutagenic in S. typhimurium[5-7], usually with S-9 activation. It also induced sex-linked recessive lethal mutations in Drosophila malanogaster[8] (sulfate form) with peak activity in the active germ cells (spermatids and spermatocytes). Preliminary results from an NCI study indicates that rats and mice fed this chemical (0.12 - 0.24%) had an excess of site specific (thyroid and skin) malignant tumors[9,10]. Also two epidemiologic studies suggest excess cancer among cosmetologists[9]. Diaminoanisole is on the NIOSH Safety Alert list for its carcinogenic potential[10] and will be considered a probable carcinogen for this project.

Production and Persistance

NIOSH is unaware of any current domestic production but cites that it is imported on the order of 25,000 pounds per year[10].

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[1]Palmer, K. A., et al., "The Mutagenic Assay of Some Hair Dye Components Using the Thymidine Kinane Locus of L51178Y Mouse Lymphoma Cells", (Meeting Abstract), Toxicol, Appl. Pharmacol 37 (1), 108, 1976.

[2]Kinkel, H. J. and Holzmann, S., "Study of Long-term Percutaneous Toxicity and Carcinogenicity of Hair Dyes (Oxidizing Dyes) in Rats", Food Cosmet. Toxicol. 11 (4), 641-648, 1973.

[3]Burnett, C. et al., "Long-Term Toxicity Studies on Oxidation Hair Dyes", Food Cosmet. Toxicol. 31 (3), 353-357, 1975.

[4]Burnett, C., et al., "Dominant Lethal Mutagenicity Study on Hair Dyes", J. Toxicol. Environ. Health 2 (3), 657-662, 1977.

[5]Dybing, E. and Thorgeirsson, S. S., "Metabolic Activation of 2,3-Diaminoanisole, a Hair-Dye Component", Biochem Pharmacol. 26 (8) 729-734, 1977.

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[7]Ames, B. N., et al., "Hair Dyes are Mutagenic. Identification of a Variety of Mutagenic Ingredients", Proc. Natl. Acad. Sci. (U.S.A.) 72(6), 2423-2427, 1975.

[8]Blijleven, W. G., "Mutagenicity of Four Hair Dyes in Drosophila Melanogaster", Mutat. Res. 48 (2), 181-185, 1977.

[9]"Health Hazards; 2,4-Diaminoanisole", Occupational Safety and Health Reporter, 7 (35), 1331, 1978.

[10]"2,3-Diaminoanisole (4-methoxy-m-phenylenediamine) in Hair and Fur Dyes", Current Intelligence Bulletin 19, January 13, 1978.

Diazinon

Diazinon has been reported to be slightly teratogenic in rats when given on the eleventh day of gestation[1]. An increase in chromatid breaks has been noted in the lymphocytes of humans after ingestion of phosphate insecticides including Diazinon[2] and in cultivated human lymphocytes[3].

On the otherhand, Diazinon has been found to be non-mutagenic in Salmonella typhemurium mutation tests[4].

Diazinon also does not cause mutations in the 5-MT E.coli test[5], the WP2 TRY - to prototrophy E. coli test[6], two other E.coli tests[7] or a S. cerevisiae mitotic gene conversion test[7].

Tne majority of the information indicates that Diazinon is probably not a carcinogen.

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[1]Kimbrough, R. D. and Gaines, T. B., "Effect of Organic Phosphorous Compounds and Alkylating Agents on the Rat Fetus", Arch. Environ. Health, 16, 805-808, 1968.

[2]Trinh-Van-Bao, et al., "Chromosome Aberrations in Patients Suffering Acute Organic Phosphate Insecticide Intoxication", Humangenetik 24, 33-57, 1974.

[3]Tzoneva-Maneva, M. T. et al., "Influence of Diazinon and Lindane on the Mitotic Activity and the Caryotype of Human Lymphocytes, Cultivated *in vitro*", Bibl. Haematol. Basel, 38 (1) 344-347, 1971.

[4]Marshall, T. C. et al., "Screening of Pesticides for Mutagenic Potential Using Salmonella Typhimurium Mutants", J. Agric. Food Chem. 24, 560-563, 1976.

[5]Mohn, G., "5-Methyltryptophan Resistance Mutations in Escherichia Coli K-12", Mutat. Research 20 (1), 7-15, 1973.

[6]Ashwood-Smith, M. J., et al., "Mutagenicity of Dichlorvous", Nature 240, 418-419, 1972.

[7]Fahrig, R., "Comparative Mutagenicity Studies with Pesticides", in Chemical Carcinogenesis Essays, IARC Sci. Pub. No. 10, 1974.

o-Dichlorobenzene

A negative animal study of o-dichlorobenzene (CAS No. 95-50-1) has been conducted[1], but it was a short term (<6 months) study which would not be expected to show carcinogenicity. A few positive case studies have been reported, but with insufficient supporting evidence to show cause and effect[2]. A few *in vitro* tests have been conducted[3,5]. In Aspergillus nidulans, 200 mg/ml for 60 minutes causes an increase in reversion to methionine prototropy from $3x10^6$ to $5x10^6$ reversions[6]. It was negative in a S. typhimurium spot test at 1-5 ul in eight strains[6]. Because of the limited positive test data on systems which have not been extensively evaluated, o-dichlorobenzene will be considered a probable non-carcinogen (with some significant positive data) for this project.

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[1]Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NCI, PHS-149, Volume 1.

[2]"Ortho- and para-Dichlorobenzenes", in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 7, 231-244, 1974.

[3]Guerin, M., et al., "Inhibitory Action of Chemical Carcinogens on Mitoris of Rat Lung Cell Cultures. 2. Comparative Study of Carcinogenic and Noncarcinogenic Substances," C. R. Soc. Biol. 165, 2255-2258, 1971.

[4]Prasad, I., "Mutagenic Effects of the Herbicide 3', 4'-Dichloro-propionanilide and its Degradation Products," Can. J. Microbiol. 16, 369-372, 1970.

[5]Prasad I., and Pramer, D., "Mutagenic Activity of Some Chloroanilines and Chlorobenzenes," Genetics, 60, 212-213, 1968.

[6]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274 264, 1977.

p-Dichlorobenzene

Many negative animal studies of p-dichlorobenzene (CAS No. 106-46-7) have been conducted[1], but all of them have been short term (<9 months) studies which would not be expected to show carcinogenicity. A few positive case studies have been reported but with insufficient supporting evidence to show cause and effect[2]. A few *in vitro* tests have been conducted[3,5]. It is reported that p-dichlorobenzene is a mutagen to higher plants and causes chromosonial breaks[6]. In Aspergillus nidulans, 200 mg/ml for 60 minutes causes an increase in reversion to methionine prototropy from $3x10^6$ to $11x10^6$ reversions[7]. Because of the limited positive test data on systems which have not been extensively evaluated, p-dichlorobenzene will be considered a probable non-carcinogen (with some significant positive data) for this project.

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[1] Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NCI, PHS-149, Volumes 1, 2, and 3.

[2] "ortho- and para-Dichlorobenzenes," in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 7, 231-244, 1974.

[3] Guerin, M., et al., "Inhibitory Action of Chemical Carcinogens on Mitosis of Rat Lung Cell Cultures. 2. Comparative Study of Carcinogenic and Noncarcinogenic Substances," C. R. Soc. Biol. 165, 2255-2258, 1971.

[4] Prasad, I., "Mutagenic Effects of the Herbicide 3', 4'-Dichloro-propionanilide and its Degradation Products," Can. J. Microbiol. 16, 369-372, 1970.

[5] Prasad, I., and Pramer, D., "Mutagenic Activity of Some Chloroanilines and Chlorobenzenes," Genetics, 60, 212-213, 1968

[6] Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Number PB 263 162, 1975.

[7] Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274-264, 1977.

Dichlorobenzidene

3,3'-Dichlorobenzidine (CAS No. 91-94-1) has been found to be carcinogenic in the rat following oral and subcutaneous administration and in the hamster after oral administration[1,2]. Many other positive responses are noted in Toxline and Cancerline and it is considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 2.1×10^6 Kg is produced per year with 4.5×10^3 Kg per year released[3]. Other estimates of production are 1.6×10^6 Kg in 1971[1] and 2.1×10^6 Kg per year[4]. Dichlorobenzene is somewhat reactive towards RO_2 ($t_{1/2}$ = 40 days) and very reactive towards HO and O_3 ($t_{1/2}$ = 1 day)[3]. Its melting point is 133°C[1].

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[1]"3,3'-Dichlorobenzidine" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 4, 49-55, 1974.

[2]Stula, E. F., et al., "Experimental Neoplasia in Rats from Oral Administration of 3,3-Dichlorobenzidine. . .", Toxicol. Appl. Pharmacol. 31 (1) 159-176, 1975.

[3]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 163, 1975.

[4]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Dichlorobutene

1,4-Dichlorobutene-2 is a mutagen of Salmonella typhimurium with microsomes enhancing the effect[1]. 3,4-Dichlorobutene-1 is also a mutagen in that system with or without NADP, giving 490 reverts/µmol with NADP and 345 reverts/µmol without NADP[1]. Trans-1,4-dichlorobutene-2 has been found to be a weak carcinogen to ICR/HA Swiss mice when given by subcutaneous injection or by interparental injection but not by skin application[2]. It was found not to be a tumor initiator in a two-stage test[2]. Because of the carcinogenic and mutagenic data, it has been placed on the probable carcinogen list for this project.

Production and Persistance

It is estimated that 8.7×10^5 Kg is emitted per year in the manufacture of polychloroprene[3], and has a boiling point of 158°C[4].

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[1]Bartsch, H. et al., "Alkylating and Mutagenic Metabolites of Halogenated Olefins Produced by Human and Animal Tissues", Proc. Am. Assoc. Cancer Res. 17, 17, 1976.

[2]Van Duuren, B. L. et al., "Carcinogenic Activity of Di and Trifunctional α-Chloro Ethers and of 1,4-Dichlorobutene-2 in 1 CR/HA Swiss Mice", Cancer Research 35, 2553-2557, 1975.

[3]MRC Source Assessment Data Base, July 1977.

[4]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Dichlorodifluoromethane

Dichlorodifluoromethane (Freon-12) has been shown to be non-mutagenic in S. typhimurium tests[1] but may cause some (mutagenic?) changes in conidia formation in *Neurospora crassa*[2]. More information is needed on the mutagenic and carcinogenic potential of Freons. No other information could be found on Cancerline or Toxline. At the present time, it appears as if Freons are non-carcinogens.

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[1]Andrews, A. W., et al., "The Identification of Endogenous and Exogenous Mutagenic Compounds", 4th Carcinogenesis Bioassay Program, Orlando, Florida, February 1976.

[2]Stevens, S., et al., "Phenotypic and Genetic Effects in Neurospora Crassa Produced by Selected Gases and Gases Mixed with Oxygen", Develop. Ind. Microbiol., 12, 346-353, 1971.

1,1-Dichloroethane

The primary reference cited for 1,1-dichloroethane (CAS No. 75-34-3) in the NIOSH Suspected Carcinogen list[1] shows very minor teratogenic effects even at the highest concentration used (6000 ppm). Although there are many references to 1,2-dichloroethane, Toxline and Cancerline provided no significant references on the mutagenicity or carcinogenicity of 1,1-dichloroethane. A recent report from the National Cancer Institute[2] disclosed findings indicative of a possible carcinogenic potential for this compound but could supply no conclusive evidence. They found dose related marginal increases in mammary adenocarcinomas and in hemangiosarcomas among female rats and a statistically significant increase in the incidence of endometrial stromal polyps among dosed female mice. For this project it will be classified as a possible carcinogen.

Production and Persistance

It is estimated that 2.6×10^6 Kg of dichloroethane is emitted per year from stationary sources[3]. 50% of the 1,1-dichloroethane will evaporate from a 1 ppm water solution at 25°C in 22 minutes[4]. It has a boiling point of 57.3°C and a vapor pressure of 180 mm at 20°C[4].

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[1]Schwetz, B. A., et al., "Embro- and Fetotoxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats", Toxicol. Appl. Pharmol., 28, 452-464, 1974.

[2]National Cancer Institute Draft Summaries of Bioassay Reports, 1,1-Dichloroethane", Chemical Reg. Rep. 1 (45), 1597-1598, 1978.

[3]MRC Source Assessment Data Base, July 1977.

[4]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Dichloronapthoquinone

Dichloronapthoquinone (Dichlone) did not cause point mutation in a microbial test system[1]. It has, however, been found to cause reticulum cell sarcomas (Type A) in 9/64 mice when injected subcutaneously in B6C3F1 or B6AKF1 strains of mice compared to 14/613 reticulum cell sarcomas for the subcutaneous controls[2]. This was significant at a .01 confidence level. Because of the limited number of mice involved, and the lack of other references on Cancerline and Toxline, dichloronapthoquinone will be considered a possible carcinogen for this project.

Production and Persistance

It is estimated that 900 Kg/year are emitted from stationary sources[3]. Dichloronapthoquinone has a melting point of 193°C and a 7.84 vapor density[4].

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[1]Anderson, K. J. et al., "Evaluation of Herbicides for Possible Mutagenic Properties", J. Agr. Food Chem. 20, 649-656, 1972.

[2]Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", National Technical Information Service Number PB-223 159, 1968.

[3]MRC Source ASsessment Data Base, July 1977.

[4]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Dichlorophenol

Nothing was found in Cancerline to indicate that dichlorophenol is a carcinogen or a mutagen. A 1959 reference (1) cited in the NIOSH Suspected Carcinogens list shows 2,4-dichlorophenol may be a promoter or co-carcinogen when applied to the skin of mice in combination with benzene and dimethylbenzanthracine. Other than the above reference, dichlorophenol is not listed in the "Survey of Compounds which have been Tested for Carcinogenic Activity". Because of the lack of data, dichlorophenol has been placed on the probable non-carcinogen list as a possible promoter.

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[1]Boutwell, R. K. and Borch, D. K., "The Tumor-Promoting Action of Phenol and Related Compounds for Mouse Skin", Cancer Research 19, 413-427, 1959.

Dichloropropene

1,3-Dichloropropene at 1 ppm for six months has shown to have no adverse effects[1]. Both the cis and trans isomers are mutagenic to TA1535 and TA100 S. typhimurium strains without activation[2-4]. It will be considered a possible carcinogen for this project.

Production and Persistance

It is estimated that 6×10^7 pounds of a dichloropropane/dichloropropene mixture is manufactured a year[5]. Assuming 50% dichloropropene, 3×10^7 pounds is released a year. It is said to react with OH and O_3 with a $t_{1/2}$ = 3 days, and in water $t_{1/2}$ = 7 days[5]. It has a boiling point of 104°C and 50% of a 1 ppm water solution will evaporate in 31 minutes[6].

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[1]Torkelson, T. R. and Oyen, F., "The Toxicity of 1,3-Dichloropropene as Determined by Repeated Exposure of Laboratory Animals", Am. Indust. Hyg. Assoc. J., 38 (5), 217, 1977.

[2]DeLorenzo, F., et al., "Mutagenicity of Pesticides Containing 1,3-Dichloropropene" Cancer Res., 37 (6), 1915-1917, 1977.

[3]Bignami, M., et al., "Relationship Between Chemical Structure and Mutagenic Activity in Some Pesticides: The Use of Salmonella Typhimurium and Aspergillus Nidulans", Mutat. Res. 46 (3), 243-244, 1977.

[4]Neudecher, T., et al., "In Vitro Mutagenicity of the Soil Nematicide 1,3-Dichloropropene", Experientia, 33 (8), 1084-1085, 1977.

[5]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 162, 1975.

[6]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Dichloropropionic Acid

Dichloropropionic acid (Dalapon) is a herbicide which has been found non-mutagenic in a S. typhimurium test[1]. No other significant data have been found, so it has been placed on the probable non-carcinogen list.

[1]Anderson, K. J., et al., "Evaluation of Herbicides for Possible Mutagenic Properties", J. Agr. Food Chem., 20, 649-656, 1972.

Dichlorovinyl Dimethyl Phosphate (Dichlorvos)

Dichlorovinyl dimethyl phosphate (DDP) has been shown to be mutagenic in many different short-term tests[1], including S.typhimurium tests[2], but has been shown to be non-carcinogenic by oral and inhalation studies in rats and mice[3]. Because of the mutagen studies, DDP is to be listed on the possible carcinogen list for this project.

Production and Persistance

It is estimated that 200 Kg/ycar is emitted from stationary sources[4]. It has a boiling point of 120°C at 14 mm[5].

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[1]Fahrig, R., "Comparative Mutagenicity Studies with Pesticides", in Chemical Carcinogenesis Essays, IARC Scientific Publication No. 10, p. 161-181, 1974.

[2]Shiraser, Y., et al., "Mutagenicity Screening of Pesticides in the Microbial System", Mutat. Res. 40, 19-30, 1976.

[3]Bioassay of Dichlorvos for Possible Carcinogenicity, CAS No. 62-73-7", National Cancer Institute NCI-CG-TR-10, National Technical Information Service Number PB-270 937/656, 1977.

[4]MRC Source Assessment Data Base, July 1977.

[5]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N.Y., 1977.

Dimethylacetamide

Dimethylacetamide was negative in an mitotic index test for epidermal hyperplasia[1]. It is cited in the NIOSH Registry of Toxic Effects of Chemical Substances as being teratogenic to rats after I.P. injection. One reference was found in the Survey of Chemical Substances Which Have Been Tested for Carcinogenic Activity (1966-1969) in which rats were given the chemical intergastrically at 0.1 - 30 mg/d. for 260 doses[2]. The tumors found do not appear to be related to dose. No other references could be found in Cancerline or Toxline which would suggest that dimethylasetamide is a mutagen or a carcinogen, so it will be classified as a probable non-carcinogen for this project.

[1] Rieger, M. M., "Cosmetic Science: 1975 Literature Survey", Cosmet. Perfum., 91 (4), 25-36, 1976.

[2] Hadidian, Z., et al., "J. Nat. Cancer Inst., 41 (4), 985-1036, 1968.

Dimethylamine

Dimethylamine (methanamine, N-methyl) has been reported to combine with nitrates or nitrates both *in vitro* and *in vivo* (by saliva or intestine flora) to form the carcinogen called dimethylnitrosamine or nitrosodimethylamine (more than 20 references in Toxline). Dimethylamine may also combine with ozone and nitrogen tetroxide in the atmosphere[1]. In Toxline and Cancerline there are 74 and 16 references respectively which deal with mutagenic or carcinogenic aspects of dimethylamine. These references, along with those in chemical Abstracts appear to indicate that although dimethylamine is a potent co-carcinogen, it is not by itself carcinogenic. For this project, it will be considered a non-carcinogen but will be considered when cofactors are evaluated.

[1]Dushutin, K. K. and Sopach, E. D., "The Role of the Reaction of Dimethylamine with Nitrogen Tetroxide and Ozone in Atmospheric Pollution", Gig. Sanit. 7, 14-18, 1976.

Dimethylhydrazine

1,1-Dimethylhydrazine (CAS No. 57-14-7) has been found to be carcinogenic in mice after oral administration[1]. It also causes tumors of the colon in rats (but not swine, dogs, or guinea pigs - perhaps because of toxicity) fed 30 mg/kg dimethylhydrazine[2]. Many other positive references are found in Toxline and Cancerline and it is considered a probable carcinogen for this project.

Production and Persistance

Production is estimated at $<5 \times 10^5$ Kg in 1973[1,3,4], with ~ 0.01 fraction of dispersion[4]. Since it is polar, non-volatile, and soluble in water, there would not be a significant transfer to the atmosphere[3]. It reacts with oxidizing materials in the atmosphere[4] and has an expected half life of 2.1 hours by reaction with the HO radical[3]. Dimethylhydrazine has a boiling point of 63.3°C and a vapor pressure of 157 mm at 25°C[4].

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[1]"1,1-Dimethylhydrazine" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 4, 137-143, 1974.

[2]Wilson, R. B., "Species Variation in Response to Dimethylhydrazine", Toxicol. Appl. Pharmacol. 38(3), 647-650, 1976.

[3]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[4]Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 444, 1976.

Dinitrotoluene

2,4-Dinitrotoluene has been found by the National Cancer Institute to be non-carcinogenic to mice but carcinogenic to rats[1]. It has been placed on the probable carcinogen list for this project.

Production and Persistance

It is estimated that 400 Kg dinitrotoluene is emitted per year from stationary sources[2]. It has a boiling point of 300°C[3].

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[1] "National Cancer Institute Draft Summaries of Bioassay Reports - 2,4-Dinitrotoluene", Chem. Reg. Rep. 1 (45), 1598, 1978.

[2] MRC Source Assessment Data Base, July 1977.

[3] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Dioxane

1,4-Dioxane (CAS No. 123-91-1) has been shown to be carcinogenic to rats[1,2] and guinea-pigs[3] by oral administration. It produced malignant tumors of the nasal cavity and liver in rats and tumors of the liver and gall bladder in guinea-pigs . It was also active as a promoter in a two-stage skin carcinogenesis study in mice but produced no carcinogenic effect in one inhalation study in rats[4]. For this project, it is considered a probable carcinogen.

Production and Persistance

The 1972 production has been estimated to be 6.3×10^6 Kg[3,5,6] and the 1973 production of 7.4×10^6 Kg[3], with most of this being released to the environment[6]. In the atmosphere it reacts with the HO radical with a half-life of 9.6 hours[5,6]. It has a boiling point of 101°C and a vapor pressure of 30 mm at 20°C and 37-39 mm at 25°C[3,5,7].

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[1]Kociba, R. J. et al., "1,4-Dioxane: Correlation of the Results of Chronic Ingestion and Inhalation Studies with its Dose-Dependant Fate in Rats", Aerosp. Med. Res. Lab. (Tech.Rep.) AMRL-TR-125, 345-354, 1975.

[2]Argus, M.F., et al., "Dose-Response and Ultrastructural Alternatives in Dioxane Carcinogenesis", Eur. J. Cancer 9 (4), 237-243, 1973.

[3]"1,4-Dioxane", in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 11, 247-256, 1976.

[4]Torkelson, T. R. et al., "1,4-Dioxane. II. 2-Year Inhalation Study in Rats", Toxicol. Appl. Pharmacol. 30 (2), 287-298, 1974.

[5]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 444, 1976.

[6]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 164, 1975.

[7]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Diphenyl Oxide

No positive or negative data could be found for diphenyl oxide (phenyl ether, CAS No. 101-84-8) on Toxline, Cancerline, or in the Survey of Compounds Which Have Been Tested for Carcinogenic Activity (Volumes 1-7). It is, therefore, listed as a probable non-carcinogen for this project.

Disodium Methanearsonate

Disodium methanearsonate has been cited as being carcinogenic, but no further data is given in this reference[1]. It has been found to be non-mutagenic when tested with 5 strains of S. typhimurium, mitotic recombination of S. cerevisiae and relative toxicity assays in E. coli and B. subtilis[2]. In all tests except the B. subtilis, the chemical was tested using the S-9 microsome activation. Methanearsonates have also been tested for mutagenesis by other authors[3,4]. The lack of confirming data from Toxline or Cancerline and all other indications other than the first reference demonstrate that this chemical is probably a non-carcinogen.

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[1]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[2]Simmon, V. F., et al., "*In Vitro* Mutagenic Studies of Twenty Pesticides", Toxicol, Appl. Pharmacol., 37 (1), 109, 1976.

[3]Shirasu, Y., et al., "Mutagenicity Screening of Pesticides in the Microbial System", Mutat. Res., 40, 19-30, 1976.

[4]Anderson, K. J., et al., "Evaluation of Herbicides for Possible Mutagenic Properties", J. Agr. Food Chem., 20, 649-656, 1972.

Dursban

Dursban has been shown to be more toxic to the repair deficient strains of B. subtilis and E. coli than in repair proficient strains of these organisms. It was not, however, found to be a mutagen on S. typhimurium assays or on the mitotic recombination of S. cerevisiae[1]. It is considered a non-carcinogen for this project.

[1]Simmon, V. F., et al., "*In Vitro* Mutagenic Studies of Twenty Pesticides", Toxicol. Appl. Pharmacol. 37 (1), 109, 1976.

Endosulfan

Endosulfan has been found to marginally increase (P = 0.05) the total number of tumors and the pulmonary adenomas in mice given the compound orally[1]. Endosulfan has been found to be non-mutagenic in three different E. Coli mutagen tests[2]. In a National Cancer Institute study[3], endosulfan was found to be non-carcinogenic to mice and non-carcinogenic to rats. Because of the limited amount of positive carcinogenic data and the many negative studies, endosulfan has been placed on the probable non-carcinogen list.

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[1]"Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", National Technical Information Service Number PB 223159, 1968.

[2]Fahrig, R., "Comparative Mutagenic Studies with Pesticides" in Chemical Carcinogen Essays, IARC Sci. Pub. No. 10, 1974.

[3]National Cancer Institute Draft Summaries of Bioassay Reports", Chem. Reg. Rep. 1 (45), 1608-1609, 1978.

Endrin

Endrin (CAS No. 72-20-9) has been reported to cause chromosome breakage in cells[1]. Endrin was non-mutagenic by a S.typhimurium test using mouse liver micronomes and has tested negative on several E. coli tests[3]. Rat feeding studies (up to 100 ppm) showed no increase in tumor incidence[4]. Endrin will be considered a probable non-carcinogen for this project.

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[1] Grant, W. F., "Cytological Effects of Environmental Mutagens-Pesticides," Mutat. Res. 21 (4), 221,222, 1973.

[2] Van Dyck, P. and Van de Yoorde, H., "Mutagenicity Versus Carcinogenicity of Organochloride Inpectacides", Meded. Fac. Landbouwwet., Rijksuniv, Gent., 41 (2), part 2, 1491-1498, 1976.

[3] Fahrig, R., "Comparative Mutagenicity Studies with Pesticides", in IARC Sci. Pub. No. 10, 161-181, 1974.

[4] "Endrin" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 5, 157-171, 1974.

Epichlorohydrin

Epichlorohydrin (chloromethyl oxirane, 1-chloro-2,3-epoxypropane, CAS No. 106-89-8) has been reported to be carcinogenic in mice by subcutaneous injection and active as an initiator in a two-stage skin carcinogenesis study in mice[1]. Epichlorohydrin is also a typhimurium causing chromosome aberrations, mutating S. typhimurium in a host mediated assay and E. coli, and Neurospera crassa[2]. It will be considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 2.2×10^5 Kg is emitted per year[3]. Production in 1973 was estimated[1,2,4] to be 1.6×10^8 Kg, 1.5×10^8 Kg and 8.2×10^7 Kg on another recent estimate[5] of 2.2×10^8 Kg. The production is expected to grow 4-5% a year[2]. In the atmosphere epoxides have a half life of 3 to 11 hours[4]. Epichlorohydrin has a boiling point of 117°C and a vapcr pressure of 12 mm at 20°C[6].

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[1] "Epichlorohydrin" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 11, 131-139, 1976.

[2] Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[3] MRC Source Assessment Data Base, July 1977.

[4] Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[5] Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[6] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Eptam

Eptam (ethyl di-n-propylthiocarbamate, CAS No. 759-94-4) was negative in a bone marrow chromosomal aberration test when fed to rats at 1/5 LD50 (LD50 = 1630 mg/Kg)[1]. Eptam may have had an effect on Vicia faba[2]. It is cited as belonging to the C4 classification of pesticides[3] (negative, but in only one species of animal) but also referenced as being a neoplastic agent[4]. Neither of these primary references could be found on Cancerline, Toxline, Medline, or the entire collection of the "Survey of Compounds Which Have Been Tested for Carcinogenic Activity". For this project it will be classified as a non-carcinogen.

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[1]Kurinnyi, A. I., "Mutagenic Activity of Some Pesticides, Derivatives of Urea, Carbamic and Thiocarbamic Acids", Tsitol. Genet. 11 (4), 357-359, 1977.

[2]Hakeek, H. and Shehab, A., "Cytological Effects of Eptam and Cotoran on Vicia Faba", Egypt. J. Bot., 16 (1-3), 303-311, 1974.

[3]Jurek, A., "Carcinogenicity of Pesticides", Roczn. Panstw. Zakl. Hig., 25 (5), 563-576, 1974.

[4]Dorigan, J., et al., "Preliminary Scoring of Selected Air Pollutants, Appendix II", National Technical Information Service Number PB 264 444, 1976.

Ethanol

Much has been written about the mutagenicity or carcinogenicity of ethanol[1] (87 references in Toxline) with both positive[2] and negative[3] results. It has been tested extensively in animal systems[4]. In general it is considered a non-carcinogen and non-mutagen and has been removed from the latest NIOSH Suspected Carcinogens list. It will be considered a probable non-carcinogen for this project.

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[1] Rydberg, U. and Skerfuing, S., "The Toxicity of Ethanol. A Tentative Risk Evaluation," Adv. Exp. Med. Biol., 85B, 403-419, 1977. (57 references)

[2] Braun, R. and Schoeneick, J. "Influences of Ethanol and Carbon Tetrachloride on the Mutagenic Effectivity of Cyclophosphamide in the Host-Mediated Assay with Salmonella Typhimurium," Mutat, Res. 31 (3), 191-194, 1975.

[3] Charbey, R.C., et al., "Evaluation of the Effect of Ethanol on the Frequency of Micronuclei in the Bone Marrow of Swiss Mice," Mutat, Res. 43 (3), 441,444, 1977.

[4] Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NIH, PAS-149, Volumes 1, 2, 3, 4, 5, 6, and 7.

Ethyl Benzene

No data have been found to indicate that ethyl benzene is a mutagen or a carcinogen. A review of its use as a fragrance is noted[1]. Ethyl benzene has been found non-carcinogenic to rats, guinea pig, rabbit and monkey by inhalation and to rats orally[2]. It is negative on the viral enhancement of hamster cell transformation[3]. It is therefore classified as a non-carcinogen for this project.

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[1]Opdyke, D. L., "Monographs on Fragrance Raw Materials Ethylbenzene", Food Cosmet. Toxicol. 13, Suppl., 803-804, 1975.

[2]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[3]Personal communication from B. C. Caston on 9 February 1978.

Ethylene

No data was found to indicate that ethylene is a mutagen or a carcinogen. It is also a normal metabolite of the human body. It is therefore classified as a probable non-carcinogen for this project.

Ethylene Dibromide

Ethylene dibromide (1,2-dibromoethane, ethylene bromide, CAS No. 106-93-4) has been found to produce squamous-cell carcinomas of the forestomach in mice and rats after its oral adminstration[1]. It has also been reported to be mutagenic in Salmonella typhimurium, Escherichia coli, Neurospora crassa, Saccharomyces cerevisiae, Tradescantia, Serratia marcescens, and Drosophila melanogaster test systems[2,3,4]. Ethylene dibromide will be considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 8.9×10^5 Kg of ethylene dibromide is emitted per year from stationary sources[5]. Another reference cites a production of 1.43×10^8 Kg with 1.38×10^8 Kg released[6]. Other references cite production of $1.5 \times 10^{?}$ Kg (1974)[1, 7], 1.4×10^8 Kg[8], and 1.5×10^8 Kg, 1.2×10^8 Kg for 1974 and 1975[2]. The use of ethylene dibromide in gasoline is predicted to drop by 10% a year through 1980 while its use as a fumigant may be terminated by EPA action in light of the above animal studies[2]. Its air pollution potential has been assessed[4]. Atmosphere oxidation of alkyl halides is reported to have a half life of less than 20 hours while the half life of HO radical attack is 234 days[7]. It boiling point is 131.6°C and it has a vapor pressure of 11 mm at 25°C[1].

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[1]"Ethylene Dibromide", in IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 195-209, 1977.

[2]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[3]Fishbein, L., "Industrial Mutagens and Potential Mutagens I. Halogenated Aliphatic Derivatives", Mutat. Res. 32, 267-308, 1976.

[4]Johns, R., "Air Pollution Assessment of Ethylene Dibromide", National Technical Information Service Number PB 256 736, 1976.

[5]MRC Source Assessment Data Base, July 1977.

[6]Brown, L. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[7]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[8]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Ethylene Dichloride

Ethylene dichloride (1,2-dichloroethane, ethylene chloride, CAS No. 107-06-2) has been found in preliminary results to be carcinogenic when fed to male and female rats by the National Cancer Institute[1]. Ethylene dichloride fed rats had a significant excess of site-specific malignant and non-malignant tumors. In other studies its has been negative by inhalation in rats, guinea pigs and monkeys but mutagenic to fruit flies[2]. Because of the positive animal studies, it is included on the probable carcinogen list for this project.

Production and Persistance

It is estimated that 6.7×10^7 Kg ethylene dichloride is emitted per year from stationary sources[3]. Other references cite a production of 3.9×10^9 Kg produced with 2.1×10^8 Kg released[4], 4.2×10^9 Kg (1973)[5] produced, and production of 4.2×10^9 Kg, 3.6×10^9 Kg, and 3.6×10^9 Kg in 1974, 1975, and 1976[6]. An air pollution assessment of ethylene dichloride has been made[2]. Ethylene dichloride reacts slowly with provides with a half life of 1000 days and is resistant to photochemical degradation[2]. The HO reaction half life has been estimated to be 234 hours[7]. It has a boiling point of 83.5°C and a vapor pressure of 61 mm at 20°C[8].

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[1] "New Findings on Two Carcinogens Reported to Subcommittee by NIOSH", Occupational Safety & Health Reporter 7 (35) 1331, 1978.

[2] Johns, R., "Air Pollution Assessment of Ethylene Dichloride", National Technical Information Service Number PB 256 733, 1976.

[3] MRC Source Assessment Data Base, July 1977.

[4] Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[5] Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 274 264, 1977.

[6] Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[7] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Ethylene Glycol

Although ethylene glycol (1,2-ethanediol) has been reported to give neoplastic effects at 4 gm/kg on mouse skin[1], no other confirming reports of carcinogenicity or mutagenicity have been found. Many reports indicate that ethylene glycol is non-carcinogenic in different species by various routes of administration. These include 18 tests reported in 8 articles before 1950 on rats, mice, and rabbits in food, drinking water, interveneously, subcutaneously, intermuscularly, and via inhalation - all with negative results[2].

More recently, tests have been negative for ethylene glycol[3] including subcutaneous rat tests[4], subcutaneous newborn mice tests[5], and inhalation tests using rat, guinea pig, rabbit, dog, and monkey[6]. It is also negative in the Salmonella test for mutagens[7,8] All in all, ethylene glycol will be considered a non-carcinogen for this project.

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[1]Fuller, B. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 444, 1976.

[2]Hartwell, J. L., "Survey of Compounds Which Have Been Tested for Carcinogenic Activity", National Technical Informational Service Number PB 216 478, Page 36, 1951.

[3]Homburger, F., "Carcinogenicity of Several Compounds", National Technical Information Service Number PB 183 027, 26 pp., 1968.

[4]Mason, M. M., "Toxicology and Carcinogenesis of Various Chemicals Used in the Preparation of Vaccines", National Technical Information Service Number PB 195185, 55 pp., 1969.

[5]Derse, P. H., "Injection of Newborn Mice with Seven Chemical Adjuvants to Help Determine Their Safety", National Technical Information Service Number PB 195 153, 135 pp., 1969.

[6]Coon, R., et al., "Animal Inhalation Studies on Ammonia, Ethylene Glycol, Formaldehyde, Dimethylamine, and Ethanol", Toxicol. Appl. Pharmacol. 16(3), 646-645, 1970.

[7]McCann, J., et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals", Proc. Nat. Acad. Sci. (USA) 72 (12), 5135-5139, 1975.

[8]Allport, J. et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

Ethylene Oxide

Ethylene oxide (oxirane, 1,2-epoxyethane, CAS No. 75-21-8) has been found negative on skin painted mice and subcutaneously injected rats[1]. Short term inhalation tests (6 months) on dogs, mice, rats, rabbits, guinea pigs, and monkeys were negative[1]. An excess of tumors were found in mice exposed to ethylene oxide treated ground-corncob bedding as an experiment not designed to test for carcinogenicity of ethylene oxide[1]. Ethylene oxide is a mutagen in Salmonella typhimurium, Neurospora crassa and Drosphila melanogaster tests[1,2]. It will be considered a possible carcinogen for this project based on the *in vitro* mutagenicity data.

Production and Persistance

It is estimated that 4.5×10^6kg ethylene oxide is emitted per year from stationary sources[3]. Other estimates of production includes 1.8×10^9 kg produced with 4.5×10^7 kg released[4], 1.8×10^9kg produced[5], 1.8×10^9 kg produced in 1974[6], 1.9×10^9 kg produced in 1975[1], and 1.8×10^9 and 2.0×10^9 produced in 1974 and 1975[2]. Its primary use as an intermediate is expected to grow at 4.7-5.2% per year until 1980[2]. Dispersed in the atmosphere, epoxides would be oxidized by HO radicals with a 3-11 hour half life [6]. Its reaction with HO radicals has also been estimated to give half lifes of 1.6 days[4] and 23 hours[6]. It has a boiling point of 11°C and a vapor pressure of 1095 mm at 20°C[7].

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[1] "Ethylene Oxide" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 11, 157-167, 1976.

[2] Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274 264, 1977.

[3] MRC Source Assessment Data Base, July 1977.

[4] Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Service Number PB 263 164, 1975.

[5] Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants," National Technical Information Service Number PB 264 444, 1976

[6]Radding, S. L., et al., "Review of the Environmental Fate of selected Chemicals," National Technical Information Service Number PB 267 121, 1977.

[7]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Ethylenimine

Ethylenimine (Aziridine, CAS No. 151-56-4) is well documented as being a potent mutagen, and is used as a mutagen in many plant studies (533 references on Toxline to its use as a mutagen or carcinogen). It has also been found to be carcinogenic in at least two strains of mice following oral administration and producing liver-cell and pulmonary tumors[1]. Subcutaneous injection of single doses in suckling mice produced increased incidence of lung tumors in males. Subcutaneous injection in oil produced local tumors in rats[1]. It is considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 2.7×10^4 Kg is released to the environment per year[2]. Estimates of production are 2.3×10^6 Kg, 1.4×10^6 Kg, 2.2×10^6 Kg (1974), and 2.3×10^6 Kg per year[2,5]. Ethylenimine infinitely soluble in water[5], basic, and polar, and could therefore be expected to be very slow to escape from water to the atmosphere[4]. Its reaction with HO in the atmosphere has been found to have a half-life of 1.5 days[2], 47 hours[4] and 56 hours[4]. It has a boiling point of 56°C and a vapor pressure of 160 mm at 20°C[1].

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[1] "Aziridine" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemistry to Man, Volume 9, 37-46, 1976.

[2] Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 164, 1975.

[3] Allport, J. et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[4] Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 121, 1977.

[5] Fuller, B. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

Fluoranthene

Fluoranthene (CAS No. 206-44-0) was tested for carcinogencity in 1935 and 1938 on mice by skin (0.3% in benzene for 501 days) and oral (10 mg for 18 months) routes of administration with negative results [1]. Arcos and Argus reported in 1974 that in 1963 or 1964 others had found fluoranthene negative by subcutaneous tests in XVII nc/Z strain of mice[2], and is generally considered non-carcinogenic[2]. Recent tests of mouse skin application, alone or followed by croton oil, were negative after 15 months and 20 weeks respectively[3]. It has been tested on TA98, 100 and 1537 strains of S. typhimurium for mutagencity[4]. It is considered a probable non-carcinogen for this project.

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[1]Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NCI, PHS-149, Volume I.

[2]Arcos, J. C. and Argus, M. F., Chemical Induction of Cancer, Volume IIA, Academic Press, New York, 1974, pp. 26, 237.

[3]Hoffman, D., et al., J. Natl. Cancer Inst. 49, 1165-1175, 1972.

[4]Rao, T. K., et al., "Environmental Mutagenesis of Energy-Related Effluents", Genetics, 83, S60, 1976.

Formaldehyde

Formaldehyde (methanal, formalin, methyl aldehyde, CAS No. 50-00-0) has been tested for carcinogenicity with negative results on many animal species in short term(usually less than a year) tests[1]. However, 1300 mg/kg (65 weeks) caused neoplastic effects in rats[2] and 1 ml of 0.4% formaldehyde solution caused spindle cell sarcomas and fibrosarcomas at the injection site of 4/10 rats evaluated at least 649 days[3]. Formaldehyde has been shown to be a mutagen in Drosophila melanogaster, E. coli, barley, Vicia faba, yeast, and viral transformation enhancement tests[4-6], but negative on the mouse dominant lethal test[7]. For this project formaldehyde will be considered a possible carcinogen.

Production and Persistance

It is estimated that 4.1×10^7 kg formaldehyde is emitted per year from stationary sources with 82% of this being from charcoal manufacture and catalytic cracking in petroleum refining[8]. Other estimates of production include 2.6×10^9 kg produced and 2.4×10^7 kg released[2], 2.6×10^9 kg produced and 6.4×10^7 kg released[4], 2.6×10^9 kg produced (1974)[9], and 2.9×10^9 kg and 2.6×10^9 kg produced in 1973 and 1975[10]. The production of formaldehyde is projected to grow by 4-5% per year in the next five years[10]. In solution it is essentially non-volatile, but in the air it will react with HO radical with a half life of 2.6 hours[9] or 1.2 hours[4]. As a gas it has a boiling point of -21°C and a vapor pressure of 1946 mm at 25°C[2]. Its environmental fate, biological, and environmental effects have been studied[11].

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[1]Survey of Chemicals Which Have Been Tested for Carcinogenic Activity, National Cancer Institute, PHS-149, Volumes 1, 2, 3, 4, and 5.

[2]Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants," National Technical Information Service Number PB 264 445, 1976.

[3]Watanabe, F., et al., Gann 45, 451-452, 1954. (From Survey of Chemicals ... - Reference 1, Volume 3)

[4]Brown, S. I., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Number PB 263 164, 1975.

[5]Sawicki, E., "Chemical Composition and Potential Genotoxic Aspects of Polluted Atmosphere," in IARC Sci. Pub. No. 16, 127-157, 1977.

[6]Personal Communication with B. C. Casto on 9 February 1978.

[7]Epstein, S. S., et al., "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse," Toxicol. Appl. Pharmacol. 23. 299-325, 1972.

[8]MRC Source Assessment Data Base, July 1977.

[9]Radding, S. L., et al., "Review of the Environmental Fate of Selected Chemicals," National Technical Information Service Number PB 267 121, 1977.

[10]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274 264, 1977.

[11]Atlantic Research Corp., "Investigation of Selected Potential Environmental Contaminants: Formaldehyde" (Prepared for EPA), National Technical Information Service Number PB 256 839, 1976.

Guthion

Guthion has been found to be mutagenic in that it induced chromosome breaks in WI-38 cells and in HE$_D$-2 cells[1]. Guthion also increased mitotic recombination in S. cerevisiae[2]. However, it did not prove to be a mutagen in S. typhimurium assays[2] or in E. coli or B. subtilis systems[2] and did not induce dominant lethal effects in mice[3]. For this project it is considered a non-carcinogen.

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[1]Alam, M. T. and Kasatiya, S. S., "Cytological Effects of an Organic Phosphate Pesticide on Human Cells *in vitro*," Can. J. Genet. Cytol. 18 (4), 665-671, 1976.

[2]Simmon, V. F., et al., "*In Vitro* Mutagenic Studies of Twenty Pesticides", Toxicol. Appl. Pharmacol. 37 (1), 109, 1976.

[3]Jorgenson, T. A., et al., "*In Vivo* Mutagenesis Investigations of Ten Commercial Pesticides", Toxicol. Appl. Pharmacol. 37 (1) 109, 1976.

Heptachlor

The IARC monograph on heptachlor (heptachloro-tetrahydro-methanoindene, CAS No. 76-44-8) shows this compound to have both positive and negative data, with more negative than positive[1]. It is a mutagen as tested by the enhancement of viral transformation[2]. Recent NCI tests[3] with rats and mice demonstrated that heptachlor is a carcinogen for the liver in mice under the conditions of their bioassay. It is considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 1.1×10^4 Kg heptachlor is emitted per year from stationary sources[4]. Estimates of production include 2.7×10^6 Kg (1971)[1] and 2.7×10^6 Kg produced[5]. It has a melting point of 95°C and a vapor pressure of 3×10^{-4} mm at 25°C[1].

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[1] "Heptachlor" in IARC Monograph on the Evaluation of Carcinogenic Risk of Chemicals to Man", Volume 5, 173-191, 1974.

[2] Personal communications with B. C. Casto on 9 February 1978.

[3] "Bioassay of Heptachlor for Possible Carcinogenicity, CAS No. 76-55-8", National Technical Information Service Number PB 271 967.

[4] MRC Source Assessment Data Base, July 1977.

[5] Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 445, 1976.

Hexachlorobenzene

Hexachlorobenzene (benzene hexachloride, CAS No. 118-74-1) induces microsomal enzymes[1], is only slightly teratogenic[2] and tests positive/negative[3] and negative[2] on the dominant lethal test in rats. When fed to rats it was non-carcinogenic[4], and by S. typhimurium tests (using mouse liver microsomes) it was negative[5].

Hexachlorobenzene was, however, mutagenic when tested with Saccharomyces cerevisiae at 100 ppm[6] and when fed to 6 week old Syrian golden hamsters at concentrations up to 200 ppm it induced heptomas, hemangiomas and thyroid adenomas in a dose response manner[7]. It is therefore considered a possible carcinogen for this project.

Production and Persistance

It has a $t_{1/2} \approx 2$ days in the air reacting with OH to form pentachlorophenal. Its production is estimated to be 1.3×10^6 pounds per year and 0.3×10^6 pounds is used in a dispersive manner as a fungicide for a total of 0.5×10^6 pounds released[8]. It has a boiling point of 322-326°C[9].

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[1] Dybing, E. and Aune, T., "Hexachlorobenzene induction of 2,4-Diaminoamide Mutagenicity in Vitro", Acta Pharmacol Toxicol. 40 (5), 575-583, 1977.

[2] Khera, K. S., "Hexachlorobenzene: Teratogenicity and Dominant Lethal Studies in Rats", Toxical. Appl. Pharmacol. 29 (1), 109, 1974.

[3] Epstein, S. S., et al., "Detection of Chemical Mutagenes by the Dominant Lethal Assay in the Mouse", Toxical. Appl. Pharmacol. 23, 288-325, 1972.

[4] Boyland, E., et al., "Kidney Tumors in Rats Following Treatment with 2-Acetylaminofluorene, Tryptophan and 14-Saccharolactone and the Failure of Substances Which Cause Porphyrinuria to Induce Tumors", pp. 58-59 in British Empire Cancer Campaign 1963 - Part 2: Scientific Report, 707 pp., 1963.

[5] Van Dijck, P. and Van de Voorde, H., "Mutagenicity Versus Carcinogenicity of Organochloride Insecticides", Meded. Fac. Landbouwwet., Rijksuniv. Gent, 41 (2) part 2, 1491-1498, 1976.

[6] Guerzoni, M. E., et al., "Mutagenic Activity of Pesticides", Riv. Sci. Tecnol. Alimenti Nutr. Um. (Ital) 6 (3), 161-165, 1976.

[5] Cabral, J. R. P., et al., "Carcinogenic Activity of Hexachlorobenzene in Hamsters", Nature 269 (5628), 510-511, 1977.

[6] Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[7] Verschueren, K., Handbook of Environmental Data on Organic Chemical, Van Nostrand Reinhold Co., New York, 1977.

Hexachlorobutadiene

Hexachlorobutadiene injected I.P. in mice apparently caused no lung adenomas[1]. A two year study with rats on diets containing hexachlorobutadiene showed no effects at 0.2 mg/kg/day or less, but renal tubular adenomas and adenocarcinomas at 2 and 20 mg/kg/day[2,3]. A reproduction study also showed no effects at 0.2 but effects at 20 mg/kg/day. At the high doses some toxicity was also evident. A 90 day feeding study (0.3-30 ppm) on Japanese quail showed little effect of this chemical[4]. NIOSH has a safety alert out on the basis of the above tests and it is considered a possible carcinogen for this study.

Production and Persistance

It is estimated that 8×10^6 pounds is produced in the USA with 7.3×10^6 pounds being released per year[5]. It reacts with OH and O_3 with a t1/2 of less than one day and has a low water-soluability[5]. The boiling point of hexachlorobutadiene is 210°C with a vapor pressure of 22 mm at 100°C[6].

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[1]Test for Carcinogenicity of Organic Contaminants of United States Drinking Waters by Pulmonary Tumor Response in a Strain of Mice," Cancer Res. 37 (8), 2717,2720, 1977

[2]Results of a Two-year Chronic Toxicity Study with Hexachlorobutadiene in Rats (Meeting Abstract) Toxical. Appl. Pharmacol. 41 (1), 204,1977.

[3]Kociba, R. J., et al., "Results of a Two-year Chromic Toxicity Study with Hexachlorobutadiene in Rats," Am. Ind. Hyd. Assoc. J., 38 (11), 589-602, 1977.

[4]"Reproduction Study in Japanese Quail Fed Hexachlorobutadiene for 90 days," Toxical. Appl. Pharmacol. 30 (2), 255-265, 1974.

[5]Brown, S. L., et al." Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Number PB 263 161, 1975.

[6]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N.Y., 1977.

Hexamethylenetetramine

Hexamethylenetetramine (CAS No. 100-97-0) has been extensively tested in both rats and mice[1]. Almost all of these tests show that this chemical is non-carcinogenic when given either orally (up to 5% of drinking water) or subcutaneously (25 gm/Kg)[2]. It has been tested on E. coli differential growth (pol A) test with positive results which was considered a false positive[3]. It has also been reported to be non-mutagenic to Drosophila, positive in oral mouse dominant lethal test, negative in an interperitoneal mouse dominant lethal test, and positive on a chromosomal aberration test in cultured lyphocytes[4]. Hexamethylenetetramine will be considered a non-carcinogen (with some positive data) for this project because of the extensive negative animal data.

[1] "Survey of Compounds Which Have Been Tested for Carcinogenic Activity", PHS-149, Volume 1 - Number 1230, Volume 3 - Number 847, Volume 4-Number 1234, Volume 5 - Number 704, Volume 6 - Number 534.

[2] Della Porta, G., et al., "Non-Carcinogenicity of Hexamethylenetetramine in Mice and Rats", Food Cosmet. Toxicol., 6 (6), 707-715, 1968.

[3] Fluck, E. R. et al., "Evaluation of a DNA Polymerase - Deficient Mutant of E. Coli for the Rapid Detection of Carcinogens", Chem. Biol. Interact. 15, 219-231, 1976.

[4] Allport, J. et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

Hydrazine

Hydrazine (diamine, CAS No. 302-01-2) has been shown to be carcinogenic in mice after oral and interperitoneal administration and in rats following oral administration[1]. It was negative in hamsters after oral administration[1]. Hydrazine is considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 3.5×10^3kg hydrazine is emitted per year[2]. In 1966, production of hydrazine was 7×10^6 kg per year with more than 70% of this going toward rocket fuels[1]. In 1971 it was estimated that production was 1.4×10^6 kg and 1.7×10^7 kg in 1974[3-4]. The demand for hydrazine is expected to increase 15-17% a year until 1985[4]. Hydrazine is polar, non-volatile and water soluable suggesting that it will not transfer to the atmosphere at significant rates[3]. Oxidation by HO radicals in the gas phase is reported to be rapid with a half life of less than one hour[3]. It has a boiling point of 113°C and a vapor pressure of 16 mm at 20°C[5].

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[1] "Hydrazine" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 5, 127-136, 1974.

[2] MRC Source Assessment Data Base, July 1977.

[3] Radding, S. B., etal., "Review of the Environmental Fate of Selected Chemicals," National Technical Information Service Number PB 267 121, 1977.

[4] Allport, J., etal., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274 264, 1977.

[5] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Hydroquinone

Hydroquinone is listed on the NIOSH Suspected Carcinogen list, but it is apparently there by mistake. The 1955 reference cited[1] shows 20 mg of hydroquinone applied to the skin of mice (in benzene) developed only one tumor out of 22 surviving mice as compared with one tumor out of 22 surviving mice for the croton oil control. A more recent reference cites hydroquinone as a bladder carcinogen when implanted in cholesterol pellets producing 32% tumors vs. 12% for the cholesterol control[2]. Hydroquinone is said to be an inhibitor of 3,4-benzpyrene carcinogenesis[3], inactive as a promoter[4], and slightly active as a promoter[5] of carcinogenesis.

Hydroquinone has been reported as more toxic to repair deficient E. coli (pol A$^-$) indicating that it may induce DNA damage[6], but negative in inducing antibiotic resistance in Micrococcus pyrogens[6]. Chromosome aberrations have been noted in several plant systems after treatment with hydroquinone[6]. These mutagenic references almost place hydroquinone on the possible carcinogen list, but they involve test systems which have not been extensively evaluated. Hydroquinone will be considered a probable non-carcinogen (with some significant positive data) for this project.

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[1]Roe, F. J. C. and Salaman, M. H., "Further Studies on Incomplete Carcinogenesis", British J. of Cancer, 9, 177-203, 1955.

[2]Boyland, E. et al., "Further Experiments on Implantation of Materials into the Urinary Bladder of Mice", British J. of Cancer, 18, 575-581, 1964.

[3]Van Duuren, B. L. and Goldschmidt, B. M., "Cocarcinogenic and Tumor-Promoting Agents in Tobacco". J. Nat'l. Cancer Inst., 56, 1237-1242, 1976.

[4]"Study of Tobacco Carcinogenesis. XIII. Tumor-Promoting Subfractions of the Weakly Acidic Fraction", Toxline.

[5]Interaction between Hydroquinone and Cigarette Smoke Condensate in Short-Term Skin Tests for Carcinogenicity", Toxline.

[6]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

Kelthane

Kelthane has been found non-mutagenic to E. coli bacteria in the WP2 TYR to prototrophy test[1]. It is considered a probable non-carcinogen for this project.

[1]Ashwood-Smith, M. J., "Mutagenicity of Dichlorvos", Nature 240, 418-419, 1972.

Malathion

Malathion has been demonstrated not to be a teratogen[1] and Ames et.al consider it not to be a mutagen[2]. It has been found to be a non-mutagenic in four test systems[3], and a study by the National Cancer Institute found it to be non-carcinogenic to rats and non-carcinogenic to mice[4]. Malathion was found non-mutagenic by a dominant lethal test in mice[5] but was a slight promoter in rats when given with dimethylbenz (a) anthracine[6]. For this project Malathion is classed as a probable non-carcinogen.

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[1]Kimbrough, R. D. and Gaines, T. B., "Effect of Organic Phosphorous Compounds and Alkylating Agents on the Rat Fetus", Arch. Environ. Health, 16, 805-808, 1968.

[2]McCann, J., et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals", Proc. Nat. Acad. Sci. (USA), 72, 5135-5139, 1975.

[3]Fahrig, R., "Comparative Mutagenicity Studies with Pesticides", in Chemical Carcinogenesis Essays, International Agency for Research on Cancer-Scientific Publication No. 10, p. 161-181, 1974.

[4]National Cancer Institute Draft Summaries of Bioassay Reports", Chem. Reg. Rep. 1 (45), 1597-1618, 1978.

[5]Jorgensen, T. A., et al., "*In Vivo* Mutagenesis Investigations of Ten Commercial Pesticides", Toxicol. Appl. Pharmacol. 37 (1), 109, 1976.

[6]Silinskas, K. C., and Okey, A. B., "Protection by DDT Against Mammary Tumors and Leukemia During Prolonged Feeding of 7,12-Dimethylbenz (a) anthracene to Female Rats", J. Nat'l. Cancer Inst., 55 (3), 653-658, 1975.

Maleic Anhydride

Only one 1963 reference cites maleic anhydride as a carcinogen[1]. In this paper three rats of an unspecified species were injected 550 times with maleic anhydride. Two of the three rats developed fibrosarcomas at the injection site. No other indications could be found in the literature which suggests that maleic anhydride may be a mutagen or a carcinogen in any test systems. In the atmosphere maleic anhydride could be expected to be converted rather rapidly to maleic acid for which no evidence has been found to suggest it has any carcinogenic or mutagenic potential. Since maleic anhydride has some degree of toxicity and is a lacramator, animal studies will probably show it to be a non-carcinogen.

[1]Dickens, F. and Jones, H. E. H., "Further Studies on the Carcinogenic and Growth-Inhibitory Activity of Lactones and Related Substances", British Journal of Cancer, 17, 100-108, 1963.

Mercaptobenzothiazole

Mercaptobenzothiazole (2-benzothiazolethiol, Captax, CAS No. 149-30-4) was one of the 80 chemicals evaluated as having the greatest potential for environmental effects[1]. The study they cite is a negative mice feeding study[2] in which two groups of 36 mice of slightly different strains were given 464 mg/kg mercaptobenzothiazole in gelatin orally on days 7-28 and then 1492 ppm in their diet for 17 months with no increase in tumors found. Seventeen mouths is a little on the short side for carcinogen evaluation by present standards.

In another study[3] it was given orally and subcutaneously at 100 and 215 mg/kg respectively to two mouse strains (36 mice per strain). It was found to cause a statistically significant (0.01 level) increase in type A reticulum cell sarcomas when given subcutaneously. It may have been tested for mutagenicity[4] and teratogenic activity but the results are unclear[5]. Because of the limited tests thus far conducted, more *in vivo or in vitro* data might change its classification, but it will be considered a possible carcinogen for this project.

Production and Persistance

The production of mercaptobenzothiazole is estimated at 6×10^6 pounds per year with the release of 6×10^4 pounds per year[1]. It is reactive towards RO ($t_{\frac{1}{2}}$=8 days), HO ($t_{\frac{1}{2}}$=1 day) and O_3 ($t_{\frac{1}{2}}$=9.6 hrs.)[1].

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[1]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Number PB 263 161, 1975.

[2]Innes, J. R. M., et al., J. Nat. Cancer Inst. 42, 1101-1114, 1969. (From PHS-149; Survey of Compounds Which Have Been Evaluated for Carcinogenic Activity.)

[3]"Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume 1." National Technical Information Service Number PB 223 159, 1968.

[4]Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals. Volume III." National Technical Information Service Number PB 223 161, 1968.

[5] "Evaluation of Carcinogenic, Teratogenic and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, Volume II." National Technical Information Service Number PB 223 160, 1968.

Methyl Bromide

Methyl bromide has been tested on barley and is said to be a methylating compound[1]. No other references were found on the mutagenic or carcinogenic potential of methyl bromide so it has been placed on the probable non-carcinogen list.

[1]Ehrenberg, L., et al., "On the Reaction Kinetics and Mutagenic Activity of Methylating and Beta-Halogenoethylating Gasoline Additives", Radiat. Bot. 14 (3), 185-194, 1974.

Methyl Chloride

No data have been found indicating that methyl chloride (chloromethane, CAS No. 74-87-3) is a carcinogen (e.g. Toxline, Cancerline Survey of Compounds). However, it does appear to be a mutagen to Salmonella typhimurium[1]. Because of the close correlation between mutagens and carcinogens, methyl chloride has been placed on the possible carcinogen list.

Production and Persistance

It is estimated that 2.3×10^7 Kg methyl chloride is emitted per year from stationary sources[2]. Another estimate[3] is 7.6×10^6 Kg/year released from a production of 2.1×10^8 Kg. Other production estimates are 2.1×10^6 Kg, and 2.2×10^6 Kg, 1.6×10^6 and 1.7×10^6 Kg produced in 1974, 1975, and 1976, with a projected growth of 6% per year[4,5]. Reaction in the atmosphere with the HO radical is slow with a half-life of about one year[3]. It takes 27 minutes for 50% of a 1 ppm water solution to evaporate at 25°C[6]. Methyl chloride has a boiling point of -24°C and a vapor pressure of 3800 mm (5 atm) at 20°C and 2150 mm (2.83 atm) at 25°C[4,6].

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[1]Andrews, A. W. et al., "A Comparison of the Mutagenic Properties of Vinyl Chloride and Methyl Chloride", Mutat. Res. 40 (3), 273-275, 1976.

[2]MRC Source Assessment Data Base, July 1977.

[3]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 164, 1975.

[4]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 445, 1976.

[5]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[6]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Methyl Ethyl Ketone

Methyl ethyl ketone (MEK, 2-butanone) is included on the NIOSH Suspected Carcinogen list because of a teratogenic reference and as a priority pollutant. MEK does appear to be embryotoxic, fetotoxic, and perhaps teratogenic when tested at high concentrations (1000-3000 ppm)[1,2]. Rat feeding studies conducted in 1939 and 1940 were negative[3,4]. Mouse skin application tests in 1965 of mixtures containing MEK were generally negative in the absence of benzo(a)pyrene[5]. MEK has also been tested on TA 1535, 1536, 1537, and 1538 strains of S. typhimurium bacteria (Ames Test) and on E. coli WP2 - try mutagen tests with both being negative[5]. No other references could be found on Toxline or Cancerline which indicate that MEK is a mutagen or a carcinogen. It is considered a probable non-carcinogen for this project.

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[1]Schwetz, B. A., et al., "Embryo-and Fetotoxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats", Toxicol. Appl. Pharmacol. 28 (3), 452-464, 1974.

[2]Embryo Toxicity and Feto Toxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane, and Methyl Ethyl Ketone in Rats", Toxicol. Appl. Pharmacol. 29 (1), 123, 1974.

[3]Nakahara, W. and Mori, K., Proc. Imp. Acad., Japan, 15, 278-281, 1939. (From Survey of Chemical Which Has Been Evaluated for Carcinogenic Activity).

[4]Nakahara, W. and Mori, K., Proc. Imp. Acad., Japan, Cann 34, 143-145, 1940. (From Survey of Chemicals Which Have Been Evaluated for Carcinogen Activity).

[5]Horton, A. W., et al., Cancer Research 25, 1759-1763, 1965. (From Survey of Chemicals Which Have Been Evaluated for Carcinogenic Activity).

[6]Shirasu, Y., et al., "Mutagenicity Screening of Pesticides in the Microbial System", Mutat. Res., 40, 19-30, 1976.

Methyl Methacrylate

Methyl methacrylate is on the NIOSH Suspected Carcinogen list because of a paper which shows that 0.25 mg/kg of the compound (1/5 LD_{50}) caused 8% of the rat fetuses to have gross abnormalities (hemangiomas) but no skeletal malformations. A search of the literature could find no other references indicating methyl methacrylate to be a mutagen or a carcinogen. It is therefore listed as a probable non-carcinogen for this project.

[1]Singh, A. R. et al., "Embryonic-Fetal Toxicity and Teratogenic Effects of a Group of Methacrylate Esters in Rats", J. Dental Research, 51, 1632-1638, 1972.

4,4'-Methylene Bis(2-Chloroaniline)

4,4'-Methylene bis(2-chloroaniline) or MOCA (CAS No. 101-14-4) has been found to be a carcinogen in mice and rats after oral administration and produces distant tumors in the rat after subcutaneous administration[1]. It is an OSHA regulated carcinogen[2]. Many other positive references are found in Toxline and Cancerline and it is considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 4.5×10^4 Kg is emitted per year from a 3×10^6 Kg production[3]. Other estimates of production are $1.5\text{-}2.5 \times 10^6$ Kg in 1970[1] and 3.5×10^6 Kg in 1972[1,4,5]. The reaction with the HO radical in the atmosphere is estimated to yield a half-life of 12 hours[4] or one day[3] while the O_3 half-life is one day[3] and the RO_2 half-life is 39 days[3]. It is said to have a melting point of 110°C[1] and a negligible vapor pressure[5].

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[1]"4,4'-Methylene Bis(2-Chloroaniline)" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 4, 65-71, 1974.

[2]OSHA Compliance Guide, 29 CFR Part 1910, 1978.

[3]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Service Number PB 263 162, 1975.

[4]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PB 267 127, 1977.

[5]Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 445, 1976.

Methylene Chloride

There are no positive data on methylene chloride (dichloromethane) in Toxline or Cancerline. Interim results of carcinogenic tests in a two-year inhalation study involving nearly 2,000 animals exposed to concentrations of methylene chloride as high as 3500 ppm were negative[1]. One recent report cites methylene chloride as being a positive in the Ames test[2]. Methylene chloride is still considered a non-carcinogen for this project until further testing is completed because of the negative NCI animal data.

[1] "Methylene Chloride Passes Early Tests", Chem. Eng. News., 55 (19), 6, 1977.

[2] Mutation Research, Volume 53, January 1978.

Methylenedianiline

The IARC monograph[1] on methylenedianiline (4,4-diaminodiphenyl methane, bis(p-aminophenyl) methane, CAS No. 101-77-9) indicates both positive and negative data have been obtained from animal testing of the compound. Given orally to rats, it was found to be non-carcinogenic. Apparently methylenedianiline is on the NIOSH safety alert list (this list has been requested from NIOSH) and because of significant positive results[2,3] it can at least be considered a possible carcinogen.

Production and Persistance

It is estimated that 2.6×10^4 Kg is emitted per year from stationary sources[4]. The production has been estimated to be 5×10^5 Kg, 7×10^5 Kg, and 1×10^6 Kg in 1965, 1966, and 1972[1]. It has a melting point of 93°C and a boiling point of 231°C at 11 mm[5].

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[1] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man - Volume 4, 79-85, 1974.

[2] Schoental, R., "Carcinogenic and Chronic Effects of 4,4'-Diaminodiphenylmethane, an Epoxyresin Hardner", Nature 219, 1162-1163, 1968.

[3] Steinhoff, D. and Grundmann, E., "Zur Cancerogenen Wirkung von 4,4'-Diaminodiphenylmethan und 2,4'-Diaminodiphenylmethan" Naturioissenschaften 57, 247-248, 1970.

[4] MRC Source Assessment Data Base, July 1977.

[5] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Methylstyrene

One reference cited in the NIOSH Suspected Carcinogen list shows methylstyrene to be a teratogen[1]. Permissible exposure limits have been determined for methylstyrene[2]. Application of methylstyrene to rabbit[3] inhalation or rat skin[3,4] demonstrated only a reversible[4] irritating response to the chemical. Other toxic responses have been noted in rats, rabbits[5], and housefly larvae[6], but no indication of carcinogenic or mutagenic responses were found on Toxline or Cancerline.

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[1]Gigiena i Santariya, 34, 40, 1969. (Translated in a different volume of Hygiene and Sanitation).

[2]"Toxic Substances. Proposed Occupational Safety and Health Standards for Alkyl Benzenes, Cyclohexane, Ketones, and Ozone", Fed. Regist. 40 (196), 47262-47313, 1975.

[3]"Effect of Alpha-Methylstyrene and Tert-Dodecyl Mercaptan on the Skin of Animals", Vop. Gig. Tr. Profzabol., Mater. Nauch. Konf.; p. 247-249, 1972.

[4]"Reversible Damage to the Skin of Experimental Animals Subjected to the Inhalation of Butadiene and Alpha-Methylstyrene", Mater. Nauch. Sess., Posoyashck. 50-Letiyu Obrazov. SSSR, Omsk. Gas. Med. Inst.; p. 871-873, 1972.

[5]Effect of Isopropylbenzene and Alpha-Methylstyrene on Leucopoiesis", Farmakol Toksikol, 35 (4), 491-492, 1972.

[6]"Effect of the Wastes from Phenol Production on Housefly Larvas", Mater. Konf. Molodykh. Uch. Stud., Posvyashch. 50-Letiyu SSSR; p. 375-377, 1973.

Morpholine

Morpholine (diethyleneimide oxide, tetrahydro-1, 4-isoxazine, CAS No. 110-91-8) is cited in one reference as causing neoplastic effects in the mouse after oral administration of 6.33 gm/kg over 28 weeks[1]. This refers to a study (with no control animals) in which 40 swiss mice (20M,20F) were given neutralized morpholine in their food[2]. After 40 weeks, 5 malignant lymphomas and 5 lung adenomas were found in the surviving 38 animals. (When given in combination with sodium nitrite, many more tumors were found.)

In another study, 100 g/kg morpholine as 0.5% of the diet for rats produced no tumors, but 0.5% sodium nitrite added gave 7 tumors[3]. Many other studies have been conducted with sodium nitrite add to produce nitrosomorpholine *in vivo* and *in vitro*. In Russian studies, morpholine in the air in 0.009-0.07 mg/l concentrations for four months caused mutagenic chromosomal aberrations in bone marrow cells in rats[4] and guinea pigs[5]. The future classification of morpholine requires more data, but for this project it will be considered a possible carcinogen.

Production and Persistance

It is estimated that 1×10^7 Kg is produced and 5.5×10^6 Kg is emitted per year[1].

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[1]Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants. Appendix III.," National Technical Information Service Number PB 264 445, 1976.

[2]Greenblatt, M., et al., J. National Cancer Inst. 46 (5), 1029-1034, 1971. (From PHS-149; Survey of Compounds Which Have Been Tested for Carcinogenic Activity)

[3]Sander, J. and Bunkle, G., Z. Krebsforsch 73 (1), 54-66, 1969 (From PHS-149)

[4]Fomenko, V. N. and Strekalova, E. E., "Mutagenic Action of Some Industrial Poisons as a Function of Concentration and Exposure Time," Toksikol. Nov. Prom.Khim. Veshchestv. 13, 51-57, 1973. (CA 79, 143228)

[5]Migukina, N. V., "Evaluation of the Danger of Morpholine During Chronic Action," Toksikol. Nov. Prom.Khim. Veshchestv. 13, 92-100, 1973. (CA 79, 143345)

Naptha

Naptha (coal tar naptha) was found in the report "Preliminary Scoring of Organic Air Pollutants" (PB 264 446) cited as a recognized carcinogen. Actually napthas vary in composition depending on their source with coal tar naptha being mainly benzene and its homologs[1]. From other sources naptha could be principally paraffins, methanol and acetone, or gasoline[1]. Even as a mixture, naptha is not found in the Survey of Compounds Which Have Been Tested for Carcinogenic Activity. Of the primary ingredients of naptha, only benzene is a recognized carcinogen and since it is covered separately, naptha will be dropped from consideration.

[1]Your dictionary.

1-Naphthlamine

1-Naphthylamine (alpha-naphthylamine, CAS No. 134-32-7) had no carcinogenic effect when given orally to hamsters and both oral and subcutaneous tests with mice give inconclusive results[1]. In dogs, it was demonstrated that 1-naphthylamine, if carcinogenic at all, was less so than the 2-isomer[1]. Other tests on dogs[2], hamsters, mice rats, and rabbits[3] show that 1-naphthylamine may be carcinogenic and also it is generally contaminated with the 2-isomer which is a potent carcinogen[1,4]. It is an OSHA regulated carcinogen (Code of Federal Regulations 29 CFR 1910.1004) whether or not it is truly a carcinogen[4]. It is also a positive on the S. typhimurium test[5], and an enhancement of viral transformation test[6]. For these reasons, it is considered a possible carcinogen for this project.

Production and Persistance

Production has been estimated to be 5×10^5 Kg in 1963[7] and 3.2×10^6 Kg in 1974[8]. It reacts with oxidizing materials in the atmosphere[7] and reacts with the HO radical in air with a 12 hour half-life[8]. It has a boiling point of 300.8°C and a vapor pressure of 1 mm at 104.3°C[7].

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[1] "1-Naphthylamine" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 4, 87-96, 1974.

[2] Hartwell, J. L., "Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Second Edition", National Technical Information Service Number PB 216 478, 1951.

[3] Shubik, P., et al., "Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Supplement I", National Technical Information Service Number PB 216 248, 1957.

[4] OSHA Compliance Guide, 29 CFR Part 1910, P. 298-300, 1978.

[5] McCann, J., et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test", Proc. Nat. Acad. Sci. (USA) 72 (12), 5135-5139, 1975.

[6]Personal communication with B. C. Casto on 9 February 1978.

[7]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 445, 1976.

[8]Raddig, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number PI 267 121, 1977.

Napthalene

Napthalene (CAS No. 91-20-3) has generally been negative when given to rats and mice by various routes of aministration (including 10 g total oral dose over 33 months) with only a few tumors reported by other authors in experiments without control animals[1]. It is generally considered to be a non-carcinogen by various authors[2]. It has been tested in G46 S. typhimurium and K-12 E. coli strains[3]. Another reference reports negative results for S. typhimurium strains TA 98, 100, 1535 and 1537[4]. Napthalene is considered a probable non-carcinogen for this project.

[1] Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NCI, PHS-149, Volumes 1, 2, 3, and 4.

[2] Arcos, J. C. and Argus, M. F., Chemical Induction of Cancer, Volume IIA, Academic Press, New York, 1974, Pages 194, 237, and 278.

[3] Kraemer, M. et al., "S. Typhimurium and E. Coli to Detect Chemical Mutagens", Naunyn Schmiedebergs Arch Pharmakol, 284, 46R, 1974.

[4] McCann, J. et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals", Proc. Nat. Acad. Sci. (USA), 72 (12) 5135-5139, 1975.

Napthoquinone

Napthoquinone is on the NIOSH Suspected Carcinogen list because of a 1940 Japanese reference[1]. In this paper α-napthoquinone (in benzene) painted on daily on the back of mice caused 3/77 skin cancers and 11/77 papillomas compared to 0/46 skin cancers and 1/46 papillomas for benzene alone on mice surviving 200 days. β-Napthoquinone produced no cancers or papillomas out of 25 mice surviving 200 days.

A survey of recent literature from Toxline, Cancerline, and the Volumes 1 - 7 of the "Survey of Compounds which Have Been Tested for Carcinogenic Activity" found no pertinent references. Since the only positive reference is outdated and used benzene as the solvent, napthoquinone is being placed on the probable non-carcinogen list for this project.

[1]Takizawa, N., "On the Carcinogenic Action of Certain Quinones", Proc. Imperial Acad. (Tokyo) 16, 309-312, 1940.

1-NapthyI Methylcarbamate

The primary reference to this compound carcinogenic potential from a Russian journal has not been obtained. Another Russian reference from the same year[1] declares that 2-napthyl methylcarbamate is carcinogenic while 1-napthyl methylcarbamate is non-carcinogenic. 1-Napthyl methylcarbamate tested on male and female mice of two strains was found to be non-carcinogenic[2]. No other references were found in Cancerline to indicate that this chemical is a carcinogen. There are negative mice feeding studies (18 months) and rat intergastic studies reported[3]. It is probably a non-carcinogen based on the available literature.

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[1]Zabezhinskiy, M. A., "Investigations on Possible Carcinogenic Effects of Beta-Sevin", Vopr. Onkol. 16 (11), 106-107, 1970.

[2]"Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals, National Technicla Information Service Number PB-223 159, 1968.

[3]Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NCI, PHS-149, Volumes 5 and 6.

Nitrobenzene

Although on structural basis nitrobenzene (CAS No. 98-95-3) has been predicted to be a carcinogen, there was no positive indication from actual tests of the chemical cited in "Air Pollution Assessment of Nitrobenzene"[1] or on Cancerline or Toxline. It has been reported to induce sex-linked recessive lethal mutations in Drosophila melanogaster when administered as a vapor for 8-10 days[2]. With only one *in vitro* positive test reported, nitrobenzene will be considered a non-carcinogen (with some positive data) for this project.

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[1]Dorigan, J. and Hubbon, J., "Air Pollution Assessment of Nitrobenzene", National Technical Information Service Number PB-257 776, May 1976.

[2]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

Nitrophenol

No data on the carcinogenicity of nitrophenols could be found on Cancerline or Toxline but p-nitrophenol has been found to be mutagenic by one test system and non-mutagenic by five other test systems[1]. When comparing S. typhimurium test results with other systems, Ames classified nitrophenol as a non-mutagen[2]. For this project, nitrophenols will be classed as probable non-carcinogens.

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[1]Fahrig, R., "Comparative Mutagenicity Studies with Pesticides" in Chemical Carcinogenesis Essays, International Agency for Research on Cancer-Scientific Publication No. 10, P. 161-181, 1974.

[2]McCann, J. et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Testi Assay of 300 Chemicals", Proc. Nat. Acad. Sci. (USA) 72, 5135-5139, 1975.

Nitrosodimethylamine

There are much data showing nitrosodimethylamine (dimethylnitrosamine) to be a potent carcinogen[1]. It has, therefore, been placed on the probable carcinogen list for this project. In the final selection of carcinogens, however, it may not be advantageous to select this compound. This is because nitrosodimethylamine rapidly decomposes in sunlight[2], under normal conditions is of no significance as an air pollutant[2], and is generally only found in the air near certain manufacturing plants which had (now repaired) leaks in their system[3].

Production and Persistance

Nitrosodimethylamine is emitted in less than 100 Kg/year quantities from the dimethylhydrazine stationary sources[4]. One estimate of production is less than 450 Kg/year[5]. Photolysis of nitrosodimethylamine is reported to be rapid with a half life of less than one hour[5]. It has a boiling point of 152°C[6].

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[1] IARC Monographs: Evaluation of the Carcinogenic Risk of Chemicals to Man - Volume 1, 95-106, 1972.

[2] Bretschneider, K. and Matz, J., "Occurrence and Analysis of Nitrosamines in Air", in Environmental N-Nitroso Compounds, Analysis and Formation, IARC Sci. Pub. No. 14, 395-399, 1976.

[3] Fine, D. H. et al., "N-Nitroso Compounds in Air and Water", in Environmental N-Nitroso Compounds, Analysis and Formation, IARC Sci. Pub. No. 14, 401-408, 1976.

[4] MRC Source Assessment Data Base, July 1977.

[5] Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals", National Technical Information Service Number, PB 267 121, 1977.

[6] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Nitrochlorobenzene

Nitrochlorobenzene (chloronitrobenzene) has been found to mutate Salmonella typhimurium[1] and is indicated as a carcinogen causing neoplasms in another reference summary sheets while listed as not tested in the same appendix[2]. For this project it will be considered a possible carcinogen.

Production and Persistance

It is estimated that 3×10^2 Kg nitrochlorobenzene is emitted per year from stationary sources[3]. An estimate of production is 6.4×10^7 Kg, produced of each of the isomers in 1967[2]. Nitrochlorobenzene reacts with oxidizing materials in the atmosphere[2]. In the soil, microflora decomposes this chemical in 64 days[3]. The m,p, and 0-isomers have boiling points of 236, 242, and 245°C with a vapor pressure of 10 mm at 25°C[2].

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[1]Tardiff, R. G., et al., "Halogenated Organics in Tap Water: A Toxicological Evaluation" in The Environmental Impact of Water Chlorination, National Technical Information Service Number CONF 751096, p. 213-228, 1976.

[2]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 441, 1976.

[3]MRC Source Assessment Data Base, July 1977.

[4]Verschuren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Parathion

Nothing was found in Cancerline to indicate that parathion is a mutagen or carcinogen. The NIOSH Suspected Carcinogen list reference cites parathion as being a slight teratogen only when given in sufficient quantity as to cause toxic poisioning to be apparent in the dams[1]. It has been found to be non-mutagenic by several different *in vitro* tests[2], but does cause an antimitotic action in cells.[3] It is therefore classified as a probable non-carcinogen for this project.

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[1]Kimbrough, R. D. and Gaines, T. B., "Effect of Organic Phosphorus Compounds and Alkylating Agents on the Rat Fetus", Arch. Environ. Health, 16, 805 - 808, 1968.

[2]Fahrig, R., "Comparative Mutagenic Studies with Pesticides", in Chemical Carcinogen Essays, IARC Scientific Publication No. 10, 1974.

[3]Grant, W. F., "Cytological Effects of Environmental Mutagens - Pesticides", Mutat. Res. 21 (4), 221-222, 1973.

Pentane

Although n-pentane is cited as a carcinogen in one reference[1], no primary references could be found to substantiate this allegation from Toxline, Cancerline, or the Survey of Compounds Which have been Tested for Carcinogenic Activity. It is said that aliphatic hydrocarbons may be co-carcinogens[2]. For this project pentane will be considered a non-carcinogen.

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[1]Fuller, B. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[2]Sawicki, E., "Chemical Composition and Potential Genotoxic Aspects of Polluted Atmospheres", IARC Sci. Pub. No. 16, 127-157, 1977.

Pentachlorophenol

Pentachlorophenol (CAS No. 87-86-5) has been found negative in some relatively short studies on rabbit skin and orally in rats, and cats[1]. More recently it has been found negative in two strains of mice both orally and subcutaneously[2]. Pentachlorophenol is also negative in Drosophila tests[3], in a host-mediated assay in mice[4], and other microbial systems[5].

Some authors consider pentachlorophenol a known mutagen[6], and there are other positive as well as negative short term tests reported[7]. It is also positive at the 100 µg level in the hamster embryo adenovirus enhancement assay[8]. For these reasons, pentachlorophenol will be considered a possible carcinogen for this project for the first round of evaluations.

Production and Persistance

One estimate of production is 2.1×10^7 Kg (1969 capacity) and a consumption of 2.3×10^7 Kg in 1975[9]. In the soil it degrades completely in >72 days[10]. It has a boiling point of 310°C and a vapor pressure of 1.1×10^{-4} mm at 20°C[10].

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[1]Deichman, et al., (1944) in Survey of Compounds Which Have Been Tested for Carcinogenic Activity, J. L. Hartwell, editor, National Technical Information Service Number PB 216 478, 1951.

[2]"Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", National Technical Information Service Number PB 223 159, 1968.

[3]Vogel, E. and Chandler, J. L. R., "Mutagenicity Testing of Cyclamate and Some Pesticides in Drosophila Melanogaster", Experientia 30 (6), 621-623, 1974.

[4]Buselmaier, W., et al., "Comparative Investigations on the Mutagenicity of Pesticides in Mammalian Test Systems", Mutat. Res. 21 (1), 25-26, 1973.

[5]Anderson, K. J., et al., "Evaluation of Herbicides for Possible Mutagenic Properties", J. Agr. Focal Chem. 20 (3), 649-656, 1972.

[6]Daugherty, R. C. and Piotrowska, K., "Screening by Negative Chemical Ionization Mass Spectrometry for Environmental Contamination with Toxic Residues: Application to Human Urines", Proc. Natl. Acad. Sci 73 (6), 1777-1781, 1976.

[7]Fahrig, R., "Comparative Mutagenicity Studies with Pesticides", in Chemical Carcinogenesis Essays, IARC Sci. Pub. No. 10, 161-181, 1974.

[5]Personal communications with Dr. Bruce Casto, 2/17/78.

[9]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 446, 1976.

[10]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Phenol

Phenol (hydroxybenzene, CAS No. 108-95-2) has been reported to give rise to papillomas after administration on mouse skin[1,2]. Phenol has also been reported negative by injection and negative on the skin of mice[3]. It has recently been given in combination with other chemicals[3]. In mutagenicity tests, phenol has been found to be mutagenic to Drosophila, revert E. coli to streptomycin independence, and induce chromosome breakage in the root tip of Allium cepa while being inactive in reverting Neurospora crassa to adenine prototrophy[4]. Phenol is also said to cause second chromosome breaks in Drosophila, cause chromosome breaks in Vicia and Allium sativum and it is teratogenic in chickens[5]. One must also remember, however, that normal adults excrete approximately 30 mg of volatile phenols per day in their urine (mainly p-cresol and phenol) produced by gut bacterial metabolism of tyrosine[6]. Phenol has tested negative in a micronucleus test[7]. The only positive animal tests were conducted in the 50's with later negative results. The positive *in vitro* tests are with systems which have not been extensively evaluated. Although it is a borderline chemical, phenol will be considered a probable non-carcinogen (with some positive data) for this project.

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[1]Salaman, M. H. and Glendenning, O. M., Brit. J. Cancer, 11, 434-444, 1957.

[2]Boutwell, R. K. and Bosch, D. K., Cancer Research 19, 413-424, 1959.

[3]Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NIH, PHS-149, Volumes 3,4,5,6, and 7.

[4]Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[5]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 164, 1975.

[6]Bone, E. S., et al., "The Production of Urinary Phenols by Human Gut Bacteria" (Meeting Abstract). J. Med. Microbiol. 9 (2), p. vi, 1976.

[7]Hossak, D. J. and Richardson, J. C., "Examination of the Potential Mutagenicity of Hair Dye Constituents Using the Micronucleus Test", Experientia, 33 (3), 377-378, 1977.

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCB, chlorinated diphenyls, Aroclors, Kanechlors) have been cited extensively in the literature as carcinogens[1-2]. On close inspection, many of the carcinogenicity studies on PCB's have been questionable[3-4] or negative[5] and the increase in cancer among PCB workers has been questioned[6]. The latest NCI study of PCB's was negative but they concluded that from the open literature PCB's are probably promoters of carcinogenesis. The PCB's fall on the border between possible and probable carcinogens using the criteria for this project. Because of the positive animal studies[1-7], it will be classed as a probable carcinogen for this project.

Production and Persistance

It is estimated that 1.8×10^{5} kg is emitted per year[8]. Other estimates of production are 1.4×10^{7} kg, 2.5×10^{6} kg, and 1.8×10^{7} kg (1974)[9-11]. Production of PCB's has been phased out within the last year so emissions should have dropped to zero. PCB's are essentially non-volatile, but evaporation to the atmosphere is thought to be important[11]. Reaction with HO radical predicts a half life of 26 days[9]. They have a boiling point of 365-390°C and a vapor pressure less than 1 mm at 25°C[10].

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[1] "Polychlorinated Biphenyls" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 7, 261-289, 1974.

[2] Lloyd, J. W., et al., "Polychlorinated Biphenyls", J. Occup. Med. 18 (2), 109-113, 1976.

[3] Andrews, E. J., et al., "PCB Diet" Science 180 (4083), 255-257, 1973.

[4] Survey of Compounds Which Have Been Tested for Carcinogenic Activity, National Cancer Institute, PHS-149, 1972-1973 edition, Number 325.

[5] Ito, N., et al., "Histopathological Studies on Liver Tumorigenesis in Rats Treated with Polychlorinated Biphenyls," Gann, 65 (6), 545-549, 1974.

[6] Lawrence, C., "PCB? and Melanoma" (Letter to the Editor), N. Engl. J. Med. 296 (2), 108-109, 1977.

[7]NIOSH Suspected Carcinogens, 1976 edition.

[8]MRC Source Assessment Data Base, July 1977.

[9]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Number PB 263 162, 1975.

[10]Dorigan, J., et al., "Preliminary Scoring of Selected Organic Air Pollutants," National Technical Information Service Number PB 264 446, 1976.

[11]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals," National Technical Information Service Number PB 267 121, 1977.

Propanol

In 1939 and 1940, propanol (propyl alcohol, CAS No. 71-23-8) was found non-carcinogenic in rat feeding studies[1,2]. The only current references which could be found were by Gibel et al. who refer to tumor formation after oral (50g/Kg) and subcutaneous (6gm/Kg) administration of propanol to rats[3] and an E. coli test[4]. The studies which have been conducted on isopropancl have been negative[5]. Propanol will be considered a probable non-carcinogen (with some significant positive data) for this project.

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[1]Nakahara, W. and Mori, K., Proc. Imp. Acad., Japan 15, 278-281, 1939.

[2]Nakahara, W. and Mori, K., Gann 33, 143-145, 1940.

[3]Gibel, W., et al., "Experimental Study on Cancerogenic Activity of Propanol-1, 2-Methylpropanol-1 and 3-Methylbutanol", Arch. Geschwulstforsch 45 (1), 19-24, 1975.

[4]Gibel, W., et al., "Studies on the Toxicity and Mutagenicity of Single Fusel Oil Componsents on E. Coli", Acta Biol. Med. Ger. 23, 843-852, 1969.

[5]"Isopropyl Alcohol and Isopropyl Oils" in IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 15, 223-243, 1977.

Propylene Oxide

Propylene oxide (methyloxirane, 1,2-epoxypropane, CAS No. 75-56-9) has been reported to cause local sarcomas in a limited number of rats after subcutaneous injection[1]. It was negative in relatively short-term (~200 days) studies in rats, guines pigs, rabbits and monkeys given propylene oxide by inhallation[1,2]. By *in vitro* tests, transformation of hamster cells[3] occurred at 250 mg/ml[4]. It is also reported to cause reversion to adenine, prototrophy in Neurospora crassa and cause recessive lethal mutation in Drosophila melanogaster[5]. For this project it will be considered a possible carcinogen.

Production and Persistance

It is estimated that 4.4×10^6 kg propylene oxide is emitted per year[6]. Other production estimates include 7.5×10^8 kg per year[7], 8.0×10^6 kg (1974)[8], 8.0×10^8 kg (1975)[1], and 7.0×10^8 kg (1975)[5] with U. S. consumption predicted to grow by 9-10.5% a year from 1975 to 1980[5]. If dispersed in the atmosphere, epoxides would be oxidized by HO radicals with a half life of 3-11 hours[8]. The rate constant and half life for HO radical reaction predict a 23 hour half life for aliphatic epoxides[5]. Propylene oxide has a boiling point of 33.9°C and a vapor pressure of 596 mm at 25°C[7].

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[1] "Propylene Oxide" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 11, 191-199, 1976

[2] Rowe, L. K., et al., "Toxicity of Propylene Oxide Determined on Experimental Animals," Arch. Industr. Hlth., 13, 228-236, 1956.

[3] Casto, B. C., et al., "Assay of Industrial Chemicals in Syrian Hamster Cells for Enhancement of Viral Transformation" (Meeting Abstract), Proc. Am. Assoc. Cancer Res., 18, 155, 1977.

[4] Personal communication with B. C. Casto on 9 February, 1978.

[5] Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274 264, 1977.

[6] MRC Source Assessment Data Base, July 1977.

[7] Dorigan J., et al., "Preliminary Scoring of Selected Air Pollutants," National Technical Information Service Number PB 264 446, 1976.

[8]Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals," National Technical Information Service Number PB 267 121, 1977.

Pyrene

Pyrene (CAS No. 129-00-0) has generally been tested on mouse skin with negative results[1]. It has also been reported negative on mouse skin followed by croton oil or preceded by benzo(a)pyrene[1]. It is usually considered to be non-carcinogenic[2,3] and has been reported as non-mutagenic to S. Typhimurium strains TA 98, 100, 1535 and 1537[3]. It is considered a non-carcinogen for this project.

[1]Survey of Compounds Which Have Been Tested for Carcinogenic Activity, NCI, PHS-149, Volumes 1, 3, 4, 6, and 7.

[2]Arcos, J. C. and Argus, M. F., Chemical Induction of Cancer, Volume IIA, Academic Press, New York, 1974, pages 210 and 237.

[3]McCann, J. et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test: Assay of 300 Chemicals", Proc. Nat. Acad. Sci. (USA), 72 (12), 5135-5139, 1975.

Sorbic Acid

Sorbic Acid (2,4-hexadienoic acid, CAS No. 110-44-1) is a widely used food perservative. In 1966 and 1968, Dickens et al. reported several rat studies with sorbic acid. In these tests (using 6-12 rats) sorbic acid injected subcutaneously at 2 mg/injection in oil or water sometimes caused local fibrosarcomas at the injection site[1-3]. Given in the drinking water at 0.1 gm/l, no effects were seen[3]. It is now known that the pH of the injected solution may cause local fibrosarcomus in some strains of rats. In more recent dose response studies, rats[4] and mice[5] (groups of 100 animals) were given 0, 1.5, or 10% of their diet as sorbic acid with no carcinogenic response. Also sorbic acid with 1000 ppm parasorbic acid gave no carcinogenic response[6]. Several *in vitro* tests (eg B. subtilis) have been negative for sorbic acid but positive for reaction products of sorbic acid and sodium nitrite[7]. Better subcutaneous tests should be conducted on sorbic acid, but the negative results on the recent large scale feeding tests and negative *in vitro* results suggest that sorbic acid should be considered a non-carginogen at the present time.

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[1]Dickens, F., et al., Brit. J. Cancer 20, 134-144, 1966.

[2]Dickens, F. and Wayforth, H. B., Brit. Emp. Canc. Camp. 46, 108, 1968.

[3]Dickens, F., et al., Brit. J. Cancer, 22, 762-768, 1968.

[4]Grant, I. F., et al., "Long-Term Toxicity of Sorbic Acid in the Rat," Food Cosmet. Toxicol. 13 (1), 31-45, 1975.

[5]Hendy, R. J., et al., "Long-Term Toxicity Studies of Sorbic Acid in Mice," Food Cosmet. Toxicol. 14 (5), 381-386, 1976.

[6]Mason, P. L., et al., "Long-Term Toxicity of Parasorbic Acid in Rats," Food Cosmet. Toxicol. 14 (5), 387-394, 1976.

[7]Kada, T., "Mutagenicity and Carcinogenicity Screening of Food Additives by the Rec-Assay and Reversion Procedures," IARC Sci. Pub. No. 12, 105-115, 1976.

Styrene

Styrene (vinyl benzene, CAS No. 100-42-5) has been found to be both positive[1,2] and negative[3] on the Salmonella typhimurium mutagen test after activation with S-9 microsomes. Without S-9 activation it has been found negative by this test[1,3]. In other systems, styrene was found positive on a host-mediated forward mutation, gene-conversion yeast system but negative in this system with microsomes only (not host-mediated). It was negative on a Chinese hamster cell test[4], in Drosophila melanogaster and S.pombe mutation test[5], and in enhancement of viral transformation tests[6]. It would thus appear that a metabolic product of styrene is a weak mutagen and styrene should probably be considered a possible carcinogen.

Production and Persistance

It is estimated that 5.6×10^6 Kg styrene is emitted per year from stationary sources[7]. Another source estimate 2.0×10^9 Kg (1975) produced[8]. It has a 1.28 relative chemical reactivity in the atmosphere (where methane is zero, butane is 1.27, 2-pentane is 1.58 and 2-butene is 15.5)[9,10]. Styrene has a 145.2°C boiling point and a vapor pressure of 5 mm at 20°C[9].

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[1]DeMeester, C. et al., "Mutagenic Activity of Styrene and Styrene Oxide", Arch. Int. Physiol. Biochim., 85 (2), 398-399, 1977.

[2]Vainio, H., et al., "A Study on the Mutagenic Activity of Styrene and Styrene Oxide", Scand. J. Work Environ. Health, 2(3), 147-151, 1976.

[3]Stolz, D. B., "Mutagenicity Testing of Styrene and Styrene Epoxide in Salmonella Typhimurium", Bull. Environ. Contam. Toxicol., 17, (6), 739-742, 1977.

[4]Loprieno, N., et al., "Mutagenicity of Industrial Compounds: Styrene and its Possible Metabolite Styrene Oxide", Mutat. Res., 40(4), 317-324, 1976.

[5]Allport, J. et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 264, 1977.

[6]Personal communication with B. C. Casto on 5 February 1978.

[7]MRC Source Assessment Data Base, July 1977.

[8]Fuller, B. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 442, 1976.

[9]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

[10]Yeung, C. K. K. and Phillips, C. R., "Estimated of Physiological Smog Sympton Potential from Chemical Reactivity of Hydrocarbons", Atm. Environ. 7, 1973.

Sulfolane

Sulfolane (tetrahydrothiophene,-1-dioxide, CAS No. 126-33-0) was one of the eighty chemicals selected as having the greatest potential environmental effects [1]. Carcinogenicity and mutagenicity were not cited as reasons for its selection. No data could be found in any of the references searched pertaining to mutagenicity or carcinogenicity of this chemical. It is considered a probable non-carcinogen for this project.

[1]Brown, S. L. et al. "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Number PB 263 161, 1975.

Tetrabromoethane

Tetrabromoethane (CAS No. 79-27-6) was one of eighty chemicals having potential for environmental effects[1]. It has tested negative in some short term (92 day), limited exposure (15 min./day) tests on rats, mice, rabbits and guinea pigs[2]. It has tested positive in a E. coli (pol A+, pol A -) differential growth mutagen test but negative in S. typhimurium strains TA1530 and TA 1535[3,4]. With only one *in vitro* positive test (which has not been extensively validated) tetrabromoethane will be considered a probable non-carcinogen for this project.

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[1]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Numbers PB 263 162, 1975.

[2]Gray, A. W. A., Arch. Ind. Hyg., 2. 407-419, 1950. (From PHS-149: Survey of Compounds Which Have Been Tested for Carcinogenic Activity)

[3]Brem, H., et al., "The Mutagenicity and DNA-Modifying Effect of Haloalkanes," Cancer Res. 34, 2576-2579, 1974.

[4]Rosenkranz, H. S., "Mutagenicity and DNA-Modifying Activity: A Comparison of Two Microbial Assays," Mutat. Res. 41 (1), 61-70, 1976.

Tetrachloroethane

1,1,2,2-Tetrachloroethane (CAS No. 79-34-5) has been found to be mutagenic in the Salmonella typhimurium system for TA 1530 and TA 1535 strains[1]. It has been cited as a carcinogen based on a National Cancer Institute bioassay[2] where it was found to be a carcinogen for mice but not for rats[3]. It is therefore considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 0.4×10^3 Kg is emitted per year from stationary sources (in making trichloroethylene from ethylene)[4]. Evaporation of 50% from a 1 ppm solution of water at 25°C will occur in 56 minutes[5]. It has a boiling point of 146.4°C and a vapor pressure of 5 mm at 20°C[5]. Water solubility is 2.9 gm/l at 20°C[5].

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[1] Brem, H., Stein, A. B., and Rosenkranz, H. S., "The Mutagenicity and DNA-Modifying Effect of Haloalkanes", Cancer Res. 34, 2576-2579, 1974.

[2] Kraybill, H. F., "Origin, Classification and Distribution of Chemicals in Drinking Water with an Assessment of their Carcinogenic Potential", in The Environmental Impact of Water Chlorination, Oak Ridge National Laboratory, National Technical Information Service Number CONF 751096, p. 229, 1976.

[3] Chemical Regulation Reporter 1 (51), 1861, 1978.

[4] MRC Source Assessment Data Base, July 1977.

[5] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1978.

Tetrachloroethylene

The NTIS document "Air Pollution Assessment of Tetrachloroethylene"[1] cites extensive toxicological data but reports no evidence of carcinogenicity, mutagenicity or teratogenicity for tetrachloroethylene (perchloroethylene, CAS No. 127-18-4) in humans. Also no difference in the incidence of tumors were observed between control and experimental rats exposed to 300 or 600 ppm of tetrachloroethylene. A recent report by NCI however, has shown tetrachloroethylene to be a liver carcinogen in B6C3F1 of both sexes. Tetrachloroethylene has, therefore, been assigned to the PROBABLE carcinogen list.

Production and Persistance

It is estimated that 7.8×10^7 Kg tetrachloroethylene is emitted per year from stationary sources with solvent evaporation from degreasing operations accounting for better than 99% of that quantity[3]. Other estimates of production are 3.0×10^8 Kg (1975)[4], 3.3×10^8 Kg produced and 2.6×10^8 Kg released[5], and production of 3.3×10^8 Kg, 3.1×10^8 Kg, and 3.0×10^8 Kg in 1974, 1975, and 1976[6]. A 1976 forecast projected a yearly growth of 3-4% but in light of the NCI carcinogen study, lower standards for occupational exposure from NIOSH, and a decrease in fluorocarbon use, the production of tetrachloroethylene is expected to decrease[5]. It is not photoactive and has an expected HO radical reaction half-life of 8 days[5]. Another reference cites photodegradation with a half-life of 2 days[1]. Evaporation of 50% from a 1 ppm water solution at 27°C will take only 24-28 minutes[7]. It has a boiling point of 121.2°C and a vapor pressure of 14 mm at 20°C[7].

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[1] Fuller, B. B., "Air Pollution Assessment of Tetrachloroethylene", National Technical Information Service, Number PB-256 731, 99 pages, 1976.

[2] "Bioassay of Tetrachloroethylene for Possible Carcinogenicity CAS No. 127-18-4", National Technical Information Service Number PB 272 940/ 5L.

[3]MRC Source Assessment Data Base, July 1977.

[4]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 446, 1976.

[5]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[6]Allport, J. et al., "A Study of Industrial Data on Candidate Chemicals for Testing", National Technical Information Service Number PB 274 364, 1977.

[7]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Tetraethyl Lead

Tetraethyl lead (tetraethyl plumbane, CAS No. 78-00-2) has been found to induce lymphomas when injected subcutaneously into neonatal mice[1] although the significance of this test has been questioned[2]. Oral doses were not found to be teratogenic[3] and an epidemiological study found no health hazard from occupational exposure[4].

Tetraethyl lead has been found to cause DNA fragmentation and to enhance viral transformation in hamster embryo at the 12.5 μg level[5]. Tetraethyl lead is considered a possible carcinogen for this project.

Production and Persistance

One estimate of release to the environment is 1.3×10^8 Kg per year[6] from a production of 1.4×10^8 Kg. The release figure notes that most of this is through use in gasoline where it is converted to lead halides and some lead phosphates[6]. Another set of figures cites a release of 6.6×10^6 Kg from a production of 1.6×10^8 Kg in 1973[7]. The 1971 production has been estimated to be 2.4×10^8 Kg[2]. The production of tetraethyl lead is expected to decrease rapidly from these figures because of regulations requiring less lead in gasoline[2]. In the air it has a half-life of 2-3 days from reactions with HO and O_3 radicals[6,7]. It has a boiling point of 200°C (decomposes) and a vapor pressure of 0.15 mm at 20°C[7,8].

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[1]Epstein, S. S. and Mantel, N., "Carcinogenicity of Tetraethyl Lead:, Experientia, 24 (6), 580-581, 1968.

[2]"Tetraethyl and Tetramethyllead", in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 2, 150-160, 1973.

[3]Kennedy, G. L., et al., "Teratogenic Evaluation of Lead Compounds in Mice and Rats", Food Cosmet. Toxical. 3 (6), 629-632, 1975.

[4]Robinson, T. R., "Health, How Can It Be Measured", HEW Publ. (NIOSH), 76 134, 114, 30, 1976.

[5]Personal communication with Dr. Bruce C. Casto 2/17/78.

[6]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 164, 1975.

[7]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 264 446, 1976.

[8]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Toluene

An extensive search of Cancerline and Toxline along with the NTIS document "Air Pollution Assessment of Toluene"[1] and the Stanford Research Institute hazard priority ranking[2] failed to find data which would indicate that toluene is a carcinogen. It tested negative[3] in a differential growth mutagen test using E. coli (pol. A) and will be considered a non-carcinogen for this project.

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[1]Walker, P., "Air Pollution Assessment of Toluene", National Technical Information Service Number PB 256 735, 1976.

[2]Brown, S. L. et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals", National Technical Information Service Number PB 263 161, 1975.

[3]Fluck, E. R. et al., "Evaluation of a DNA Polymerane-Deficient Mutant of E. Coli for the Rapid Detection of Carcinogens", Chem. Biol. Interact. 15, 219-231, 1976.

Toluene Diisocyanate

There is no data on Toxline or Cancerline to indicate that toluene diisocyanate is a mutagen or a carcinogen.

Toluenediamine

Toluenediamine (toluene-2,4-diamine, CAS No. 95-80-7), generally used as a hair dye, has been found by several studies to be non-carcinogenic when applied to the skin of mice[1,2] and rats[3] although the same data can be interpreted to show increased lung tumors and total tumors in the test groups[4]. Toluenediamine has been reported to produce hepatomas in rats when fed at 9.1 percent of diet for 35 weeks[5] or 11 gm/kg for 36 weeks[6]. In rats, 280 mg/Kg (35 weeks) subcutaneously is reported to cause neoplasms[7]. It has also been found to casue morpohological transformation in primary Syrian hamster embryo cells. It also mutates Salmonella typhinimurium strains TA 1538 and TA 98 at 0.5 ug/ml when activated with the S9 microsomes[5,8]. With positive *in vivo* and in *in vitro* tests, toluene-diamine will be considered a probable carcinogen for this project.

Production and Persistance

One estimate of production is 2.9×10^7 Kg per year with 0.015 as a fraction of production loss[7]. It has a boiling point of 292°C and a vapor pressure of 1 mm at 106.5C[7].

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[1]Giles, A. L., et al., "Dermal Carcinogenicity Study by Mouse-Skin Painting with 2,4-Toluenediamine Alone or in Represenative Hair Dye Formulations", J. Toxical. Environ. Health 1 (3), 433-440, 1976.

[2]Burnett, C., et al., "Long-Term Toxicity Studies on Oxidation Hair Dyes", Food Cosmet. Toxicol. 13 (3), 353-357, 1975.

[3]Kinkel, H. J. and Holzmann, S., "Study of Long-Term Percutaneous Toxicity and Carcinogenicity of Hair Dyes (Oxidizing Dyes) in Rats", Food Cosmet. Toxicol. 11 (4), 641-648, 1973.

[4]Bridges, B. A. and Green, M. H., "Carcinogenicity of Hair Dyes by Skin Painting in Mice" (letter to Editor), J. Toxicol. Environ. Health 2 (1), 251-252, 1976.

[5]Shah, M. J. et al., "Comparative Studies of Bacterial Mutation and Hamster Cell Transformation Induced by 2,4-Toluenediamine" (Meeting Abstract), Proc. Am. Assoc. Cancer Res. 18, 22, 1977.

[6]Cancer Research 29, 1137, 1969.

[7]Dorigan, J. et al., "Preliminary Scoring of Organic Air Pollutants", National Technical Information Service Number PB 264 446, 1976.

[8]Pienta, R. J. et al., "Correlation of Bacterial Mutagenicity and Hamster Cell Transformations with Tumorigenicity Induced by 2,4-Toluenediamine", Cancer Lett. (Amsterdam) 3 (1/2), 45-52, 1977.

Toxaphene

No significant data were found to indicate that toxaphene is a mutagen or a carcinogen. It tests negative on the dominant lethal test for mice[1]. It has been placed on the probable non-carcinogen list for this project.

[1]Epstein, S. S. et al., "Detection of Chemical Mutagens by the Dominant Lethal Assay in the Mouse", Toxicol. Appl. Pharmacol. 23, 288-325, 1972.

Trichlorfon

Trichlorfon has been found to be carcinogenic to mice, rats, and cats given orally, subcutaneously, cutaneously, or intermuscularly. It has also been found to be mutagenic by at least five different test systems. It is, therefore, to be considered a probable carcinogen.

Production and Persistance

It is estimated that 100 Kg/year of trichlorfon is emitted from stationary sources[1].

[1]MRC Source Assessment Data Base, July 1977.

Trichloroethane

A National Cancer Institute bioassay of 1,1,1-trichloroethane found no correlation between this chemical and any cancers which developed in the control versus the test rats and mice[1]. It was negative on an enhancement of viral transformation test[2]. It has been placed on the non-carcinogen list for this project.

[1] "Bioassay of 1,1,1-Trichloroethane for Possible Carcinogenicity", Carcinog. Tech. Rep. Ser. - Nat'l. Cancer Inst. (U.S.); ISS NCI-CG-TR-3, 70 pp., 1975.

[2] Personal communication with B. C. Casto on 9 February 19798.

Trichloroethylene

Trichloroethylene (trichloroethene, TCE, CAS No. 79-01-6) has been found to induce a high incidence of hepatocellular carcinoma in B6C3F1 mice of both sexes by NCI[1]. It has also been found to be weekly mutagenic in E. coli and to TA100 strain of S. typhimurium (0.8-2.0% vapor dose response when exposed one hour) in the presence of activated microsomes[2]. A review of the production, uses and environmental effects has been compiled by Fishbein[3]. TCE is considered a probable carcinogen for this project.

Production and Persistance

It is estimated that 1.6×10^8 kg of TCE is emitted per year with 95% of that coming from solvent evaporation in degreasing operations[4]. Another estimate is a production of 1.93×10^8 kg with 1.95×10^8 kg released[5]. Other production estimates[6,7] include 1.8×10^8 kg (1974) and 1.3×10^8 kg/year, with about 60% of the production released to the environment[8]. Production has also been reported to be 1.8×10^8 kg (1974), 1.3×10^8 (1975) and 1.4×10^8 kg (1976) with a 1% decling predicted for future years[2]. Since that prediction, OSHA has lowered the standard for occupational exposure and NCI found that TCE causes tumors in mice which will mean a much greater decline in the expected production[2]. TCE has a high atmospheric photodegredation rate with a half life of 0.3 days at sea level[8]. Other sources predict atmospheric reaction with the HO radical with a half life of 36 hours[6] or less than 50 hours[5]. With its high volatility and low water soluability it is expected to fairly rapidly migrate into the atmosphere. In fact 50% of a 1 ppm solution will evaporate from water at 25°C in 19-24 minutes[9]. Its boiling point is 86.7°C and it has a vapor pressure of 60 mm at 20°C[9].

"Carcinogenesis Bioassay of Trichloroethylene, CAS No. 79-01-6" National Cancer Institute Carcinogenesis Technical Report Services, Number 2, February 1976 (NCI-CG-TR-2).

Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274 264, 1977.

Fishbein, L., "Industrial Mutagens and Potential Mutagens I. Halogenated Aliphatic Derivatives," Mutat. Res. 32, 267-308, 1976.

[4]MRC Source Assessment Data Base, July 1977.

[5]Brown, S. L., et al., "Research Program on Hazard Priority Ranking of Manufactured Chemicals," National Technical Information Service Number PB 263 161, 1975.

[6]Radding, S. L., et al., "Review of the Environmental Fate of Selected Chemicals," National Technical Information Service Number 267 121, 1977.

[7]Fuller, B., et al., "Preliminary Scoring of Organic Air Pollutants," National Technical Information Service Number PB 264 442, 1976.

[8]Fuller, B. B., "Air Pollution Assessment of Trichloroethylene," National Technical Information Service Number PB 256 730, 1976.

[9]Verscheoren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

Trichlorofluoromethane

In mice, trichlorofluoromethane (Freon-11, F-11) in combination with the insecticidal synergist piperonyl butoxide increased the incidence of malignant heptomas while Freon-11 by itself was found to be non-carcinogenic[1]. No other carcinogenic data was on Freon-11 and it has been found to be non-mutagenic in Salmonella typhimurium tests with and without microsonal activation[2]. Preliminary results from an NCI bioassay shows no difference between control and treated male or female rats[3]. It is probably not a carcinogen.

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[1]Epstein, S. S., et al., "Synergistic Toxicity and Carcinogenicity of 'Freons' and Piperonyl Butoxide", Nature 214, 526-528, 1967.

[2]Uehleke, H., et al., "Metabolic Activation of Haloalkanes and Tests *in vitro* for Mutagenicity", Xenobiotica 7 (7), 393-400, 1977.

[3]NCI preliminary data on trichlorofluoromethane, Nov. 27, 1976.

Trichlorophenol

Trichlorophenol (2,4,6-trichlorophenol, Dowicide 2S, CAS No. 88-06-2) has been found to be a carcinogen in mice when given orally but not subcutaneously[1,2]. 7/72 heptomas, 6/72 pulmonary adenomas, and 7/72 reticulium cell sarcomas were found. (2,4,5-trichlorophenol was only evaluated by subcutaneous route[1] and was found negative by this route of administration, as was 2,4,6-trichlorophenol). Trichlorophenol may cause abnormal pollen in broad bean plants[3]. No other pertinent literature reference were found on Toxline or Cancerline to substantiate or refute the carcinogenic potential of trichlorophenol. It has been placed on the possible carcinogen list for this project.

Production and Persistance

It is estimated that 5 x 10^2 Kg trichlorophenol is emitted from stationary sources per year[4]. Since this is used as a pesticide, non-stationary sources (or total production) should be considered. It completely disappears in soil suspensions in 5 days[5]. Trichlorophenol (2,4,6) has a boiling point of 244.5°C and a solubility of 800 mg/l at 25°C[5].

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[1]Evaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals", National Technical Information Service Number PB 223 159, 1968.

[2]Innes, J. R. M., et al., "J. Nat. Cancer Inst., 42, 1101-1114, 1969.

[3]"Cytological Effects of Pesticides. V. Effects of Some Herbicides on Vicia Faba", Cytologia 39 (4), 663-643, 1974.

[4]MRC Source Assessment Data Base, July 1977.

[5]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Urethane*

Urethane (ethyl carbamate, CAS No. 51-79-6) has been shown to be carcinogenic in mice, rats and hamsters following administration by the oral, inhalation, subcutaneous or intraperitoneal routes[1]. It generally causes lung tumors, lymphomas, hepatomas, melanomas, and vascular tumors. With all of this positive data, urethane is considered a probable carcinogen for this project.

Production and Persistance

The only production data which could be found cited production from one US company with data not given and production below 454 Kg from a second company[1]. It has a boiling point of 183°C and sublimes at 102°C at 54 mm Hg, and is volatile at room temperature[1].

*The name urethane is sometimes applied to high molecular weight polyurethanes used as forms, elastomers and coatings. Such products are not made from the chemical urethane and do not generate it on decomposition.

[1] "Urethane" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 7, 111-140, 1974.

Vinyl Acetate

Vinyl acetate (CAS No. 108-05-4) has been found to be non-carcinogenic in rats at 2,500 ppm for 4 hrs./day for 12 months by C. Maltoni[1]. It has also been found negative on mouse skin[2], mouse sebaceous glands[3], and S. typhimurium tests[4-6]. Both commercial vinyl acetate[7] and repeated tests of purified vinyl acetate[8] have been found to be mutagenic at a level of 150 µg/ml in viral transformation, vinyl acetate will be considered a possible carcinogen for this project for the first round of evaluations.

Production and Persistance

It is estimated that 6.8×10^5 Kg is emitted per year from stationary sources[9]. Another estimate is a release of 7.8×10^6 Kg from a production of 5.5×10^8 Kg[10]. It reacts with oxidizing materials in the atmosphere[10], and has a boiling point of 73°C and a vapor pressure of 83 mm at 20°C[11].

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[1]"Survey of Compounds Which Have Been Tested for Carcinogenic Activity, 1972 - 1973 Volume", U. S. Department of Health, Education and Welfare, DHEW Publication No. (NIH) 75, Public Health Service Publication No. 149.

[2]Garibyan, D. K. and Papoyan, S. A., "Study of the Blastomogenic Activity of Certain Chemical Substances Using a High-Speed Test Method", Gig. Sanit. 8, 74-76, 1977.

[3]Garibyan, D. K. and Papoyan, S. A., "Use of Sebaceous Gland Reactions as a Test for Rapid Determination of Carcinogenic Activity of Chemicals", Nekot. Itogi Izuch. Zagryazneniya Vnesh. Sredy Kanstserogen, Veschestoami; 112-115, 1972.

[4]McCann, J. et al., "Detection of Carcinogens as Mutagens in the Salmonella/Microsome Test", Proc. Nat. Acad. Sci. (USA) 72(12), 5135-5139, 1975.

[5]Bartsch, H., et al., "Alkylating and Mutagenic Metabolites of Halogenated Olefins Produced by Human and Animal Tissues", Proc. Am. Assoc. Cancer Res. 17, 17, 1976.

[6]Bartsch, H. et al., "The Predictive Value of Tissue - Mediated Mutagenicity Assays to Assess the Carcinogenic Risk of Chemicals", IARC Sci. Pub. No. 12, 467-491, 1976.

[7]Casto, B. C. et al., "Assay of Industrial Chemicals in Syrian Hamster Cells for Enhancement of Viral Transformation", (Meeting Abstract), Proc. Am. Assoc. Cancer Res. 18, 155, 1977.

[8]Personal Communication with B. C. Casto on 9 February 1978.

[9]MRC Source Assessment Data Base, July 1977.

[10]Dorigan, J. et al., "Preliminary Scoring of Selected Organic Air Pollutants", National Technical Information Service Number PB 364 446, 1976.

[11]Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., New York, 1977.

Vinyl Bromide

Vinyl bromide (bromoethylene, CAS No. 593-60-2) has not been tested very much. It was not found on the Survey of Compounds Which Have Been Tested for Carcinogenic Activity and from Cancerline and Toxline only one author has conducted *in vitro* tests on it. In this test, Salmonella typhimurium strain TA100 was found to give a dose-response mutation frequency of 26 and 9 revertants per micromole per hour with and without the S9 liver microsome fraction[1]. It was also found that liver fractions from human biopsies converted vinyl bromide to more mutagenic compounds. Another study by the same authors demonstrated that vinyl bromide is activated by the liver homogenates in the same manner as vinyl chloride. Although there is not much data with which to base any decision, vinyl bromide will be considered a possible carcinogen for the first phase of this project.

Production and Persistance

It is estimated that 4×10^3 kg/year of vinyl bromide is emitted from stationary sources.[3]

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[1] Bartsch, H. et al., "Alkylating and Mutagenic Metabolites of Halogenated Olefins Produced by Human and Animal Tissues," Proc. Am. Assoc. Cancer Res. 17: 17, 1976.

[2] Barbin, A., et al., "Liver-Microsome-Mediated Formation of Alkylating Agents from Vinyl Bromide and Vinyl Chloride," Biochem. Biophys. Res. Comm. 67 (2), 596-603, 1975.

[3] MRC Source Assessment Data Base, July 1977.

Vinyl Chloride

Vinyl chloride (CAS No. 75-01-4) has been found to cause lung tumors, mammary carcinomas and angiosarcomas in mice following exposure by inhalation[1]. Similiar exposure for rats produces angiosarcomas of the liver and other organs, zymbal gland carcinomas and nephroblastomas[1]. In view of the extreme rarity of angiosarcoma of the liver in the general population, 16 cases in vinyl chloride workers is evidence of a causal relationship. It has also been found to be a mutagen of S. typhimurium (Ames test)[2] and in enhancement of viral transformation[3].

Production and Persistance

It is estimated that 1.4×10^8 kg is emitted per year[4]. The 1973 production of vinyl chloride was 2.4×10^9 kg in the United States of which 97% was used for production of polyvinyl chloride[1]. A 1974 EPA estimate was 9×10^7 kg released to the atmosphere[1]. Other estimates of production are 2.5×10^9 kg (1974)[5] and 2.5×10^9 kg, 1.9×10^9 kg and 2.6×10^9 kg in 1974, 1975, and 1976[6]. The demand for PVC is expected to increase at an annual rate of 8-10% through 1981[6]. In the atmosphere it reacts with the HO radical with a 12 hour half life[5]. It has a boiling point of -14 °C and a vapor pressure of 2660 mm at 25 °C[7].

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[1] "Vinyl Chloride" in IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 7, 291-305, 1974.

[2] Bartsch, H., et al., "The Predictive Value of Tissue - Mediated Mutagenicity Assays to Assess the Carcinogenic Risk of Chemicals,: IARC Sci. Publ No. 12, 467-491, 1976.

[3] Verschueren, K., Handbook of Environmental Data on Organic Chemicals, Van Nostrand Reinhold Co., N. Y., 1977.

[4] Personal communication with B. C. Casto on 9 February 1978.

[5] MRC Source Assessment Data Base, July 1977.

[6] Radding, S. B., et al., "Review of the Environmental Fate of Selected Chemicals," National Technical Information Service Number PB 267 121, 1977.

[7] Allport, J., et al., "A Study of Industrial Data on Candidate Chemicals for Testing," National Technical Information Service Number PB 274 264, 1977.

Vinylidene Chloride

Vinylidene chloride (1,1-dichloroethylene, CAS No. 75-35-4) has been found to be mutagenic in the Salmonella typhimurium test[1-3] and in a metabolizing *in vitro* system with E. coli K12[4]. It has also been reported to be carcinogenic in rats and rabbits[5] and in preliminary studies 200 ppm were carcinogenic to rats and mice by inhalation[6]. One reference concludes that airborne emissions of vinylidene chloride are not likely to pose a significant risk to the general population[7]. Vinylidene chloride has been placed on the probable carcinogen list for this project.

Production and Persistance

It is estimated that 2.1×10^5 Kg are emitted a year from stationary services, with 70% of this coming from the oxychlorination of ethylene dichloride[8]. Other estimates of production and release are production of 2.7×10^7 Kg with 4.1×10^5 Kg released[9], production of 1.2×10^8 Kg with $1.4 - 1.8 \times 10^6$ emitted and a 5 - 10% growth rate predicted[7], 1.2×10^8 Kg produced with 1.1×10^6 Kg released[10], 7.7×10^7 Kg produced from 1973 - 1975 with a 7% growth predicted[11], and 2.7×10^7 Kg produced in 1972[12]. The O_3 and HO reactions are estimated to give less than a one-day half life[10] while another reference cites HO half life of 26 hours[12]. Evaporation of 50% from a 1 ppm solution at 25°C will occur in 22 minutes[13]. It has a vapor pressure of 617 mm at 25°C and a boiling point of 37°C[10].

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[1]Bartsch, H., et al., "Alkylating and Mutagenic Metabolites of Halogenated Olefins Produced by Human and Animal Tissue", Proc. Am. Assoc. Cancer Res. 17, 17, 1976.

[2]IARC, "Information Bulletin on the Survey of Chemicals being Tested for Carcinogenicity", International Agency for Research on Cancer, Lyon, Bulletin No. 5, July 1975.

[3]Bartsch, H., et al., "The Predictive Value of Tissue - Mediated Mutagenicity Assays to Assess the Carcinogenic Risk of Chemicals", IARC Sci. Pub. No. 12, 467-491, 1976.

[4]Greim, H. G., et al., "Mutagenicity *in vitro* and Potential Carcinogenicity of Chlorinated Ethylenes as a Function of Metabolic Oxdrane Formation", Biochem. Pharmacol., 24, 2013-2017, 1975.