

2,4-D

CASRN: 94-75-7

*For other data, click on the Table of Contents***Best Sections****Non-Human Toxicity Excerpts :**

Forms of 2,4-dichlorophenoxyacetic acid ... are herbicides used to control a wide variety of broadleaf and woody plants. Doses in the 2-year chronic/oncogenicity rat study were 0, 5, 75, and 150 mg/kg/day. The chronic toxicity paralleled subchronic findings, and a NOEL of 5 mg/kg/day was established. A slight increase in **astrocytomas** observed (in males only) at 45 mg/kg/day in a previously conducted chronic rat study was not confirmed in the present study at the high dose of 150 mg/kg/day. Doses in the 2-year mouse oncogenicity studies were 0, 5, 150, and 300 mg/kg/day for females and 0, 5, 62.5, and 125 mg/kg/day for males. No oncogenic effect was noted in the study. [Charles JM, et al; Fundam Appl Toxicol 33 (2): 166-172 (1996)]**PEER REVIEWED**

Human Toxicity Excerpts :

A cohort of herbicide applicators was formed in 1972 from the personnel records of four main Finnish employers involved in chemical brushwood control. ... The cohort included 1971 male workers who had been exposed to chlorinated phenoxyacids for at least two weeks during 1955-1971. Forty-five individuals had died during the same period. Thus there were 1926 persons alive in the beginning of 1972 through 1980, and for **cancer** morbidity from 1972 through 1978. ... During the nine year prospective follow-up period ... 105 persons had died from natural causes versus 155 expected (observed/expected 0.68). ... The ... most common types of tumor ... lung and stomach ... **cancers** closely corresponded to the expected figures. ... When the ten year period of latency was taken into account there were no significant differences between the observed and expected figures although for some tumors greater numbers were found than expected: 9 cases of lung **cancer** (6.6 expected), 2 bladder tumors (0.9 expected) and 2 lip **cancers** (0.5 expected). ... After making allowance for 10 and 15 year periods of latency which restricted the relatively small number of person years even more, no incr of **cancer** mortality was uncovered. ... This study /did not/ ... allow any assessment of the soft tissue sarcoma risk because the number of persons having a sufficiently long latency period is too small. /Chlorinated phenoxyacids/

[Riihimaki V et al; Chemosphere 12 (4/5): 79-84 (1983)]**PEER REVIEWED**

Human Toxicity Excerpts :

Some recent epidemiologic studies have suggested that chlorinated phenoxy acid herbicides are human carcinogens. The mortality experience in a cohort of 1,926 men who had sprayed 2,4-dichlorophenoxyacetic acid (2,4,-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) during 1955-1971 has been followed prospectively from 1972 to 1980. The total phenoxy acid exposure was generally rather low because the duration of work had mostly been less than two months. In 1972-1976 mortality from all natural causes in the cohort was only 54% of the expected value (based on age-specific rates for the general population), and in the succeeding 4 yr period 81% of the expected value. In the assessment of **cancer**, mortality allowance was made for 10- and 15-yr periods of latency between the first exposure and the start of the recording of vital status during the follow-up. No increase in **cancer** mortality was detected, and the distribution of **cancer** types was unremarkable. No

cases of death from lymphomas or soft tissue sarcomas were found. The study results must, however, be viewed with great caution owing to the small size of the cohort, the low past exposure, and the brief follow-up period.

[Riihimaki V et al; Scand J Work Environ Health 8: 37-42 (1982)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

The distribution of 3 common (14)C-labelled chlorophenoxyacetic acid herbicides (2,4-dichlorophenoxyacetic acid or 2,4-D, 2-methyl-4-chlorophenoxyacetic acid or MCPA, 2,4,5-trichlorophenoxyacetic acid or 2,4,5-T) into the different **brain** areas was studied in rats pretreated with toxic doses of the herbicides (238-475 mg/kg). Also, their binding to proteins in rat plasma was determined in vitro by increasing the concns of chlorophenoxyacetic acids in the incubate from 0 to 1 mg/ml. Both 2,4-D & 2-methyl-4-chlorophenoxyacetic acid pretreatments increased **brain** concns of (14)C-labelled herbicides more markedly than 2,4,5-T pretreatments. No essential differences were found in the distribution between the different **brain** areas. Protein-unbound fractions of 2,4-D & 2-methyl-4-chlorophenoxyacetic acid in the plasma were higher than those of 2,4,5-T but the highest herbicide concn increased the protein-unbound fraction of 2,4,5-T more (7-13 fold) than of 2,4-D & 2-methyl-4-chlorophenoxyacetic acid (5 fold). The greater incr in the penetration into the **brain** of 2,4-D & 2-methyl-4-chlorophenoxyacetic acid than of 2,4,5-T during their intoxication is due to factors other than the changes in their binding to plasma proteins & enhanced diffusion through the blood **brain** barrier.

[Tyynel a K et al; Arch Toxicol 64 (1): 61-5 (1990)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

Brain uptake is membrane-limited via a blood-**brain** barrier with saturable clearance from the CSF into the venous blood by the choroid plexus. The body has both a central and a deep compartment with saturable renal clearance from the central compartment. The model was used to examine venous plasma time course curves with experimental data from rats given 2,4-D by i.v. (5 or 90 mg/kg) or by oral ingestion (10, 50, or 150 mg/kg). The model was then extended to examine studies in which rabbit plasma, **brain**, and CSF concentrations were measured at 2 h after i.p. injection (40 mg/kg). In the rat, elimination was saturable ($V_{max2} = 3.45$ mg/h; $K_{m2} = 86$ mg/l) and the deep-compartment transfer coefficients were K_{12} (0.013 l/h) and K_{21} (0.048 l/h) between body and deep tissue compartment. Both oral and i.v. data were well described with these values. Limited single time point **brain** data from rabbits were analyzed with a lumped **brain** model assuming the generic model for 2,4-D in rat applies to the rabbit.

[Kim CS, et al; Toxicol Lett 74 (3): 189-201 (1994)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

The effects of 2,4-dichlorophenoxyacetic acid on **brain** and CSF biogenic amines and their acidic metabolites were studied in rats. Male Wistar rats were injected sc with 10, 30, 100, or 200 mg/kg sodium 2,4-dichlorophenoxyacetate, and then observed for clinical signs of toxicity. Rats were killed 0.5, 3.5, 7.5, 15.5, or 31.5 hours later and the CSF and **brains** were taken and assayed for dopamine, noradrenaline, 5-hydroxytryptamine, homovanillic acid, 3,4-dihydroxyphenylacetic acid, 5-hydroxyindoleacetic acid, and tryptophan. In rats injected with 200 mg/kg sodium 2,4-dichlorophenoxyacetate, **brain** 5-hydroxytryptamine was slightly increased after 3.5 hours and 5-hydroxyindoleacetic acid was increased by 3.2 times the control value 0.5 to 7.5 hours after dosing. Dopamine concentrations were slightly increased. CSF 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenylacetic acid, and homovanillic acid concentrations were significantly increased between

0.5 and 7.5 hours after dosing. The increases in CSF 5-hydroxyindoleacetic acid, 3,4-dihydroxyphenylacetic acid, and homovanillic acid concentration correlated well with the appearance of symptoms such as myotonia and lethargy. The 30 and 100 mg/kg doses caused significant increases in **brain** 5-hydroxyindoleacetic acid and CSF 3,4-dihydroxyphenylacetic acid, 5-hydroxyindoleacetic acid, and homovanillic acid concentrations after 1.5 hours. The 100 mg/kg dose caused a significant increase in **brain** homovanillic acid concentration at the same time point. The 10 mg/kg dose did not induce any increases in concentration of any of the amines or their metabolites. The 10 and 30 mg/kg doses did not induce any clinical signs of intoxication.

[Elo HA, MacDonald E; Arch Toxicol 63 (2): 127-30 (1989)]**PEER REVIEWED**

Interactions :

The effects of prenatal exposure to a 2,4-dichlorophenoxyacetic acid (2,4-D)/2,4,5-trichlorophenoxyacetic acid mixture on **brain** glutamate, gamma-aminobutyric acid (GABA), protein, DNA, and RNA were studied in rats. Pregnant Sprague Daley rats were orally administered 0, 50, or 125 mg/kg per day of a 1:1 mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid on gestational days six to 15. The mixture was known to contain 0.0125 ppm of 2,3,7,8-tetrachlorodibenzo-p-dioxin. On postnatal days one, 15, or 22, **brains** of neonates were separated into cerebrum, cerebellum, neocortex and thalamus/hypothalamus, and assayed for glutamate, DNA, RNA, protein and gamma-aminobutyric acid. Regional **brain** concentrations of protein, DNA, and RNA were not affected by prenatal exposure to the mixture, except for a decrease in the protein/DNA ratio in the hypothalamus induced by the 50 and 125 mg/kg doses on postnatal day 22. Glutamate was significantly reduced in the cerebrum and cerebellum in 1 day old neonates exposed prenatally to 50 and 125 mg/kg 2,4-dichlorophenoxyacetic acid/2,4,5-trichlorophenoxyacetic acid, while levels were not significantly altered in offspring examined at 15 and 22 postnatal days. gamma-Aminobutyric acid was not significantly affected in any **brain** region at any time.

[Mohammad FK, St Omer VEV; Bull Environ Contam Toxicol 40 (2): 294-300 (1988)]
PEER REVIEWED

Absorption, Distribution & Excretion :

The distribution of 2,4-dichlorophenoxyacetic acid (2,4-D) was examined in maternal & fetal rabbits. Pregnant New Zealand rabbits (28-30 d gestational age) were anesthetized with ketamine/xylazine & the femoral vein & artery were catheterized for compound admin & sampling. Dams received iv [14C] 2,4-D (12.5 microCi/kg) with unlabeled sodium 2,4-D (1, 10, or 40 mg/kg) in saline. Blood & tissue were collected up to 2 hr after dosing. Fetal to maternal plasma AUC ratios were 0.09, 0.07, & 0.16 after the 1, 10, or 40 mg/kg dose, respectively. Extraplasmic AUCs were greatest in maternal kidney & uterus & lowest in maternal & fetal **brain**. A >fourfold elevation in fetal AUC was found when the dose was increased from 10 to 40 mg/kg, suggesting saturation of maternal plasma binding of 2,4-D. Although the in vitro fetal **brain** tissue to incubation media ratio was unity (1.03 + or - 0.1, mean + or - SD), fetal **brain** AUCs were 10% or less of the fetal plasma AUCs, indicating the **brain** barrier system to 2,4-D is functioning in the late-gestation fetal rabbit.

[Sandberg JA, et al; J Toxicol Environ Health 49 (5): 497-509 (1996)]**PEER REVIEWED**

Human Toxicity Excerpts :

A previous case-control study which used the occupational information available on the New Zealand Cancer Registry found that agricultural workers were at increased risk of developing non-Hodgkin's lymphoma. The findings are now presented for the second phase of the study which entailed

interviewing 83 cases of non-Hodgkin's lymphoma registered under code 202 of the International Classification of Diseases together with 168 controls with other types of **cancer** and 228 general population controls. The findings for the two control groups were similar, and there were no significant differences between cases and controls regarding potential exposure to phenoxyherbicides (odds ratio= 1.4, 90% confidence limits 0.7-2.5, p= 0.26) or chlorophenols (odds ratio= 1.3, 90% confidence limits 0.6-2.7, p= 0.39). The odds ratio for fencing work, necessitating exposure to several potential risk factors including arsenic and sodium pentachlorophenate was 2.0 (90% confidence limits 1.3-3.0, p= 0.01). The odds ratio for employment in a meat works, necessitating potential exposure to 2,4,6-trichlorophenol and zoonotic viruses, was 1.8 (90% confidence limits 1.1-3.1, p= 0.04). There was a significant statistical interaction between the risks associated with these two activities, the odds ratio for involvement in both activities compared with involvement in neither being 5.7 (90% confidence limits 2.3-14.3, p= 0.03). /Phenoxyherbicides, chlorophenols, arsenic, and sodium pentachlorophenate/

[Pearce NE et al; Br J Ind Med 43: 75-83 (1986)]**PEER REVIEWED**

Human Toxicity Excerpts :

Phenoxyherbicides ... have been widely used in New Zealand for over 30 years. In the light of the Swedish studies reporting an association between exposure to phenoxyherbicides or chlorophenols and soft tissue sarcoma, a case-control study was undertaken that involved interviewing 82 subjects (cases) with soft tissue sarcoma and 92 controls with other types of **cancer**. For those potentially exposed to phenoxyherbicides for more than one day not in the five years before **cancer** registration, the estimate of relative risk was 1.3, with 90% confidence limits of 0.6-2.5. The comparable relative risk estimate for chlorophenol exposure was 1.5 with 90% confidence limits of 0.5-4.5. The discovery of cases in trichlorophenol manufacturing plants in the United States lended support to the Swedish findings, but further studies are needed to conclude whether human exposure to these chemicals truly increases the risk of soft tissue sarcoma. /Phenoxyherbicides or chlorophenols/

[Smith AH et al; JNCI 73 (5): 1111-7 (1984)]**PEER REVIEWED**

Interactions :

Rats exposed in utero on gestational days 6-15, to nonfetotoxic and grossly nonteratogenic mixtures (50 or 100 mg/kg) of 2,4-D/2,4,5-T ... without significant contamination with 2,3,7,8-tetrachloro-p-dioxin manifested subtle developmental neurotoxicity. This dose did not affect maternal weight gain during pregnancy, length of gestation, total number of live pups, or male to female ratio of the litters. Maturation of swimming behavior was significantly delayed on postnatal day 7 in both treatment group. The concentration of norepinephrine in whole **brain** was significantly increased on postnatal day 15 in both treatment groups, whereas the concentration of dopamine was increased on postnatal day 15 at 100 mg/kg. The turnover and efflux rate constant of dopamine in whole **brain** were significantly reduced whereas the turnover time increased on postnatal day 3. The efflux rate constant for norepinephrine decreased and the turnover time increased significantly on postnatal day 15 at 100 mg/kg.

[St Omer VE, Mohammad FK; Neuropharmacology 26 (9): 1351-8 (1987)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

We studied offspring of dams which had received 50, 70 or 700 mg/kg of 2,4-Dichlorophenoxyacetic acid (2,4-D) during nursing. Neonatal tissues and the stomach content (milk) were examined up to 16 post natal days to detect body and organs weight alterations and 2,4-D residues after 2,4-D maternal

dosing every-other-day, from post natal day 1. We detected 2,4-D residues in stomach content, blood, **brain** and kidney of 4-day-old neonates breast-fed by 2,4-D exposed mothers and onward. 2,4-D residues were dose- and exposure-time-dependent. The highest dose impaired body growth, as well as low tissue weights and diminished stomach contents. Levels of 2,4-D residues in stomach content, blood, kidney and **brain** of post natal rats (age PD 4-PD 16) fed through lactation from dams treated with 2,4-D demonstrated that 2,4-D was transferred to the neonates and the diminished body and tissues weight during this developmental period could be due to a diminished milk intake or/and to the direct 2,4-D toxic effect. Besides, when the herbicide treatment (100 mg 2,4-D/kg) was withdrawn from the dams, 2,4-D residues remained in the stomach content of neonates for at least one week.

[Sturtz N, et al; Neurotoxicology 21 (1-2): 147-154 (2000)]**PEER REVIEWED**

Milk Concentrations :

We studied offspring of dams which had received 50, 70 or 700 mg/kg of 2,4-Dichlorophenoxyacetic acid (2,4-D) during nursing. Neonatal tissues and the stomach content (milk) were examined up to 16 post natal days to detect body and organs weight alterations and 2,4-D residues after 2,4-D maternal dosing every-other-day, from post natal day 1. We detected 2,4-D residues in stomach content, blood, **brain** and kidney of 4-day-old neonates breast-fed by 2,4-D exposed mothers and onward. 2,4-D residues were dose- and exposure-time-dependent. The highest dose impaired body growth, as well as low tissue weights and diminished stomach contents. Levels of 2,4-D residues in stomach content, blood, kidney and **brain** of post natal rats (age PD 4-PD 16) fed through lactation from dams treated with 2,4-D demonstrated that 2,4-D was transferred to the neonates and the diminished body and tissues weight during this developmental period could be due to a diminished milk intake or/and to the direct 2,4-D toxic effect. Besides, when the herbicide treatment (100 mg 2,4-D/kg) was withdrawn from the dams, 2,4-D residues remained in the stomach content of neonates for at least one week.

[Sturtz N, et al; Neurotoxicology 21 (1-2): 147-154 (2000)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

Levels of 2,4-D were measured in the rat **brain** and cerebrospinal fluid after a 100 mg/kg (slightly toxic) dose. In comparison, (250 mg/kg) produced myotonia and lethargy and resulted in 11- and 39-fold increases in 2,4-D concentration in the **brain** and cerebrospinal fluid respectively, while 500 mg/kg produced 18- and 67-fold increases, in 2,4-D concentrations, respectively. Increases in hepatic 2,4-D levels were also produced, although less dramatic.

[Vet Admin Rev Lit on Herbicides Vol 1 p.4-3 (1981) VA Contract No. V101(93) P-823]**PEER REVIEWED**

Human Toxicity Excerpts :

An earlier cohort study of Swedish railroad workers indicated a possible relationship between exposure to herbicides and an increased overall tumor morbidity and mortality. The cohort of 348 individuals has now been followed through October 1978. In this updated analysis of the causes of death among railroad workers, the observed number of tumor deaths was higher than expected, especially among individuals exposed in the earlier years of the study to both amitrol and phenoxy acids. No specific type of tumor predominated although there were three stomach and 3 lung **cancers**.
... /Amitrol and Phenoxy acids/

[Axelson O et al; Scand J Work Environ 6: 73-9 (1980)]**PEER REVIEWED**

Human Toxicity Excerpts :

The purpose of this cohort study is to shed further light on the potential carcinogenic effect indicated by a Swedish case control study of the 2,4-dichlorophenol and 4-chloro-ortho-cresol based phenoxy herbicides, unlikely to be contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. In the present study it was the intention to include all persons in manufacture of phenoxy herbicides in Denmark before 1982. The predominant product was MCPA and only a very limited /quantity/ of 2,4,5-T was processed in one of the two factories included in the study. ... 99% of the registered employees could be followed-up. ... Five cases of soft tissue sarcomas (STS) were observed among male employees in contrast to 1.84 expected cases. This result supports the Swedish observation of an increased risk of soft tissue sarcomas following exposure to phenoxy herbicides unlikely to be contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin. ... Seven cases of malignant lymphomas were observed among male employees in contrast to 5.37 expected does not support the Swedish observation of an excess risk. ... Among males thus employed 11 lung cancer cases were observed in contrast to 5.33 expected. /Phenoxy herbicides or 4-chloro-ortho-cresol/

[Lyng E; Br J Cancer 52: 259-74 (1985)]**PEER REVIEWED**

Human Toxicity Excerpts :

These studies further indicated that this crop growing area used more chlorophenoxy herbicides and fungicides than elsewhere in Minnesota. Based on frequency of use and known biology, certain herbicides, pesticide additives, fungicides, and mycotoxins are suspect agents. To define whether these agents affect developmental endpoints in vitro, 16 selected agrochemicals were examined using the MCF-7 breast cancer cell line. In the flow cytometric assay, cell proliferation in this estrogen-responsive cell line indicates xenobiotic-mediated estrogenic effects. Cell viability, morphology, ploidy, and apoptosis were incorporated in this assay. Data showed that the adjuvants X-77 and Activate Plus induced significant cell proliferation at 0.1 and 1 microg/ml. The commercial-grade herbicides 2,4-D LV4 and 2,4-D amine induced cell proliferation at 1 and 10 microg/ml. The reagent-grade 2,4-D products failed to induce proliferation over the same concentration range, suggesting that other ingredients in the commercial products, presumably adjuvants, could be a factor in these results. The fungicides triphenyltin and mancozeb induced apoptosis at concentrations of 4.1 microg/ml (10(-5) M) and 50 microg/ml, respectively. Triphenyltin also induced aneuploidy (C2/M arrest) at 0.41 microg/ml (10(-6) M).

[Lin N, Garry VF; J Toxicol Environ Health A 60 (6): 423-439 (2000)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

The effects of chlorinated phenols and phenates on biochemical parameters were investigated in liver and white blood cells of 90 day old female Sprague-Dawley rats in an effort to understand why 2,4,6-trichlorophenol (2,4,6-T) causes cancer in rodents while 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenol (2,4,5-T), which are structurally similar compounds, do not. Two oral doses of each of these compound were given to separate groups of rats 21 and 4 hours prior to sacrifice. Each dose was 1/5 of the median lethal dose. No DNA damage in rat liver or white blood cells was noted. No changes were found in serum alanine-aminotransferase activity or hepatic glutathione.

[Kitchin KT, Brown JL; Toxicol Environ Chemistry 16 (3): 165-72 (1988)]**PEER REVIEWED**

Human Toxicity Excerpts :

The risk of soft tissue sarcoma following possible exposure to phenoxy acid herbicides was studied in

354,620 Swedish men, who were employed in agriculture or forestry according to a national census in 1960. This cohort was further divided into six subcohorts. The reference cohort encompassed 1,725,845 Swedish men employed in other industries. All persons were followed up in the cancer-environment register during the period 1961-79. A total of 331 cases of soft tissue sarcomas was observed in the study cohort and there were 1,508 cases in the reference group (relative risk 0.9; 95% confidence interval, 0.8-1.0). No subcohort of agricultural or forestry workers showed any significantly increased relative risk, nor was there any significant difference in relative risk between the subcohorts. Despite the greatly increased use of phenoxy acid herbicides from 1947 to 1970, no time related increase in the relative risk of soft tissue sarcoma was found in the total cohort or in any of the subcohorts. /Phenoxy acid herbicides/

[Wiklund K, Holm LE; JNCI 76 (2): 229 (1986)]**PEER REVIEWED**

Human Toxicity Excerpts :

A female suicide victim (age not specified or body weight) ingested an unknown quantity of 2,4-D. Symptomatology included: Loss of consciousness; vomiting; uterine bleeding; tachycardia and circulatory failure. Death occurred in about 30 hr. Edema and congestion of **brain**, fatty liver cell changes, fatty changes in kidney tubules pulmonary hyperemia and edema with isolated hemorrhages /were noted/. 2,4-D concentration in tissues was 20-116 mg/kg.

[Geldmacher Von Mallinckrodt M, Lautenbach L; Arch Toxicol 21: 261-78 (1966) as cited in WHO; Environ Health Criteria: 2,4-Dichlorophenoxyacetic Acid (2,4-D) p.84 (1984)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

2,4-Dichlorophenoxyacetic acid (2,4-D), a widely used broadleaf herbicide, is under investigation in a study of peroxisome proliferators. To supplement that study, male and female rats, mice, and hamsters were dosed with ¹⁴C-2,4-D orally at 5 and 200 mg/kg and tissue distributions were determined. Blood, liver, kidney, muscle, skin, fat, **brain**, testes, and ovaries were examined. At early time points tissues from female rats consistently contained higher amounts of radioactivity than did corresponding tissues from males (up to 9 times). By 72 hr, tissue levels were equivalent and males and females had excreted equal amounts of radioactivity. This sex difference was absent in mice. In hamsters, males had higher tissue levels than females. Taurine, glycine, and glucuronide conjugates of 2,4-D were excreted along with parent. Metabolite profiles differed between species qualitatively and quantitatively; however, differences between sexes were minimal. Plasma elimination curves were generated in male and female rats after iv and oral administration. Kinetic analysis revealed significant differences in elimination and exposure parameters consistent with a greater ability to clear 2,4-D by male rats relative to females.

[Griffin RJ, et al; Drug Metab Dispos 25 (9): 1065-1071 (1997)]**PEER REVIEWED**

Interactions :

Probenecid increased the acute toxicity of chlorophenoxyacetic acids (2,4-D, 2,4,5-T and MCPA) in rats. Probenecid increased the **brain** to plasma ratios of all the three (¹⁴C)-labelled chlorophenoxyacetic acids. The increase was due only partly to the displacement of chlorophenoxyacids from their binding sites in rat plasma proteins by probenecid. 3. Probenecid did not change significantly the intracerebral distribution pattern of (¹⁴C)-labelled chlorophenoxyacetic acids.

[Ylitalo P et al; Gen Pharmacol 21 (5): 811-4 (1990)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

Pretreatment of rats with 2,4-D (250 mg/kg, sc) so occupied binding sites on plasma proteins that the distribution of (14)C-2,4-D admin iv 3.5 to 4.5 hr later was changed relative to controls, the concn being less in the plasma & kidney & greater in the liver, **brain**, spinal fluid, testis, lung, heart, & muscle.

[Hayes, Wayland J., Jr. Pesticides Studied in Man. Baltimore/London: Williams and Wilkins, 1982. 522]**PEER REVIEWED**

Absorption, Distribution & Excretion :

... Female dogfish sharks (*Squalus acanthias*) were admin (14)C-2,4-D iv. Urine, bile, & blood were collected & analyzed for radioactivity, along with tissues. Urine contained 53% of the admin dose of 2,4-D in 4 hr, 68% in 1 day, & 90% in 6 days. 2% of the dose was excreted in bile in 6 days. From 94-98% of the radioactivity in urine & bile was conjugated to taurine, 2-4% was present as 2,4-D, acid & 4% as 2 unidentified metabolites. The half-life of plasma clearance of 2,4-D was 44 min. Tissue levels for the kidney & liver were 2-40 times that for the plasma, & were lower than plasma levels for muscle, **brain**, & cerebrospinal fluid. Plasma binding ... was about 57% for concns up to 50 ug/ml herbicide. ...

[Vet Lit on Herbicides Vol 2 p.133 (1981) VA Contract No. V101(93)P-823]**PEER REVIEWED**

Human Toxicity Excerpts :

A male suicide victim 26 years of age ingested a mixture of 360 ml 2,4-D and mecoprop amine salt (10.6%, 11.6% ai) and 360 ml chlorpyrifos in kerosene (6.7% ai) plus few granules of warfarin (0.025% ai, 2,4-D= 600 mg/kg bw; Mecoprop= 600 mg/kg) symptomatology included: Coma with pinpoint pupils; tachycardia; hypertension; myoclonus; diarrhea; then hypotension; cardiac arrhythmias; asystole; and death after 30 hr. Plasma 2,4-D concentrations were 321 mg/kg at 1.6 hr, 540.9 mg/kg at 21 hr, 480.8 mg/kg at 30 hr. Urinary concentration (on admission) was 230.3 mg/kg, gastric content (on admission) was 108.2 mg/kg, tissue (post-mortem) was: **brain**, 186.4 mg/kg; blood, 389.5 mg/kg; liver, 293.5 mg/kg; heart, 301.2 mg/kg; and kidney: 315.0 mg/kg. /2,4-D, mecoprop amine salt, chlorpyrifos and warfarin/

[Osterloh J et al; J Analyt Toxicol 7: 125-9 (1983) as cited in WHO; Environ Health Criteria 29: 2,4-Dichlorophenoxyacetic Acid (2,4-D) p.85 (1984)]**PEER REVIEWED**

Emergency Medical Treatment :

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The following Overview, *** CHLOROPHENOXY COMPOUNDS *** , is relevant for this HSDB record chemical.

Life Support:

- o This overview assumes that basic life support measures have been instituted.

Clinical Effects:

SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

- o ACUTE INGESTION - Miosis, coma, fever, hypotension, emesis, tachycardia, bradycardia, ECG abnormalities, muscle rigidity, possible respiratory failure, pulmonary edema, and rhabdomyolysis may occur.
- o PATHOPHYSIOLOGY - These agents are primarily irritants, but one case of degenerative **brain** cell changes and CNS toxicity has been reported.

HEENT

0.2.4.1 ACUTE EXPOSURE

- o Eye, nose, and mouth irritation are possible with direct contact.

CARDIOVASCULAR

0.2.5.1 ACUTE EXPOSURE

- o Tachycardia, bradycardia, ECG abnormalities, asystole, other dysrhythmias, and hypotension have been reported with overdose.

RESPIRATORY

0.2.6.1 ACUTE EXPOSURE

- o Ingestion of large amounts may cause bradypnea, respiratory failure, hyperventilation, or pulmonary edema.

NEUROLOGIC

0.2.7.1 ACUTE EXPOSURE

- o LOW DOSE EXPOSURES - Vertigo, headache, malaise, and paresthesias may occur depending on the specific compound involved.
- o HIGH DOSE EXPOSURES - Muscle twitching, spasms, profound weakness, polyneuritis, and unconsciousness may occur depending on the specific compound involved.
- o IDIOSYNCRATIC REACTIONS - Peripheral neuropathies

GASTROINTESTINAL

0.2.8.1 ACUTE EXPOSURE

- o Nausea, vomiting, and diarrhea have been reported. Necrosis of the gastrointestinal mucosa has been reported.

HEPATIC

0.2.9.1 ACUTE EXPOSURE

- o Elevated LDH, AST (SGOT), and ALT (SGPT) have been reported.

GENITOURINARY

0.2.10.1 ACUTE EXPOSURE

- o Albuminuria and porphyria may occur; renal failure due to rhabdomyolysis is also possible.

FLUID-ELECTROLYTE

0.2.12.1 ACUTE EXPOSURE

- o Ingestion of 2,4-D has produced hypocalcemia, hyperkalemia, and hypophosphatemia.

HEMATOLOGIC

0.2.13.1 ACUTE EXPOSURE

- o Thrombocytopenia is the primary hematologic effect. Leukopenia has also been reported.

DERMATOLOGIC

0.2.14.1 ACUTE EXPOSURE

- o Direct contact may cause skin irritation. Chlorodioxin

contamination of products may produce chloracne with heavy exposure.

MUSCULOSKELETAL

0.2.15.1 ACUTE EXPOSURE

- o Muscle cramps, muscle rigidity, elevated creatinine kinase, and rhabdomyolysis were reported after ingestion of MCP. EMG abnormalities were described in a case of 2,4-D ester exposure.

REPRODUCTIVE HAZARDS

- o 2,4-D and 2,4,5-T have caused adverse reproductive effects in experimental animals. Allegations of human birth defects due to these compounds have not been confirmed.

CARCINOGENICITY

0.2.21.1 IARC CATEGORY

- o 2,4-D, 2,4,5-T, and MCP are classified as possibly carcinogenic in humans by the IARC.

0.2.21.2 HUMAN OVERVIEW

- o Human studies are controversial, but have suggested a relationship between chlorophenoxy herbicides and both soft tissue sarcoma and non-Hodgkin's lymphoma.

0.2.21.3 ANIMAL OVERVIEW

- o Animal studies are limited, but have generally been negative.

GENOTOXICITY

- o The chlorophenoxy herbicides have produced mixed negative and positive responses in various genotoxicity test systems.

Laboratory:

- o These herbicides can be measured in the urine, but the values are not clinically useful.
- o Erythrocyte cholinesterase is not affected by these herbicides.
- o Obtain baseline CBC, platelet count, serum electrolytes, and renal/hepatic function tests. Monitor LDH, AST (SGOT), ALT (SGPT), alkaline phosphatase, CPK, arterial pH, and bicarbonate.
- o Monitor urine for pH, protein, RBCs, myoglobin, and urinary output.

Treatment Overview:

SUMMARY EXPOSURE

- o INGESTION - No specific antidote. Monitor for seizures, gastrointestinal irritation, possible liver, kidney, peripheral nerve, or muscle damage, cardiac arrhythmias, ECG abnormalities, acidosis, dyspnea, headache, coma, hyperthermia, and hypotension.
 1. HOME - Induced emesis using syrup of ipecac may be used at home assuming no contraindications exist.
- o MEDICAL FACILITY -
 1. Gastric lavage and activated charcoal/cathartic are probably more useful decontamination methods. Monitor respiratory status, electrolytes, renal and liver function tests, CBC, platelet count, and cardiac status.
 2. Observe for adequate hydration, myoglobinuria, or metabolic acidosis. Alkaline diuresis may be necessary. Treat hyperthermia with sponge baths.
- o INHALATION - Observe for dyspnea, hypoxia, and non-cardiogenic pulmonary edema.

ORAL EXPOSURE

- o Treat ingestions of greater than 40 milligrams per kilogram with gastric decontamination if within 4 hours of ingestion.
- o ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.
- o URINARY ALKALINIZATION - May enhance elimination and may be indicated when coma, acidosis, or myoglobinemia is present.
- o VENTRICULAR DYSRHYTHMIAS/SUMMARY: Institute continuous cardiac monitoring, obtain an ECG, and administer oxygen. Evaluate for hypoxia, acidosis, and electrolyte disorders. Lidocaine and amiodarone are generally first line agents for stable monomorphic ventricular tachycardia, particularly in patients with underlying impaired cardiac function. Sotalol is an alternative. Amiodarone and sotalol should be used with caution if a substance that prolongs the QT interval and/or causes torsades de pointes is involved in the overdose. Unstable rhythms require cardioversion.
- 1. LIDOCAINE: ADULT: LOADING DOSE: 50 to 100 mg IV at 25 to 50 mg/min, maximum 200 to 300 mg over one hour. INFUSION: 1 to 4 mg/min. PEDIATRIC: LOADING DOSE: 1 mg/kg; INFUSION: 20 to 50 mcg/kg/min. Monitor ECG continuously.

INHALATION EXPOSURE

- o INHALATION: Move patient to fresh air. Monitor for respiratory distress. If cough or difficulty breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer oxygen and assist ventilation as required. Treat bronchospasm with beta2 agonist and corticosteroid aerosols.
- o ACUTE LUNG INJURY: Maintain ventilation and oxygenation and evaluate with frequent arterial blood gas or pulse oximetry monitoring. Early use of PEEP and mechanical ventilation may be needed.

EYE EXPOSURE

- o DECONTAMINATION: Irrigate exposed eyes with copious amounts of tepid water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist, the patient should be seen in a health care facility.

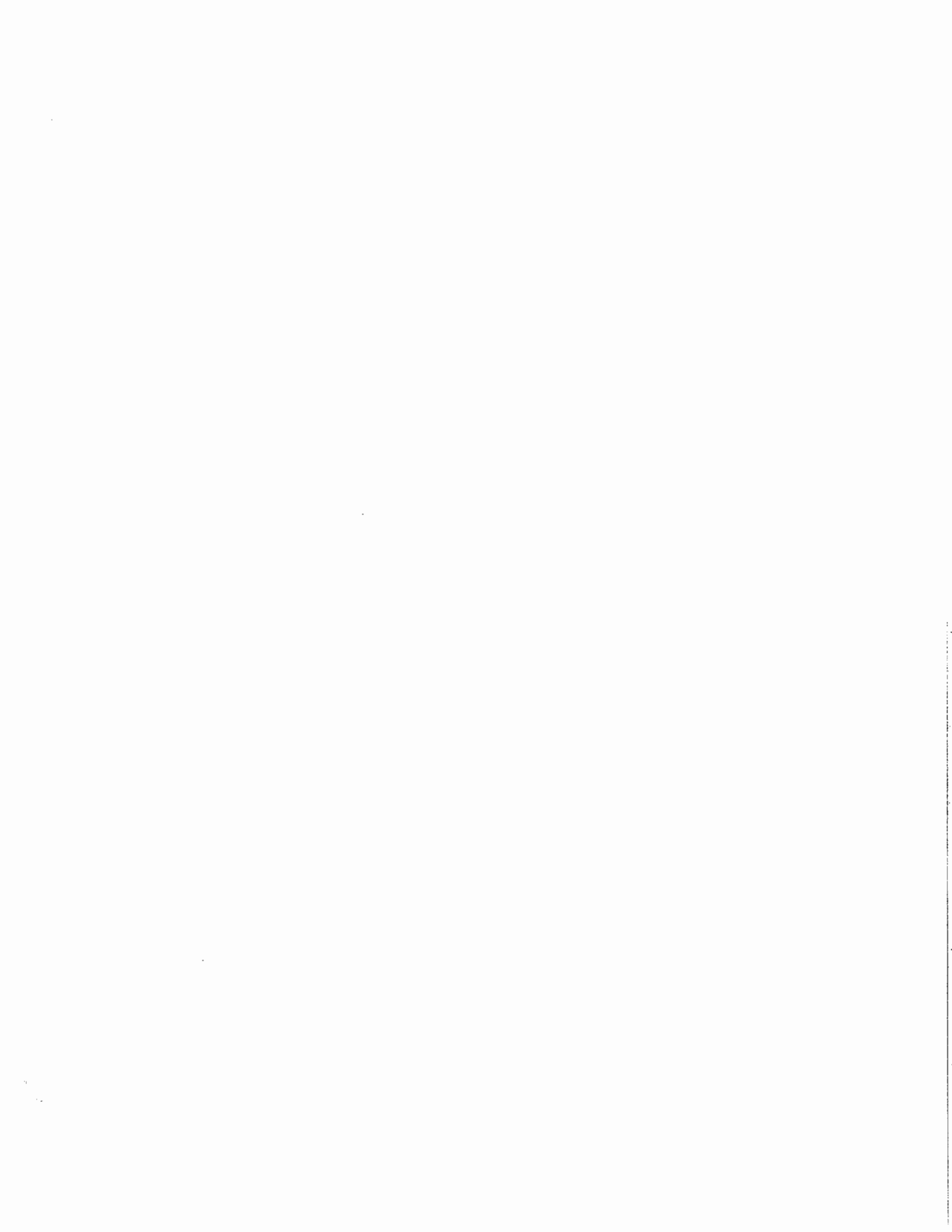
DERMAL EXPOSURE

- o DECONTAMINATION: Remove contaminated clothing and jewelry. Wash the skin, including hair and nails, vigorously; do repeated soap washings. Discard contaminated clothing.
- o Treat dermal irritation or burns with standard topical therapy. Patients developing dermal hypersensitivity reactions may require treatment with systemic or topical corticosteroids or antihistamines.

Range of Toxicity:

- o Limited data are available.
- o Fatalities have been seen following ingestion of 80 mg/kg.
- o Intravenous injection of 28 mg/kg of 2,4-D was tolerated; 50 mg/kg produced toxicity.

[Rumack BH: POISINDEX(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003. Hall AH & Rumack BH (Eds): TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003.]**PEER REVIEWED**



Absorption, Distribution & Excretion :

The levels of **1,2-dichloroethane** (1,2-EDC), & its metabolites 2-chloroethanol, monochloroacetic acid, & 2-chloroacetaldehyde were determined by gas chromatography in the organs of human cadavers in cases of acute poisoning. The highest **1,2-dichloroethane** levels were observed in the stomach & omentum; lower levels in the kidney, spleen, **brain**, heart, large & small intestines, & blood, & no detectable amounts in the liver. 2-Chloroethanol & monochloroacetic acid, minor metabolites of **1,2-dichloroethane**, were detected in small amounts in the myocardium, **brain**, stomach, & small intestine. 2-Chloroacetaldehyde, because it is a reactive intermediate in the biotransformation of **1,2-dichloroethane** was not detectable in the organs. The administration of acetylcysteine to acutely intoxicated humans showed no positive clinical effect. ...

[Luzhnikov EA et al; Sud Med Ekspert 28 (2): 47-9 (1985)]**PEER REVIEWED**

Human Toxicity Excerpts :

Neurological effects, such as CNS depression, have been reported in humans following acute oral intoxication with **1,2-dichloroethane** Morphological alterations in the nervous system were observed in patients who died of acute oral poisoning by **1,2-dichloroethane**. These alterations incl vascular disorders, diffuse changes in cerebellar cells, parenchymatous changes in **brain** and spinal cord, myelin degeneration, and hyperemia and hemorrhage of the **brain** The morphological changes observed in the cerebellum may affect the coordination of muscular movements.

[DHHS/ATSDR; Toxicological Profile for 1,2-Dichloroethane p. 51 TP-93/06 (1994)]
PEER REVIEWED

Human Toxicity Excerpts :

Fatal dichloromethane poisoning in 2 workers following inhalation exposure was described. The 2 men (50 & 55 yr old) were employed at an Italian chemical factory & were found dead in a 2 m deep well where they had been burying barrels of chemical waste. The barrels contained mixed solvent & solid wastes. On site air sampling found dichloromethane vapor concns ranging up to 582 mg/l. Concns below 6 mg/l of **1,2-dichloroethane**, 1,1,1-trichloroethane & styrene were also detected. Blood samples collected 24 hr after death contained 571.6 & 600.9 mg/l dichloromethane. Smaller concns of **1,2-dichloroethane**, 1,1,1-trichloroethane & styrene were also found. Blood carboxyhemoglobin concns of 30% saturation were also found. Autopsies revealed extensive **brain** & lung edema & congestion gastric congestion & erosive multifocal gastritis in both victims. Kidney congestion was manifested as tubular swelling & degeneration, glomerular swelling & congestion of the vessels. Congestion was also seen in the liver, spleen & adrenals. ... Both deaths were caused by acute inhalation of extremely high dichloromethane vapor concns. ...

[Manno M et al; Human Exp Toxicol 11 (6): 540-45 (1992)]**PEER REVIEWED**

Clinical Laboratory Methods :

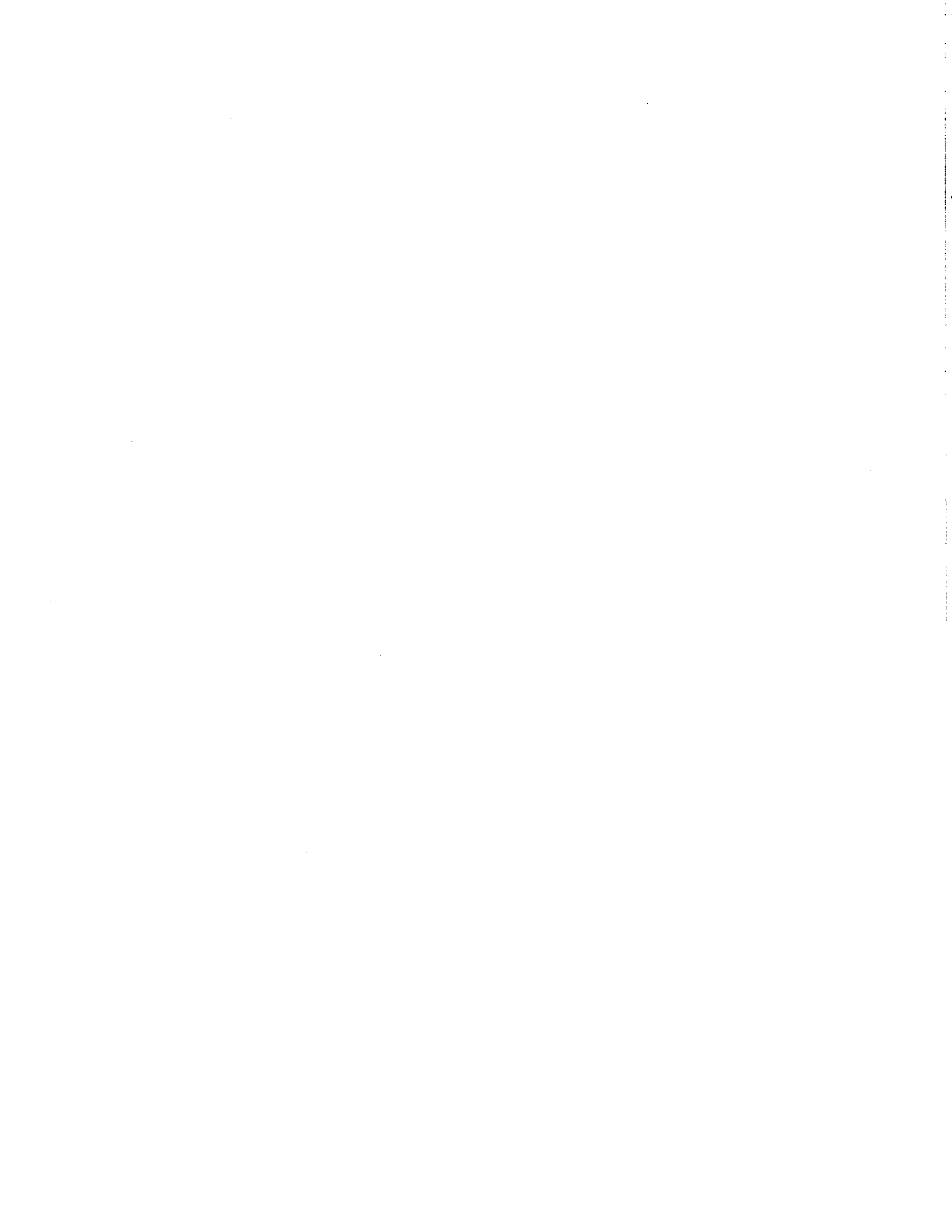
DETERMINATION OF **1,2-DICHLOROETHANE** IN RAT BLOOD, LIVER, LUNG, SPLEEN, **BRAIN**, KIDNEY & EPIDIDYMAL ADIPOSE TISSUE BY HEAD-SPACE GAS CHROMATOGRAPHY. METHOD IS SENSITIVE TO 25 NG/ML OF BLOOD OR 50 NG/G OF TISSUE.

[ZUCCATO E ET AL; ANALYTICAL LETTERS 13 (B5): 363 (1980)]**PEER REVIEWED**

Human Toxicity Excerpts :

A 51-yr old man who inhaled a concentrated vapor of **1,2-dichloroethane** for only 30 min died 4 days later from cardiac arrhythmia No attempt was made to estimate the actual exposure concn. An autopsy revealed congestion of the lungs, degenerative changes in the myocardium, liver necrosis, renal tubular necrosis, and shrunken nerve cells in the **brain**.

[DHHS/ATSDR; Toxicological Profile for 1,2-Dichloroethane p. 11 TP-93/06 (1994)]
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Public Health Statement for

Polycyclic Aromatic Hydrocarbons (PAHs)

August 1995

This Public Health Statement is the summary chapter from the Toxicological Profile for Polycyclic Aromatic Hydrocarbons (PAHs). It is one in a series of Public Health Statements about hazardous substances and their health effects. A shorter version, the ToxFAQs™, is also available. This information is important because this substance may harm you. The effects of exposure to any hazardous substance depend on the dose, the duration, how you are exposed, personal traits and habits, and whether other chemicals are present. For more information, you may call the ATSDR Information Center at 1-888-422-8737.

This statement was prepared to give you information about polycyclic aromatic hydrocarbons (PAHs) and to emphasize the human health effects that may result from exposure to them. The Environmental Protection Agency (EPA) has identified 1,408 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. PAHs have been found in at least 600 of the sites on the NPL. However, the number of NPL sites evaluated for PAHs is not known. As EPA evaluates more sites, the number of sites at which PAHs are found may increase. This information is important because exposure to PAHs may cause harmful health effects and because these sites are potential or actual sources of human exposure to PAHs.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to substances such as PAHs, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 What are PAHs?

PAHs are a group of chemicals that are formed during the incomplete burning of coal, oil, gas, wood, garbage, or other organic substances, such as tobacco and charbroiled meat. There are more than 100 different PAHs. PAHs generally occur as complex mixtures (for example, as part of combustion products such as soot), not as single compounds. PAHs usually occur naturally, but they can be manufactured as individual compounds for research purposes; however, not as the mixtures found in combustion products. As pure chemicals, PAHs generally exist as colorless, white, or pale yellow-green solids. They can have a faint, pleasant odor. A few PAHs are used in medicines and to make dyes, plastics, and pesticides. Others are contained in asphalt used in road construction. They can also be found in substances such as crude oil, coal, coal tar pitch, creosote, and roofing tar. They are found throughout the environment in the air, water, and soil. They can occur in the air, either attached to dust particles or as solids in soil or sediment.

Although the health effects of individual PAHs are not exactly alike, the following 17 PAHs are considered as a group in this profile:

- acenaphthene
- acenaphthylene
- anthracene
- benz[a]anthracene
- benzo[a]pyrene
- benzo[e]pyrene
- benzo[b]fluoranthene
- benzo[g,h,i]perylene
- benzo[j]fluoranthene
- benzo[k]fluoranthene
- chrysene
- dibenz[a,h]anthracene
- fluoranthene
- fluorene
- indeno[1,2,3-c,d]pyrene
- phenanthrene
- pyrene

These 17 PAHs were chosen to be included in this profile because (1) more information is available on these than on the others; (2) they are suspected to be more harmful than some of the others, and they exhibit harmful effects that are representative of the PAHs; (3) there is a greater chance that you will be exposed to these PAHs than to the others; and (4) of all the PAHs analyzed, these were the PAHs identified at the highest concentrations at NPL hazardous waste sites.

1.2 What happens to PAHs when they enter the environment?

PAHs enter the environment mostly as releases to air from volcanoes, forest fires, residential wood burning, and exhaust from automobiles and trucks. They can also enter surface water through discharges from industrial plants and waste water treatment plants, and they can be released to soils at hazardous waste sites if they escape from storage containers. The movement of PAHs in the environment depends on properties such as how easily they dissolve in water, and how easily they evaporate into the air. PAHs in general do not easily dissolve in water. They are present in air as vapors or stuck to the surfaces of small solid particles. They can travel long distances before they return to earth in rainfall or particle settling. Some PAHs evaporate into the atmosphere from surface waters, but most stick to solid particles and settle to the bottoms of rivers or lakes. In soils, PAHs are most likely to stick tightly to particles. Some PAHs evaporate from surface soils to air. Certain PAHs in soils also contaminate underground water. The PAH content of plants and animals living on the land or in water can be many times higher than the content of PAHs in soil or water. PAHs can break down to longer-lasting products by reacting with sunlight and other chemicals in the air, generally over a period of days to weeks. Breakdown in soil and water generally takes weeks to months and is caused primarily by the actions of microorganisms.

1.3 How might I be exposed to PAHs?

PAHs are present throughout the environment, and you may be exposed to these substances at home, outside, or at the workplace. Typically, you will not be exposed to an individual PAH, but to a mixture of PAHs.

In the environment, you are most likely to be exposed to PAH vapors or PAHs that are attached to dust and other particles in the air. Sources include cigarette smoke, vehicle exhausts, asphalt roads, coal, coal tar, wildfires, agricultural burning, residential wood burning, municipal and industrial waste incineration, and hazardous waste sites. Background levels of some representative PAHs in the air are reported to be 0.02–1.2 nanograms per cubic meter (ng/m^3 ; a nanogram is one-millionth of a milligram) in rural areas and 0.15–19.3 ng/m^3 in urban areas. You may be exposed to PAHs in soil near areas where coal, wood, gasoline, or other products have been burned. You may be exposed to PAHs in the soil at

or near hazardous waste sites, such as former manufactured-gas factory sites and wood-preserving facilities. PAHs have been found in some drinking water supplies in the United States. Background levels of PAHs in drinking water range from 4 to 24 nanograms per liter (ng/L; a liter is slightly more than a quart).

In the home, PAHs are present in tobacco smoke, smoke from wood fires, creosote-treated wood products, cereals, grains, flour, bread, vegetables, fruits, meat, processed or pickled foods, and contaminated cow's milk or human breast milk. Food grown in contaminated soil or air may also contain PAHs. Cooking meat or other food at high temperatures, which happens during grilling or charring, increases the amount of PAHs in the food. The level of PAHs in the typical U.S. diet is less than 2 parts of total PAHs per billion parts of food (ppb), or less than 2 micrograms per kilogram of food ($\mu\text{g}/\text{kg}$; a microgram is one-thousandth of a milligram).

The primary sources of exposure to PAHs for most of the U.S. population are inhalation of the compounds in tobacco smoke, wood smoke, and ambient air, and consumption of PAHs in foods. For some people, the primary exposure to PAHs occurs in the workplace. PAHs have been found in coal tar production plants, coking plants, bitumen and asphalt production plants, coal-gasification sites, smoke houses, aluminum production plants, coal tarring facilities, and municipal trash incinerators. Workers may be exposed to PAHs by inhaling engine exhaust and by using products that contain PAHs in a variety of industries such as mining, oil refining, metalworking, chemical production, transportation, and the electrical industry. PAHs have also been found in other facilities where petroleum, petroleum products, or coal are used or where wood, cellulose, corn, or oil are burned. People living near waste sites containing PAHs may be exposed through contact with contaminated air, water, and soil.

1.4 How can PAHs enter and leave my body?

PAHs can enter your body through your lungs when you breathe air that contains them (usually stuck to particles or dust). Cigarette smoke, wood smoke, coal smoke, and smoke from many industrial sites may contain PAHs. People living near hazardous waste sites can also be exposed by breathing air containing PAHs. However, it is not known how rapidly or completely your lungs absorb PAHs. Drinking water and swallowing food, soil, or dust particles that contain PAHs are other routes for these chemicals to enter your body, but absorption is generally slow when PAHs are swallowed. Under normal conditions of environmental exposure, PAHs could enter your body if your skin comes into contact with soil that contains high levels of PAHs (this could occur near a hazardous waste site) or with used crankcase oil or other products (such as creosote) that contain PAHs. The rate at which PAHs enter your body by eating, drinking, or through the skin can be influenced by the presence

of other compounds that you may be exposed to at the same time with PAHs. PAHs can enter all the tissues of your body that contain fat. They tend to be stored mostly in your kidneys, liver, and fat. Smaller amounts are stored in your spleen, adrenal glands, and ovaries. PAHs are changed by all tissues in the body into many different substances. Some of these substances are more harmful and some are less harmful than the original PAHs. Results from animal studies show that PAHs do not tend to be stored in your body for a long time. Most PAHs that enter the body leave within a few days, primarily in the feces and urine.

1.5 How can PAHs affect my health?

PAHs can be harmful to your health under some circumstances. Several of the PAHs, including benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene, have caused tumors in laboratory animals when they breathed these substances in the air, when they ate them, or when they had long periods of skin contact with them. Studies of people show that individuals exposed by breathing or skin contact for long periods to mixtures that contain PAHs and other compounds can also develop cancer.

Mice fed high levels of benzo[a]pyrene during pregnancy had difficulty reproducing and so did their offspring. The offspring of pregnant mice fed benzo[a]pyrene also showed other harmful effects, such as birth defects and decreased body weight. Similar effects could occur in people, but we have no information to show that these effects do occur.

Studies in animals have also shown that PAHs can cause harmful effects on skin, body fluids, and the body's system for fighting disease after both short- and long-term exposure. These effects have not been reported in people.

The Department of Health and Human Services (DHHS) has determined that benz[a]anthracene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene are known animal carcinogens. The International Agency for Research on Cancer (IARC) has determined the following: benz[a]anthracene and benzo[a]pyrene are probably carcinogenic to humans; benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, and indeno[1,2,3-c,d]pyrene are possibly carcinogenic to humans; and anthracene, benzo[g,h,i]perylene, benzo[e]pyrene, chrysene, fluoranthene, fluorene, phenanthrene, and pyrene are not classifiable as to their carcinogenicity to humans. EPA has determined that benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene are probable human carcinogens and that acenaphthylene, anthracene, benzo[g,h,i]perylene, fluoranthene, fluorene, phenanthrene, and pyrene are not classifiable as to human carcinogenicity. Acenaphthene has not been

classified for carcinogenic effects by the DHHS, IARC, or EPA.

1.6 Is there a medical test to determine whether I have been exposed to PAHs?

In your body, PAHs are changed into chemicals that can attach to substances within the body. The presence of PAHs attached to these substances can then be measured in body tissues or blood after exposure to PAHs. PAHs or their metabolites can also be measured in urine, blood, or body tissues. Although these tests can show that you have been exposed to PAHs, these tests cannot be used to predict whether any health effects will occur or to determine the extent or source of your exposure to the PAHs. It is not known how effective or informative the tests are after exposure is discontinued. These tests to identify PAHs or their products are not routinely available at a doctor's office because special equipment is required to detect these chemicals.

1.7 What recommendations has the federal government made to protect human health?

The federal government has set regulations to protect people from the possible health effects of eating, drinking, or breathing PAHs. EPA has suggested that taking into your body each day the following amounts of individual PAHs is not likely to cause any harmful health effects: 0.3 milligrams (mg) of anthracene, 0.06 mg of acenaphthene, 0.04 mg of fluoranthene, 0.04 mg of fluorene, and 0.03 mg of pyrene per kilogram (kg) of your body weight (one kilogram is equal to 2.2 pounds). Actual exposure for most of the United States population occurs from active or passive inhalation of the compounds in tobacco smoke, wood smoke, and contaminated air, and from eating the compounds in foods. Skin contact with contaminated water, soot, tar, and soil may also occur. Estimates for total exposure in the United States population have been listed as 3 mg/day.

From what is currently known about benzo[a]pyrene, the federal government has developed regulatory standards and guidelines to protect people from the potential health effects of PAHs in drinking water. EPA has provided estimates of levels of total cancer-causing PAHs in lakes and streams associated with a risk of human cancer development. If the following amounts of individual PAHs are released to the environment within a 24-hour period, EPA must be notified: 1 pound of benzo[b]fluoranthene, benzo[a]pyrene, or dibenz[a,h]anthracene; 10 pounds of benz[a]anthracene; 100 pounds of acenaphthene, chrysene, fluoranthene, or indeno[1,2,3-c,d]pyrene; or 5,000 pounds of acenaphthylene, anthracene, benzo[k]fluoranthene, benzo[g,h,i]perylene, fluorene, phenanthrene, or pyrene.

PAHs are generally not produced commercially in the United States except as research chemicals. However, PAHs are found in coal, coal tar,

and in the creosote oils, oil mists, and pitches formed from the distillation of coal tars. The National Institute for Occupational Safety and Health (NIOSH) concluded that occupational exposure to coal products can increase the risk of lung and skin cancer in workers. NIOSH established a recommended occupational exposure limit, time-weighted average (REL-TWA) for coal tar products of 0.1 milligram of PAHs per cubic meter of air (0.1 mg/m^3) for a 10-hour workday, within a 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends an occupational exposure limit for coal tar products of 0.2 mg/m^3 for an 8-hour workday, within a 40-hour workweek. The Occupational Safety and Health Administration (OSHA) has established a legally enforceable limit of 0.2 mg/m^3 averaged over an 8-hour exposure period.

Mineral oil mists have been given an IARC classification of 1 (sufficient evidence of carcinogenicity). The OSHA Permissible Exposure Limit (PEL) for mineral oil mist is 5 mg/m^3 averaged over an 8-hour exposure period. NIOSH has concurred with this limit, and has established a recommended occupational exposure limit (REL-TWA) for mineral oil mists of 5 mg/m^3 for a 10-hour work day, 40-hour work week, with a 10 mg/m^3 Short Term Exposure Limit (STEL).

1.8 Where can I get more information?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 888-422-8737
FAX: (404)498-0057

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: 800-553-6847 or 703-605-6000

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1995. Toxicological profile for polycyclic aromatic hydrocarbons (PAHs). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

ATSDR Information Center / ATSDRIC@cdc.gov / 1-888-422-8737

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ACRYLONITRILE

CASRN: 107-13-1

*For other data, click on the Table of Contents***Best Sections****Non-Human Toxicity Excerpts :**

Acrylonitrile was administered in the drinking water to Sprague-Dawley rats for 2 yr at dose levels of 35, 100, and 300 ppm. ~~A statistically significant incidence of tumors was observed in the brain (astrocytomas), ear canal (Zymbal gland), stomach (nonglandular portion), mammary gland (females only), tongue, pituitary gland, pancreas (males only), and uterus.~~

[USEPA; Health Assessment Document: Acrylonitrile p.13-170 (1983) EPA 600/8-82-007F]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

A three-generation reproductive study was conducted using Charles River rats. These rats and their offspring ingested water containing 100 or 500 ppm acrylonitrile starting approximately 15 days post-weaning and were mated after 100 days. Female rats were maintained on water containing acrylonitrile for 20 weeks; following delivery of the second litter, the animals were exposed to acrylonitrile for approximately 45 weeks. Following exposure, the animals in the three generations were sacrificed. ... The tumor incidence was low; only rats of the second generation at the high-dose level showed a significant increase in the number of tumors. ~~These tumors were found in the brain (astrocytomas) and ear canal (zymbal gland)/.~~

[USEPA; Health Assessment Document: Acrylonitrile p.13-101 (1983) EPA 600/8-82-007F]**PEER REVIEWED**

Evidence for Carcinogenicity :

CLASSIFICATION: B1; probable human carcinogen. BASIS FOR CLASSIFICATION: The observation of a statistically significant increase in the incidence of lung cancer in exposed workers and observation of tumors, generally **astrocytomas in the brain**, in studies in two rat strains exposed by various routes (drinking water, gavage, and inhalation) forms the basis for this classification.

[U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) on Acrylonitrile (107-13-1) from the National Library of Medicine's TOXNET System, March 28, 1994]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

Acrylonitrile was administered in the drinking water to 100 Sprague Dawley (Spartan) rats of each sex at dose levels of 0, 1, and 100 ppm. The study was terminated early due to low survival rates; females were sacrificed at 19 mo and males were sacrificed at 22 mo. ... Histopathology evaluation revealed an increased incidence of ~~astrocytomas of the brain and spinal cord~~, carcinomas and adenomas of the zymbal gland or ear canal, and squamous cell carcinomas and papillomas of the forestomach in the high-dose males and females.

[USEPA; Health Assessment Document: Acrylonitrile p.13-96 (1983) EPA 600/8-82-007F]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

In this study, acrylonitrile was administered by intubation to Sprague Dawley (Spartan) rats (100/sex/group) at three dose levels of 0, 0.10, and 10.0 mg/kg/day, 5 days/wk. ... All surviving animals in all groups were terminated during the 20th month to ensure at least 10 animals/sex for histopathological evaluation. The body weights of high-dose group males were consistently slightly lower than controls. Histopathological evaluations showed that there were statistically significant increased incidences in tumors of the brain (**astrocytomas**) and ear canal (zybal gland) in both high-dose males and females. Stomach and intestinal tumors were observed only in high-dose males, and mammary gland tumors were observed in high-dose females. Statistically significant tumor incidences were not observed in low-dose groups either in males or females.

[USEPA; Health Assessment Document: Acrylonitrile p.13-103 (1983) EPA 600/8-82-007F]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

... Acrylonitrile was administered in the drinking water to 100 Fischer 344 rats of each sex at dose levels of 1, 3, 10, 30, and 100 ppm, and the control group contained 200 animals/sex. ... All females were sacrificed at 23 months due to low survival. The males were continued on test until the 26th month when similar survival levels were reached. Mortality in the males and females receiving 100 ppm was markedly greater than in controls, while mortality in the 10 ppm males and females receiving 3 and 30 ppm was also somewhat greater than controls. ... Slight, but generally consistent reductions in hemoglobin, hematocrit, and erythrocyte counts were noted for the females receiving 100 ppm throughout the study. Histopathological evaluation revealed an increased incidence of malignant tumor-bearing animals in the groups receiving 10, 30, and 100 ppm. The observed tumors were **astrocytomas** of the central nervous system (brain and/or spinal cord) and squamous cell carcinomas of the ear canal, as well as mammary gland carcinomas in the females receiving 100 ppm.

[USEPA; Health Assessment Document: Acrylonitrile p.13-99 (1983) EPA 600/8-82-007F]**PEER REVIEWED**

TSCA Test Submissions :

Oncogenicity was evaluated in male and female Fischer 344 rats (200/sex/group) orally exposed to acrylonitrile in drinking water for 2 yrs. at concentrations of 0, 1, 3, 10, 30 or 100 ppm. There were statistically significant increases in treated animals relative to controls in the following: ~~brain~~ **astrocytomas**, combined ear canal papillomas/adenomas and carcinomas and malignant tumors (both sexes at 30 and 100 ppm, females also at 10 ppm), combined tumors (females at 300 and 100 ppm), detectable mammary masses (females at 100 ppm and males at 10 ppm), grossly detectable masses of the head (both sexes at 100 ppm and females also at 30 ppm), and squamous cell papillomas (both sexes at 30 ppm and males also at 3 and 10 ppm; there was no dose-related trend in this latter category and the overall incidence was low, 4%). There were no significant differences between treated animals and controls in the following: total mammary tumors (all female groups) and squamous cell carcinoma of the stomach (observed in only one high-level male).

[Monsanto Plastics and Resins Co.; Review of Data Contained in the Two Year Study of Fischer 344 Rats Fed Acrylonitrile Containing Drinking Water for Two Years. (1981), EPA Document No. FYI-AX-0481-0108, Fiche No. 0108-0]**UNREVIEWED**

*This document is
Very long - To avoid
paper overload -
I have attached
page "1" only as
an example of
Health Effects*

ACRYLONITRILE

CASRN: 107-13-1

For other data, click on the Table of Contents

Human Health Effects:

Evidence for Carcinogenicity:

CLASSIFICATION: B1; probable human carcinogen. BASIS FOR CLASSIFICATION: The observation of a statistically significant increase in the incidence of lung **cancer** in exposed workers and observation of tumors, generally astrocytomas in the **brain**, in studies in two rat strains exposed by various routes (drinking water, gavage, and inhalation) forms the basis for this classification.

[U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) on Acrylonitrile (107-13-1) from the National Library of Medicine's TOXNET System, March 28, 1994]**PEER REVIEWED**

A3. Confirmed animal carcinogen with unknown relevance to humans.

[American Conference of Governmental Industrial Hygienists. TLVs & BEIs: Threshold limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 2002. Cincinnati, OH. 2002.13]**QC REVIEWED**

Evaluation: There is inadequate evidence in humans for the carcinogenicity of **acrylonitrile**. There is sufficient evidence in experimental animals for the carcinogenicity of **acrylonitrile**. Overall evaluation: **Acrylonitrile is possibly carcinogenic to humans (Group 2B).**

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V71 _____ (1999)]**QC REVIEWED**

Human Toxicity Excerpts:

SEVERAL CASES OF MILD JAUNDICE ACCOMPANIED BY MILD ANEMIA & LEUKOCYTOSIS HAVE BEEN REPORTED.

[Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996. 61]**PEER REVIEWED**

WHEN POISONING CASES DO OCCUR, SYMPTOMS DERIVE FROM TISSUE ANOXIA & ARE IN ORDER OF ONSET: LIMB WEAKNESS, DYSPNEA, BURNING SENSATION IN THROAT, DIZZINESS, & IMPAIRED JUDGEMENT, CYANOSIS & NAUSEA, COLLAPSE, IRREGULAR BREATHING, CONVULSIONS & DEATH. IN LATTER STAGES COLLAPSE, IRREGULAR BREATHING OR CONVULSIONS & CARDIAC ARREST MAY OCCUR WITHOUT WARNING. SOME PATIENTS APPEAR HYSTERICAL OR MAY EVEN BE VIOLENT.

[International Labour Office. Encyclopedia of Occupational Health and Safety. Vols. I&II. Geneva, Switzerland: International Labour Office, 1983. 55]**PEER REVIEWED**

EXAMINATION OF 18 WORKERS WHO HAD BEEN EXPOSED TO ACRYLONITRILE FOR AVERAGE OF 15.3 YR & 18 WORKERS WHO HAD NOT BEEN EXPOSED TO ACRYLONITRILE SHOWED NO DIFFERENCE IN INCIDENCE OF CHROMOSOME ABERRATIONS.

ACRYLONITRILE

CASRN: 107-13-1

*For other data, click on the Table of Contents***Manufacturing/Use Information:****Major Uses:**

For **Acrylonitrile** (USEPA/OPP Pesticide Code: 000601) ACTIVE products with label matches. /SRP: Registered for use in the U.S. but approved pesticide uses may change periodically and so federal, state and local authorities must be consulted for currently approved uses./

[U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Acrylonitrile (107-13-1). Available from the Database Query page at <http://www.cdpr.ca.gov/docs/epa/epamenu.htm> as of February 5, 2001.]**PEER REVIEWED**

In the plastics, surface coatings, and adhesives industries. As chem int in synthesis of antioxidants, pharmaceuticals, dyes, surface-active agents, extra. In org synth to introduce cyanoethyl group. As modifier for natural polymers.

[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996. 24]**PEER REVIEWED**

As a pesticide fumigant for stored grain /srp: former use/

[Tomlin, C.D.S. (ed.). The Pesticide Manual - World Compendium, 11 th ed., British Crop Protection Council, Surrey, England 1997 24]**PEER REVIEWED**

**IN CO-POLYMERS WITH STYRENE & BUTADIENE; NITRILE RUBBER;
CYANOETHYLATION OF COTTON; BOTTLES FOR SOFT DRINKS /SRP: DISCONTINUED
BY FDA/**

[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991.30]**PEER REVIEWED**

COMONOMER FOR BARRIER RESINS

[SRI]**PEER REVIEWED**

COMONOMER WITH STYRENE FOR URETHANE POLYETHER POLYOLS

[SRI]**PEER REVIEWED**

COMONOMER FOR ALKYD/ACRYLONITRILE COPOLYMERS

[SRI]**PEER REVIEWED**

Monomer for acrylic and modacrylic fibers and high-strength whiskers; **acrylonitrile** butadiene styrene copolymer and **acrylonitrile** styrene copolymers; nitrile rubber; cyanoethylation of cotton; synthetic soil blocks (**acrylonitrile** polymerized in wood pulp); organic synthesis; adiponitrile; grain fumigant; monomer for a semiconductive polymer that can be used like inorganic oxide catalysts in dehydrogenation of tert-butanol to isobutylene and water.

[Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. 1997. 19]**PEER REVIEWED**

1. Acrylic fibers. More than half of **acrylonitrile** production goes into acrylic fibers used mainly in <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAATUaaXC:1:manf>

6/19/03

textile and clothing industries. 2. Copolymer resins of plastics, such as the **acrylonitrile-butadiene-styrene (ABS)** and **styrene-acrylonitrile (SAN)** resins. These are used for pipes and fitting, automotive parts, appliances, furniture, and building components, among other products. 3. Nitrile rubbers, which are resistant to chemicals, oils, solvents, heat, aging, and abrasion, are employed mainly for industrial purposes. 4. Miscellaneous uses include production of acrylamide, acrylic esters, adhesives, adiponitrile, alkyd resins, antioxidants, coatings, cyanoethylated natural fibers and paper, dielectric paper, dyes, electrically conductive rubber, emulsifying agents, insecticides, latex paints, photographic emulsions, plasticizers, synthetic leathers, wire insulation, floor polish, and inks.

[Rom, W.N. (ed.). Environmental and Occupational Medicine. 2nd ed. Boston, MA: Little, Brown and Company, 1992. 949]**PEER REVIEWED**

In the production of acrylic and modacrylic fibers by copolymerization with methylacrylate, methylmethacrylate, vinylacetate, vinylchloride, or vinylidenechloride; the manufacture of **acrylonitrile-butadiene-styrene (ABS)** and **styrene acrylonitrile (SAN)** resins; fumigant.

[Verschueren, K. Handbook of Environmental Data on Organic Chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Co., 1996. 133]**PEER REVIEWED**

Manufacture of adiponitrile, nitrile rubbers, elastomers, acrylic fibers; acrylic fibers used for apparel (e.g., sweaters, fleece wear, and sportswear), home furnishings (e.g., carpets, upholstery, draperies); manufacture of carbon fibers used in aircraft, defense, and aerospace industries; production of fatty amines, ion exchange resins, fatty amine amides used in cosmetics, adhesives, corrosion inhibitors, and water treatment resins.

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 364]**PEER REVIEWED**

Manufacturers:

BP Amoco Corp., 200 E. Randolph Dr., Chicago, IL 60601, (312) 856-6111; Production sites: Green Lake, TX 77031; Lima, OH 45802

[SRI International. 2000 Directory of Chemical Producers -- United States. SRI Consulting, Menlo Park: CA 2000 441]**PEER REVIEWED**

Cytec Industries Inc., Building Block Chemicals, Five Garret Mountain Plaza, W. Patterson, NJ 07424, (973) 357-3100; Production site: Waggaman, LA 70094

[SRI International. 2000 Directory of Chemical Producers -- United States. SRI Consulting, Menlo Park: CA 2000 441]**PEER REVIEWED**

Dupont, Dupont Specialty Chemicals, 1007 Market St., Wilmington, DE 19898, (800) 441-7515; Production site: Beaumont, TX 77704

[SRI International. 2000 Directory of Chemical Producers -- United States. SRI Consulting, Menlo Park: CA 2000 441]**PEER REVIEWED**

Solutia Inc., 575 Maryville Centre Dr., P.O. Box 66760, St. Louis, MO 63166-6760, (314) 674-1000; Production site: Alvin, TX 77511

[SRI International. 2000 Directory of Chemical Producers -- United States. SRI Consulting, Menlo Park: CA 2000 441]**PEER REVIEWED**

Sterling Chemicals Inc., 1200 Smith St., Suite 1900, Houston, TX 77002-4312, (713) 650-3700; Production site: Texas City, TX 77590

[SRI International. 2000 Directory of Chemical Producers -- United States. SRI Consulting, Menlo Park: CA 2000 441]**PEER REVIEWED**

Methods of Manufacturing:

(a) From propylene, oxygen, and ammonia with either bismuth phosphomolybdate or uranium-based compd as catalysts (b) Addition of hydrogen cyanide to acetylene with cuprous chloride catalyst (c) Dehydration of ethylene cyanohydrin.

[Weiss, G.; Hazardous Chemicals Handbook. 1986, Noyes Data Corporation, Park Ridge, NJ 1986. 18]**PEER REVIEWED**

General Manufacturing Information:

Fumigant formulations containing **acrylonitrile** with names **Acrylon**, **Carbacryl**, **Fumigrain**, **Ventox**, and **ENT-54** are no longer manufactured in the United States.

[USEPA; Health Assessment Document: Acrylonitrile p.3-1 (1983) EPA 600/8-82-007F]
PEER REVIEWED

Commercial **acrylonitrile** is stabilized against self-polymerization by ... methylhydroquinone (35-50 ppm).

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 355-63]**PEER REVIEWED**

Acrylic fibers marketed under tradenames including **Acrylan**, **Creslan**, **Orlon**, and **Zefran** ... tradenames for modacrylic fibers include **Acrylan**, **Elura**, **SEF**, and **Verel**. Acrylic and/or modacrylic fibers are manufactured from **acrylonitrile**.

[USEPA; Ambient Water Quality Criteria Doc: Acrylonitrile (Draft) p.C-2 (1980)]
PEER REVIEWED

Formulations/Preparations:

USEPA/OPP Pesticide Code 000601; Trade Names: **Acritet**, component of (with 016501), **Ventox**, component of (with 016501), **Acrylon**, component of (with 016501), **Carbacryl**, component of (with 016501), **Acrylofume**, component of (with 016501), 020701 and 081501).

[U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Acrylonitrile (107-13-1). Available from the Database Query page at <http://www.cdpr.ca.gov/docs/epa/epamenu.htm> as of February 5, 2001.]**PEER REVIEWED**

Technical grade **acrylonitrile** with greater than 99% purity.

[USEPA; Health Assessment Document: Acrylonitrile p.3-6 (1983) EPA 600/8-82-007F]
PEER REVIEWED

Acritet = 34% **acrylonitrile**, 60% **CCl4**; **ventox** = **acritet**; **carbacryl**: equal volumes of **acrylonitrile** and **CCl4**; **acrylofume**: 39.5% **acrylonitrile**, 30% **CCl4**, 30% **chloroform**, 0.5% **chloropicrin**.

[Verschueren, K. Handbook of Environmental Data on Organic Chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Co., 1996. 133]**PEER REVIEWED**

Impurities:

Polymerization grade **acrylonitrile** contains a number of impurities and additives, namely, **dimethylformamide**, **hydrogen peroxide**, **hydroxyanisole**, **methyl acrylate**, **phenyl ether-biphenyl mixture**, **sodium metabisulfite**, **sulfur dioxide**, **sulfuric acid**, and **titanium dioxide**.

[USEPA; Ambient Water Quality Criteria Doc: Acrylonitrile (Draft) p.C-1 (1980)]
PEER REVIEWED

Acetone, 300 ppm max; acetonitrile, 500 ppm max; aldehydes, 100 ppm max; hydrogen cyanide, 10 ppm max; hydroquinone monomethyl ether (inhibitor), 35-50 ppm; iron, 0.10 ppm max; nonvolatile matter, 100 ppm max; peroxides, 0.5 ppm max; water, 1.3882-1.3892 wt% max.

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 363]**PEER REVIEWED**

Consumption Patterns:

COMONOMER FOR ACRYLIC & MODACRYLIC FIBERS, 51%; COMONOMER FOR ACRYLONITRILE-BUTADIENE-STYRENE RESINS, 18%; CHEM INT FOR ADIPONITRILE, 13%; CHEM INT FOR ACRYLAMIDE, 6%; COMONOMER FOR NITRILE ELASTOMERS, 3%; COMONOMER FOR STYRENE-ACRYLONITRILE RESINS, 2%; OTHER USES, 7% (1983)

[SRI]**PEER REVIEWED**

In 1976, 282 million kg were used to make acrylic and modacrylic fibers.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). p. V19 73 (1979)]**PEER REVIEWED**

Acrylic & modacrylic fibers, 45%; acrylonitrile butadiene styrene copolymer resins, 20%; styrene acrylonitrile polymer resins, 9%; adiponitrile, 13%; acrylamide, 6%; miscellaneous, 7% (1984)

[CHEMICAL PRODUCTS SYNOPSIS: Acrylonitrile, 1985]**PEER REVIEWED**

CHEMICAL PROFILE: Acrylonitrile. Exports, 43%; acrylic and modacrylic fibers, 28%; acrylonitrile-butadiene-styrene and styrene-acrylonitrile resins, 15%; adiponitrile, 7%; acrylamide, 4%; miscellaneous, including nitrile rubber and barrier resins, 3%.

[Kavalier AR; Chemical Marketing Reporter 235 (10): 50 (1989)]**PEER REVIEWED**

CHEMICAL PROFILE: Acrylonitrile. Demand: 1988: 2.580 million lb; 1989: 2.660 million lb; 1993 /projected/: 3.025 million lb. (Includes exports but not imports, which are negligible.)

[Kavalier AR; Chemical Marketing Reporter 235 (10): 50 (1989)]**PEER REVIEWED**

Worldwide consumption of acrylonitrile increased 52% between 1976 and 1988, from 2.5X10⁶ to 3.8X10⁶ tons/yr; Consumption (worldwide): acrylic fibers (65%), 2.52X10⁶ tons (1988), 2.41X10⁶ tons (1985), 2.04X10⁶ tons (1980), 1.76X10⁶ tons (1976); ABS resins, 5.5X10⁵ tons (1988), 4.35X10⁵ tons (1985), 3.0X10⁵ tons (1980), 2.7X10⁵ tons (1976); adiponitrile, 3.1X10⁵ tons (1988), 2.35X10⁵ tons (1985), 1.6X10⁵ tons (1980), 9.0X10⁴ tons (1976); other (including nitrile rubber, SAN resin, acrylamide, and barrier resins), 4.6X10⁵ tons (1988), 3.9X10⁵ tons (1985), 2.4X10⁵ tons (1980), 4.2X10⁵ tons (1976).

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (91) 364]**PEER REVIEWED**

Adiponitrile (33%); acrylic fibers (25%); ABS/SAN resins (23%); acrylamide (9%); nitrile elastomers (3%); miscellaneous, including polymers, polyols, barrier resins and carbon fibers (7%).

[ChemExpo; Chemical profile for Acrylonitrile (107-13-1). May 8, 2000. Available from the Database Query page <http://www.chemexpo.com/news/PROFILE000508.cfm> as of Dec 27, 2000.]**PEER REVIEWED**

U.S. Demand (which equals production minus exports): 1997) 1.753X10⁹ lbs; (1998) 2.186X10⁹ lbs; (2002) 1.95X10⁹ lbs (est)

[ChemExpo; Chemical profile for Acrylonitrile (107-13-1). May 8, 2000. Available

from the Database Query page <http://www.chemexpo.com/news/PROFILE000508.cfm> as of Dec 27, 2000.]**PEER REVIEWED**

U. S. Production:

(1983) 9.53X10+11 G

[SRI]**PEER REVIEWED**

(1978) 7.95X10+11 G

[SRI]**PEER REVIEWED**

(1977): 745,000 million tons

[Suta BE; Assessment of Human Exposures to Atmospheric Acrylonitrile, EPA Contract No 68-02-2835 p.2 (1979)]**PEER REVIEWED**

(1985) 1.06X10+12 g

[USITC. SYN ORG CHEM-U.S. PROD/SALES 1985 p.264]**PEER REVIEWED**

38th highest-volume chemical produced in USA (1985)

[Sax, N.I. and R.J. Lewis, Sr. (eds.). Hawley's Condensed Chemical Dictionary. 11th ed. New York: Van Nostrand Reinhold Co., 1987. 19]**PEER REVIEWED**

(1990) 2.68 billion lb

[Chem & Engineering News 70 (26): 36 (6/29/92)]**PEER REVIEWED**

(1991) 2.65 billion lb

[Chem & Engineering News 71 (15): 11 (4/12/93)]**PEER REVIEWED**

(1991) 3,055 million lb

[SRI. 1992 Directory of Chemical Producers-United States of America. Menlo Park, CA: SRI International, 1992. 443]**PEER REVIEWED**

(1992)2.83 billion lb

[Chem & Engineering News 72 (15): 13 (4/11/94)]**PEER REVIEWED**

(1993) 2.51 billion lb

[Chem & Engineering News 72 (15): 13 (4/11/94)]**PEER REVIEWED**

1.17X10+6 tons (1988)

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present.,p. V1 (91) 362]**PEER REVIEWED**

(1997) 3.29X10+9 lbs; (1998) 3.12 X10+9 lbs

[ChemExpo; Chemical profile for Acrylonitrile (107-13-1). May 8, 2000. Available from the Database Query page <http://www.chemexpo.com/news/PROFILE000508.cfm> as of Dec 27, 2000.]**PEER REVIEWED**

U. S. Imports:

(1977) 8.54X10+7 G

[SRI]**PEER REVIEWED**

(1982) 1.00X10+6 G

[SRI]**PEER REVIEWED**

(1985) 2.00X10+5 g

[BUREAU OF THE CENSUS. U.S. IMPORTS FOR CONSUMPTION AND GENERAL IMPORTS 1985 p.1-574]**PEER REVIEWED**

Negligible

[ChemExpo; Chemical profile for Acrylonitrile (107-13-1). May 8, 2000. Available from the Database Query page <http://www.chemexpo.com/news/PROFILE000508.cfm> as of Dec 27, 2000.]**PEER REVIEWED**

U. S. Exports:

(1978) 1.09X10+11 G

[SRI]**PEER REVIEWED**

(1983) 3.88X10+11 G

[SRI]**PEER REVIEWED**

(1977) 109,000 million tons

[Suta BE; Assessment of Human Exposures to Atmospheric Acrylonitrile, EPA Contract No. 68-02-2835, p.13 (1979)]**PEER REVIEWED**

(1985) 4.28X10+11 g

[BUREAU OF THE CENSUS. U.S. EXPORTS, SCHEDULE E, 1985 p.2-80]**PEER REVIEWED**

Total: (1988) 5.1X10+5 tons, (1987) 6.10X10+5 tons

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 362]**PEER REVIEWED**

(1997) 1.538 X10+9 lbs; (1998) 9.34 X10+8 lbs

[ChemExpo; Chemical profile for Acrylonitrile(107-13-1). May 8, 2000. Available from the Database Query page <http://www.chemexpo.com/news/PROFILE000508.cfm> as of Dec 27, 2000.]**PEER REVIEWED**

ACRYLONITRILE

CASRN: 107-13-1

*For other data, click on the Table of Contents***Chemical/Physical Properties:****Molecular Formula:**

C3-H3-N

PEER REVIEWED

Molecular Weight:

53.06

[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996. 24]**PEER REVIEWED**

Color/Form:**Clear, colorless liquid**

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (91) 353]**PEER REVIEWED**

Colorless to pale-yellow liquid

[NIOSH. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication No. 97-140. Washington, D.C. U.S. Government Printing Office, 1997. 8]**PEER REVIEWED**

Odor:**PRACTICALLY ODORLESS, OR WITH A VERY SLIGHT ODOR OF PEACH KERNELS**

[Lefaux, R. Practical Toxicology of Plastics. Cleveland: CRC Press Inc., 1968. 71]**PEER REVIEWED**

Sweet odor

[WHO; Environ Health Criteria: Acrylonitrile p.15 (1983)]**PEER REVIEWED**

Irritating odor

[U.S. Coast Guard, Department of Transportation. CHRIS - Hazardous Chemical Data. Volume II. Washington, D.C.: U.S. Government Printing Office, 1984-5.])**PEER REVIEWED**

Unpleasant odor.

[NIOSH. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication No. 97-140. Washington, D.C. U.S. Government Printing Office, 1997. 8]**PEER REVIEWED**

Onion, garlic, pungent

[Verschuere, K. Handbook of Environmental Data on Organic Chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Co., 1996. 133]**PEER REVIEWED**

Boiling Point:

77.3 deg C @ 760 mm Hg

[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996. 24]**PEER REVIEWED**

Melting Point:**-82 deg C**

[Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. 1997. 18]**PEER REVIEWED**

Corrosivity:**Attacks copper and copper alloys ... attacks aluminum in high conc.**

[U.S. Coast Guard, Department of Transportation. CHRIS - Hazardous Chemical Data. Volume II. Washington, D.C.: U.S. Government Printing Office, 1984-5.])**PEER REVIEWED**

Critical Temperature & Pressure:**Critical temperature: 246 deg C; critical pressure: 3.54 MPa**

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 353]**PEER REVIEWED**

Density/Specific Gravity:**0.8004 @ 25 deg C/4 deg C**

[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996. 24]**PEER REVIEWED**

Heat of Combustion:**1761.5 kJ/mol @ 25 deg C (liquid)**

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 354]**PEER REVIEWED**

Heat of Vaporization:**32.65 kJ/mol @ 25 deg C**

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 354]**PEER REVIEWED**

Octanol/Water Partition Coefficient:**log Kow= 0.25**

[Hansch, C., Leo, A., D. Hoekman. Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American Chemical Society., 1995. 5]**PEER REVIEWED**

pH:

6.0-7.5 (5% aqueous solution)

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 353]**PEER REVIEWED**

Solubilities:**SOL IN ISOPROPYL ALCOHOL**

[Weast, R.C. (ed.) Handbook of Chemistry and Physics. 69th ed. Boca Raton, FL: CRC Press Inc., 1988-1989. 4864]**PEER REVIEWED**

Sol in ethanol

[Lide, DR (ed.). CRC Handbook of Chemistry and Physics. 81st Edition. CRC Press LLC, Boca Raton: FL 2000, p. 3-289]**PEER REVIEWED**

Acrylonitrile is ... miscible with ethanol, carbon tetrachloride, ethyl acetate, ethylene cyanohydrin, liquid carbon dioxide, ... toluene, petroleum ether, and xylene.

[Miller LM, Villaume JE; Investigation of Selected Potential Environmental Contaminants EPA 560/2-78-003 (1978) as cited in USEPA; Health Assessment Document: Acrylonitrile p.3-2 (1983) EPA 600/8-82-007F]**PEER REVIEWED**

In water, 7.45X10+4 mg/l @ 25 deg C

[Yalkowsky SH, Dannenfelser RM; The AQUASOL dATABASE of Aqueous Solubility. Fifth Ed, Tucson, AZ: Univ Az, College of Pharmacy (1992)]**PEER REVIEWED**

Spectral Properties:**Index of refraction: 1.3888 @ 25 deg C/D**

[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996. 24]**PEER REVIEWED**

MAX ABSORPTION (ALCOHOL): 203 NM (LOG E= 3.79); SADTLER REF NUMBER: 386 (IR, PRISM); V15 (NMR)

[Weast, R.C. (ed.). Handbook of Chemistry and Physics. 60th ed. Boca Raton, Florida: CRC Press Inc., 1979., p. C-465]**PEER REVIEWED**

Surface Tension:**26.6 dyn/cm @ 25 deg C**

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 353]**PEER REVIEWED**

Vapor Density:**1.8 (Air =1)**

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V1 (1991) 353]**PEER REVIEWED**

Vapor Pressure:**109 mm Hg @ 25 deg C**

[Daubert, T.E., R.P. Danner. Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, D.C.: Taylor and Francis, 1989.])**PEER REVIEWED**

REVIEWED**

Relative Evaporation Rate:

4.54 (Butyl Acetate= 1)

[29 CFR 1910.1045 (7/1/85)]**PEER REVIEWED**

Viscosity:

0.34 cP at 25 deg C

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present.,p. V1 (1991) 354]**PEER REVIEWED**

Other Chemical/Physical Properties:

... Yellowing upon exposure to light indicates photo-alteration to saturated derivatives.

[USEPA; Health Assessment Document: Acrylonitrile p.3-6 (1983) EPA 600/8-82-007F]
PEER REVIEWED**Solubility of water in acrylonitrile: 3.1 parts water/100 parts acrylonitrile**

[Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996. 24]**PEER REVIEWED**

Henry's Law constant = 1.38×10^{-4} atm cu m/mole @ 25 deg C

[Bocek K; Experientia Suppl 23: 231-40 (1976)]**PEER REVIEWED**

Hydroxyl radical rate constant = 4.10×10^{-12} cu cm/molecule-sec at 25 deg C

[Kwok ESC, Atkinson R: Estimation of hydroxyl radical reaction rate constants for gas-phase organic compounds using a structure-reactivity relationship: an update. Riverside, CA: Univ CA, Statewide Air Pollut Res Ctr. CMA Contract No. ARC-8.0-OR (1994)]**PEER REVIEWED**

Saturated concn = 257 g/cu m @ 20 deg C, 383 g/cu m @ 30 deg C

[Verschueren, K. Handbook of Environmental Data on Organic Chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Co., 1996.]**PEER REVIEWED**

Dielectric constant @ 33.5 MHz = 38; dipole moment = 1.17×10^{-29} C-m (liquid phase), 1.924×10^{-29} C-m (vapor phase); molar refractivity (D line) = 15.67; molar heat of fusion = 6.61 kJ/mol; ionization potential = 10.75 eV; free energy of formation = 195 kJ/mol @ 25 deg C; enthalpy of formation (@ 25 deg C): 185 kJ/mol (gas), 150 kJ/mol (liquid); molar heat capacity: 2.09 kJ/kg K (liquid), 1.204 kJ/kg K (gas @ 50 deg C and 1 atm); entropy (gas @ 25 deg C, 1 atm) = 274 kJ/mol K

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present.,p. V1 (1991) 353-4]**PEER REVIEWED**

Forms azeotropes with tetrachlorosilane, water, isopropyl alcohol, benzene, methanol, carbon tetrachloride, chlorotrimethylsilane.

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present.,p. V1 (1991) 354]**PEER REVIEWED**

ACRYLONITRILE

CASRN: 107-13-1

For other data, click on the Table of Contents

Synonyms and Identifiers:

Synonyms:

ACRITET

PEER REVIEWED

ACRYLNITRIL (GERMAN, DUTCH)

PEER REVIEWED

ACRYLON

PEER REVIEWED

ACRYLONITRILE (DOT)

PEER REVIEWED

ACRYLONITRILE MONOMER

PEER REVIEWED

AI3-00054

PEER REVIEWED

AKRYLONITRYL (POLISH)

PEER REVIEWED

Carbacryl

PEER REVIEWED

Caswell No. 010

PEER REVIEWED

CIANURO DI VINILE (ITALIAN)

PEER REVIEWED

CYANOETHYLENE

PEER REVIEWED

CYANURE DE VINYLE (FRENCH)

PEER REVIEWED

ENT 54

PEER REVIEWED

Pesticide Code: 000601

PEER REVIEWED

FUMIGRAIN

****PEER REVIEWED****

MILLER'S FUMIGRAIN

****PEER REVIEWED****

NCI-C50215

****PEER REVIEWED****

NITRILE ACRILICO (ITALIAN)

****PEER REVIEWED****

NITRILE ACRYLIQUE (FRENCH)

****PEER REVIEWED****

PROPENENITRILE

****PEER REVIEWED****

2-PROPENENITRILE

****PEER REVIEWED****

TL 314

****PEER REVIEWED****

VCN

****PEER REVIEWED****

VENTOX

****PEER REVIEWED****

VINYL CYANIDE

****PEER REVIEWED****

VINYLYANID

****PEER REVIEWED****

Formulations/Preparations:

USEPA/OPP Pesticide Code 000601; Trade Names: Acritet, component of (with 016501), **Ventox**, component of (with 016501), Acrylon, component of (with 016501), **Carbacryl**, component of (with 016501), Acrylofume, component of (with 016501), 020701 and 081501).

[U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Acrylonitrile (107-13-1). Available from the Database Query page at <http://www.cdpr.ca.gov/docs/epa/epamenu.htm> as of February 5, 2001.] ****PEER REVIEWED****

Technical grade acrylonitrile with greater than 99% purity.

[USEPA; Health Assessment Document: Acrylonitrile p.3-6 (1983) EPA 600/8-82-007F] ****PEER REVIEWED****

Acritet = 34% **acrylonitrile**, 60% CCl₄; **ventox** = acritet; **carbacryl**: equal volumes of **acrylonitrile** and CCl₄; **acrylofume**: 39.5% **acrylonitrile**, 30% CCl₄, 30% chloroform, 0.5% chloropicrin.

[Verschueren, K. Handbook of Environmental Data on Organic Chemicals. 3rd ed. New York, NY: Van Nostrand Reinhold Co., 1996. 133] ****PEER REVIEWED****

Shipping Name/ Number DOT/UN/NA/IMO:

UN 1093; **Acrylonitrile**, inhibited and uninhibited

IMO 3.2; **Acrylonitrile**, inhibited

Standard Transportation Number:

49 064 20; **Acrylonitrile**

EPA Hazardous Waste Number:

U009; A toxic waste when a discarded commercial chemical product or manufacturing chemical intermediate or an off-specification commercial chemical product or a manufacturing chemical intermediate.

ETHYLENE OXIDE

CASRN: 75-21-8

For other data, click on the Table of Contents

*Example
under Pesticide***Best Sections****Human Toxicity Excerpts :**

Mortality from **cancer** among workers exposed to ethylene oxide (EtO) has been studied in 10 distinct cohorts that include about 29800 workers and 2540 deaths. This paper presents a review and meta-analysis of these studies, primarily for leukemia, nonHodgkin's lymphoma, stomach **cancer**, pancreatic **cancer**, and **cancer** of the **brain** and nervous system. The magnitude and consistency of the standardized mortality ratios (SMRs) were evaluated for the individual and combined studies, as well as trends by intensity or frequency of exposure, by duration of exposure, and by latency (time since first exposure). Exposures to other workplace chemicals were examined as possible confounder variables. Three small studies ... initially suggested an association between EtO and leukemia, but in seven subsequent studies the SMRs for leukemia have been much lower. For the combined studies the SMR = 1.06 (95% confidence interval (95% CI) 0.73-1.48). There was a slight suggestion of a trend by duration of exposure ($p = 0.19$) and a suggested incr with longer latency ($p = 0.07$), but there was no overall trend in risk of leukemia by intensity or frequency of exposure; nor did a cumulative exposure analysis in the largest study indicate a quantitative association. There was also an indication that in two studies with increased risks the workers had been exposed to other potential carcinogens. For non-Hodgkin's lymphoma there was a suggestive risk overall (SMR = 1.35, 95% CI 0.93-1.90). Breakdowns by exposure intensity or frequency, exposure duration, or latency did not indicate an association, but a positive trend by cumulative exposure ($p = 0.05$) was seen in the largest study. There was a suggested incr in the overall SMR for stomach **cancer** (SMR = 1.28, 95% CI 0.98-1.65 (CI 0.73-2.26 when heterogeneity among the risk estimates was taken into account)), but analyses by intensity or duration of exposure or cumulative exposure did not support a causal association for stomach **cancer**. The overall SMRs and exposure-response analyses did not indicate a risk from EtO for pancreatic **cancer** (SMR = 0.98), **brain** and nervous system **cancer** (SMR = 0.89), or total **cancer** (SMR = 0.94). Although the current data do not provide consistent and convincing evidence that EtO causes leukemia or non-Hodgkin's lymphoma, the issues are not resolved and await further studies of exposed populations.

[Shore Re et al; British J Indust Med 50 (11): 971-97 (1993)]**PEER REVIEWED**

Human Toxicity Excerpts :

18,254 employees at 14 US industrial plants where ethylene oxide had been used to sterilize medical supplies or spices or in the testing sterilizing equipment /were followed/. The plants were selected because they held adequate records on personnel and exposure and their workers had accumulated at least 400 person-years at risk before 1978. Only workers with at least three months of exposure to ethylene oxide were included in the cohort. Forty five percent of the cohort were male, 79% were white, 1,222 were sterilizer operators and 15,750 were employed before 1978. Analysis of 627 8 hr personal samples indicated that average exposure during 1976-85 was 4.3 ppm (7.7 mg/cu m) for sterilizer operators; the average level for other exposed workers, on the basis of 1,888 personal samples, was 2.0 ppm (3.6 mg/cu m). Many companies began to install engineering controls in 1978, and exposures before that year were thought to have been higher. There was no evidence of confounding exposure to other occupational carcinogens. The cohort was followed to 1987 through

the national death index and records of the Social Security Administration, the Internal Revenue Service and the US Postal Service, and 95.5% were traced successfully. The expected numbers of deaths were calculated from rates in the US population, stratified according to age, race, sex and calendar year. In total, 1,177 cohort members had died (1,454.3 expected), including 40 for whom no death certificate was available. There were 343 deaths from **cancer** (380.3 expected). The observed and expected numbers of deaths were 36/33.8 from all lymphatic and hematopoietic **cancer**, including 8/5.3 from lymphosarcoma-reticulosarcoma (ICD9 200), 4/3.5 from Hodgkin's disease, 13/13.5 from leukaemia, 8/6.7 from non-Hodgkin's lymphoma (ICD9 202) and 3/5.1 from myeloma; 6/11.6 from **cancer of the brain and nervous system**; 11/11.6 from **cancer of the stomach**; 16/16.9 from **cancer of the pancreas**; 8/7.7 from **cancer of the oesophagus**; and 13/7.2 from **cancer of the kidney**. Mortality ratios for subjects first exposed before 1978 were virtually identical to those for the full cohort. No significant trend in mortality was observed in relation to duration of exposure, but the mortality ratios for leukaemia (1.79 based on five deaths) and non-Hodgkin's Lymphoma (1.92 based on five deaths) were higher after allowance for a latency of more than 20 years. Among the sterilizer operators, mortality ratios (and observed numbers of deaths) were 2.78 (two) for leukaemia and 6.68 (two) for lymphosarcoma/reticulosarcoma; no death from stomach **cancer** was seen.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V60 94-5. (1994)]**PEER REVIEWED**

Human Toxicity Excerpts :

A retrospective cohort study /was reported/ of 767 men employed at a chemical plant in eastern Texas, USA, between 1955 and 1977 where ethylene oxide was produced. All of the men had worked at the factory for at least five years and were potentially exposed to the compound. Potential exposure to ethylene oxide was determined by personnel at the company on the basis of work histories. In an industrial hygiene survey in all samples taken in the ethylene oxide production area contained less than 10 ppm (18 mg/cu m). Vital status was ascertained for more than 95% of cohort members from a combination of plant records, personal knowledge and telephone follow-up. Altogether, 46 deaths were recorded, whereas 80 were expected on the basis of US vital statistics. Death certificates were obtained for 42 of the 46 deceased subjects. Eleven deaths were from **cancer** (15.2 expected), and nonsignificant excesses were seen of **cancers of the pancreas** (3/0.8) and **brain and central nervous system** (2/0.7) and of Hodgkin's disease (2/0.4); no death from leukaemia was found.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V60 90-1 (1994)]**PEER REVIEWED**

FIFRA Requirements :

As the federal **pesticide** law FIFRA directs, EPA is conducting a comprehensive review of older **pesticides** to consider their health and environmental effects and make decisions about their future use. Under this **pesticide** reregistration program, EPA examines health and safety data for **pesticide** active ingredients initially registered before November 1, 1984, and determines whether they are eligible for reregistration. In addition, all **pesticides** must meet the new safety standard of the Food Quality Protection Act of 1996. Ethylene oxide is found on List A, which contains most food use **pesticides** and consists of the 194 chemical cases (or 350 individual active ingredients) for which EPA issued registration standards prior to FIFRA, as amended in 1988. Case No: 2275; **Pesticide type**: insecticide, fungicide, rodenticide, antimicrobial; Case Status:In Pre-Special Review. The **pesticide** is in or has completed the reregistration process and, meanwhile, is also the subject of an in-depth Special Review.; Active ingredient (AI): Ethylene oxide; Data Call-in (DCI) Date(s): 05/24/91; AI



Bromomethane

CASRN: 74-83-9

*For other data, click on the Table of Contents***II.A.4. Supporting Data for Carcinogenicity:**

Supporting Data for Carcinogenicity

Bromomethane has been shown to produce mutations in Salmonella strains sensitive to alkylating agents and to E. coli both with and without the addition of a metabolic activation system (Voogd et al., 1982; Moriya et al., 1983; Kramers et al., 1985; Djalali-Behzad et al., 1981). **Bromomethane** was also mutagenic in a modification of the standard Salmonella assay employing vapor phase exposure (Simmon and Tardiff, 1978; Simmon, 1978, 1981; Simmon et al., 1977). **Bromomethane** was observed to be mutagenic for Drosophila and for mouse lymphoma cells (Voogd et al., 1982; Kramers et al., 1985).

Bromomethane is structurally related to bromoethane which, when tested in mice and rats of both sexes, has shown clear evidence of carcinogenicity in some cases and equivocal in others. NTP (1988) conducted an inhalation bioassay on bromoethane, and the results were recently released in a draft report. Groups of F344/N rats (50/sex) and B6C3F1 mice (50/sex) were exposed to 0, 100, 200 or 400 ppm bromoethane 6 hours/day for 5 days/week. A statistically significant increase in uterine adenomas, adenocarcinomas, or squamous cell carcinomas was observed in female mice exposed to 200 and 400 ppm, indicating clear evidence of carcinogenic activity. Equivocal evidence of carcinogenic activity was reported for male and female rats and male mice. While alveolar/bronchiolar adenomas or carcinomas and pheochromocytomas were observed in male rats, the incidences were not dose-related and were within the historical ranges for NTP studies. Granular cell tumors of the brain were also observed in male rats and, although not statistically significant, the incidence was higher than historical incidence in either the study lab or NTP studies. The incidence of alveolar/bronchiolar neoplasms in exposed male mice was marginally greater than control or historical incidence. An increased incidence of gliomas in exposed female rats was significant by the trend test; however, the incidence was not significantly greater when compared with the controls in the study and the controls used in NTP studies.

I.B.4. Additional Studies/Comments (Inhalation RfC):

Additional Studies/Comments (Inhalation RfC)

NTP conducted a 13-week subchronic study in B6C3F1 mice and F344 rats and a 6-week target organ study (Eustis et al., 1988; NTP, 1990). A chronic study on the toxicology and carcinogenesis of **bromomethane** following inhalation exposure to B6C3F1 mice was also conducted (NTP, 1990).

In the 13-week study, 18 rats/sex/group were exposed to target concentrations of 0, 30, 60, or 120 ppm (0, 117, 233, or 466 mg/cu.m, respectively) **bromomethane** 6 hours/day, 5 days/week (duration-adjusted concentrations are 0, 20.9, 41.6, and 83.2 mg/cu.m, respectively). Mice (18- 27/sex/group) were exposed to 0, 10, 20, 40, 80, or 120 ppm (0, 38.8, 77.6, 155, 311, or 466 mg/cu.m, respectively) **bromomethane** 6 hours/day, 5 days/week (duration-adjusted concentrations are 0, 6.93, 13.9, 27.7, 55.5, or 83.2 mg/cu.m, respectively). Hematological parameters were measured and organ weights

were determined for the adrenals (rats only), **brain**, heart, kidney, lung, spleen (rats only), testis, and thymus (mice only). Pseudocholinesterase activity was measured in the mice only. Neurobehavioral testing was conducted on 8 rats and 8 mice/sex/group at weeks 0, 6, and 12, and neuromorphological studies were conducted on 4 rats/sex from the control and 120-ppm group and on 4 mice/sex for each concentration. Histopathological examination of approximately 40 tissues from control and 120-ppm animals were carried out, including lungs, bronchi, and nasal turbinates. Exposure-related changes seen in the mice were a significant (58%) body weight gain reduction and a 17% increase in mortality in mice exposed to 120 ppm **bromomethane**. Mice exposed to this level exhibited severe curling and crossing of the hindlimbs and twitching of the forelimbs; these effects were more severe in the males. Hematological parameters that were found to be statistically significantly different from control values in mice included decreased mean cell hemoglobin, decreased mean cell count, and increased erythrocyte count in males exposed to 40, 80, and 120 ppm; and increased hemoglobin in males exposed to 120 ppm. No exposure-related effects were seen upon histopathological examination. In the rats there was no increase in mortality, but the males exposed to 120 ppm and the females exposed to 60 and 120 ppm **bromomethane** exhibited significant decreases in body weight gain. Mild neurobehavioral effects were noted in the high-concentration rats of both sexes. Females exposed to 120 ppm were found to have significantly lower hematocrit, hemoglobin, and erythrocytes counts, but the males did not exhibit these changes. The only exposure-related effect noted at histopathological examination was an increase in the incidence of olfactory epithelial dysplasia and cysts in the rats of both sexes exposed to 120 ppm [LOAEL(HEC) = 12 mg/cu.m]. Based on these results a NOAEL of 80 ppm [NOAEL(HEC) = 8 mg/cu.m] for nasal olfactory epithelial changes in rats is established.

Because no significant target organ toxicity was noted in the 14-day or 13-week studies, a special 6-week target organ toxicity study at a near lethal concentration was conducted in F344 rats and B6C3F1 mice (Eustis et al., 1988; NTP, 1990). Groups of 5 animals/sex were exposed to 0 or 160 ppm (621 mg/cu.m) **bromomethane** 6 hours/day for either 3 consecutive days (rats), or 5 days/week over 2 weeks (rats and mice) or 6 weeks (rats). Fifteen mice/sex/dose were exposed to 0 or 160 ppm (621 mg/cu.m) 6 hours/day, 5 days/week, for 6 weeks. Endpoints studied included clinical observations, mortality, body and organ weights, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology of a standard set of tissues, including the lungs and nasal turbinates. The female rats were the only group to demonstrate more than 50% survival, with mice being more sensitive than rats (mortality exceeded 50% after 6-8 exposures in both the male and female mice and after 14 exposures in the male rats). Because of the high mortality, the male and female mice and male rats were killed after 10, 8, or 14 exposures, respectively. Neurological signs exhibited by both rats and mice, but to a lesser extent in the rats, included lethargy and curling and crossing of hindlimbs, forelimb twitching, and tremors. Decreases in body weight gain were observed in the exposed animals as compared to controls (18% in the mice and 32% in the rats). The mean organ weights of most organs were significantly reduced in both species. Notable hematological effects were seen mostly in the female mice and included decreased RBC and increased WBC counts. Target organs affected by exposure to 160 ppm **bromomethane** were the **brain**, kidney, nasal cavity, heart, adrenal gland, liver, and testes. Species differences were noted in the responses of these organs. For example, neuronal necrosis in the cerebral cortex, hippocampus, and thalamus of the **brain** were seen in the rats whereas neuronal necrosis was seen predominantly in the internal granular layer of the cerebellum of the mice. Nephrosis, characterized by degeneration, necrosis, and sloughing of the epithelium of the cortical convoluted tubules was seen in all of the exposed mice and was considered by the authors to be partially responsible for the increase in mortality, but these lesions were not observed in the rats. Degeneration and atrophy of the seminiferous tubules was observed in several of the exposed rats and mice, but was less severe in the mice. Olfactory epithelial degeneration was

observed in the rats of both sexes, and this was seen to a lesser degree in the male mice, with only one female mouse exhibiting this lesion. Myocardial degeneration was seen in rats of both sexes, and to a lesser degree in the male mice. Atrophy of the inner zone of the adrenal cortex was observed in the female mice, and cytoplasmic vacuolation of the adrenal cortex was seen in rats.

In the chronic study (NTP, 1990), a total of 86 mice/sex/concentration were exposed to 0, 10, 33, or 100 ppm (0, 38.8, 128, or 388 mg/cu.m, respectively) **bromomethane** 6 hours/day, 5 days/week (duration-adjusted concentrations are 0, 6.93, 22.9, or 69.3 mg/cu.m, respectively). Exposures to 10 and 33 ppm were for 103 weeks, with interim sacrifices at 6 and 11 months. Exposure to 100 ppm produced 47% mortality in the males and 10% mortality in the females by 20 weeks, so exposure was discontinued in this group at this time and the surviving animals were observed for an additional 84 weeks, except for the females scheduled for the 15-month sacrifice. The endpoints studied were the same as those described for the 6-week target organ toxicity study in addition to neurobehavioral assessments in 16 mice/sex/group and neuropathological examination on 3-8 animals/sex/group at 20 weeks and 6, 15, and 24 months. Body weights were significantly depressed in the animals exposed to 100 ppm (33% in the males and 31% in the females) beginning at week 11 and persisting until study termination. Significant body weight changes were not observed in the lower exposure groups. Because of the reduced body weight in the 100-ppm animals, organ weight changes were difficult to interpret, but reduced absolute and relative thymus weights were observed in both the males and females exposed to 100 ppm **bromomethane**. Clinical signs of toxicity observed almost exclusively in the 100-ppm animals that persisted throughout the 103 weeks included tremors, abnormal posture, and limb paralysis. Functional neurobehavioral changes consisting of hypoactivity, a heightened startle response, and higher hindlimb grip scores and hot plate latency were observed in both sexes exposed to 100 ppm at various times during exposure, but were more pronounced in the males. The target organs of toxicity identified in this study were the **brain**, bone (sternum), heart, and nose, with lesions in these organs occurring more frequently in the males. In the **brain**, there was a statistically significant increase in the incidence of cerebellar degeneration in the animals exposed to 100 ppm. Cerebral degeneration was also observed in these animals, but the incidence of this lesion was statistically significant in the males only. Because this lesion was observed more frequently in the animals that died prior to study termination, it may have contributed to the early mortality in this group. Dysplasia of the sternal bone marrow was observed at a statistically significantly increased rate in both the males and the females exposed to 100 ppm, but because it was observed more frequently in the animals that survived to study termination than in those that died early, it was not considered to be a contributing factor to the death of these animals. Myocardial degeneration and chronic cardiomyopathy were also observed at a statistically higher incidence in both males and females exposed to 100 ppm **bromomethane**, and occurred at a higher incidence in those animals dying early. Finally, a statistically significant increase in the incidence of olfactory epithelial necrosis and metaplasia was seen in the nasal cavities of both the male and female mice exposed to 100 ppm. Necrosis was seen only in the animals dying early, whereas metaplasia was exhibited mainly in those animals surviving until study termination. Histopathological changes in other organs were observed and considered to be secondary to stress and weight loss rather than a direct toxic effect of **bromomethane**. Animals exposed to lower concentrations did not exhibit significant increases in any of the lesions described above. Based on the results of this study, a NOAEL of 33 ppm (HEC = 4.4 mg/cu.m for respiratory effects and 23 mg/cu.m for extrarespiratory effects) and a LOAEL of 100 ppm (HEC = 13 mg/cu.m for respiratory effects and 69 mg/cu.m for extrarespiratory effects) are established based on toxicity in multiple organs.

Male Fischer 344 rats (10/group) were exposed to 0, 90, 175, 250, or 325 ppm (0, 350, 680, 971, or 1,262 mg/cu.m, respectively) **bromomethane** (99.9% pure) 6 hours/day for 5 days (Hurt et al.,

1987). The **brain**, nasal cavity, liver, kidney, adrenal glands, testes, and epididymides were examined histopathologically. The lungs were not examined. Three animals exposed to 325 ppm died after the fourth exposure. Diarrhea, hemoglobinuria, gait disturbances, convulsions and hepatocellular degeneration were observed in animals exposed to 250 ppm or greater; vacuolar degeneration of the zona fasciculata of the adrenal gland and cerebellar granule cell degeneration were observed in rats exposed at 175 ppm and greater. Minor alterations in testicular histology and cerebrocortical degeneration were observed in the 350-ppm exposure group. A concentration-dependent degeneration of the nasal olfactory sensory cells was observed in rats exposed to 175 ppm **bromomethane** or greater. This degeneration affected 50-80% of the olfactory mucosa, and was characterized by complete or partial destruction of the olfactory epithelium at the higher concentrations. Small foci of hepatocellular coagulative necrosis were observed in animals exposed to the two highest concentrations. No exposure-related lesions were noted in the kidneys.

In a subsequent study, Hurtt et al. (1988) investigated the ability and time-course of the olfactory epithelium to regenerate following acute exposure to **bromomethane**. Male Fischer 344 rats were exposed to 0 (n=5) or 200 ppm (n=40) 99.9% pure **bromomethane** (777 mg/cu.m) 6 hours/day for 1-5 days. Five animals/group were killed after 1, 3, or 5 days of exposure and 1, 2, 3, 5, or 10 weeks after cessation of treatment. In a companion study, 6 animals/group were exposed to 0, 90, or 200 ppm (0, 350, or 777 mg/cu.m) **bromomethane** for 6 hours and olfactory function was studied by determining the effects of **bromomethane** on the ability of food-deprived animals to locate buried food pellets. Additional animals similarly exposed were killed at various times following the single 6-hour exposure to assess the state of morphological regeneration at the time of functional recovery. Only the nasal cavities were examined histopathologically in these studies. No clinical signs of toxicity were observed in the exposed animals. Extensive destruction of the olfactory epithelium, characterized by epithelial disruption, fragmentation, and exfoliation, was evident after a single 6-hour exposure to 90 or 200 ppm, with the most severe effects observed in the sustentacular and mature sensory cells, and the basal cell remaining intact. Regeneration of the olfactory epithelium, characterized at first by replacement with a squamous cell layer that increased in thickness, began by the third day of exposure and was essentially complete by 10 weeks after the last exposure. It is important to note that regeneration began even though exposure to **bromomethane** was still ongoing. Olfactory function was impaired in animals exposed to 200 ppm **bromomethane**, but not 90 ppm. Recovery of this function was evident by 4-6 days after exposure, which preceded morphological regeneration.

Similar results were obtained by Hastings (1990). In this study, rats were exposed to 200 ppm (777 mg/cu.m) **bromomethane** 4 hours/day 2 days/week for 2 weeks. Prior to exposure, rats were food-deprived and trained to find buried food pellets. Morphological as well as biochemical (carnosine content in the olfactory bulb, which is an indication of the integrity of the olfactory primary sensory neurons) studies were performed as well to assess the integrity of the olfactory epithelium. Extensive damage to the olfactory epithelium was seen, as evidenced by both morphological analysis and decreased carnosine content after a single 4-hour exposure. Olfactory function was also impaired after 4 hours, as evidenced by the inability of the rats to find the buried food pellets. However, olfactory function began to return after the second week of exposure and the animals performed as well as their controls by the end of the exposure period whereas regeneration of the olfactory epithelium, as indicated by morphological and biochemical analysis was not complete until 30 days from the start of exposure.

The most common signs of acute intoxication with **bromomethane** in humans are neurotoxic in nature and include headache, dizziness, fainting, apathy, weakness, tiredness, giddiness, delirium,

stupor, psychosis, loss of memory, mental confusion, speech impairment, visual effects, limb numbness, tremors, muscle twitching, paralysis, ataxia, seizures, convulsions, and unconscious. Several studies have been conducted on the longer-term effects of occupational exposure to **bromomethane**. None of these studies can serve as the basis for the derivation of an RfC for **bromomethane** because of concurrent exposures to other chemicals, inadequate quantitation of exposure levels and/or durations, and other deficits in study design.

In a cross-sectional occupational study conducted by Anger et al. (1986), soil and structural fumigators underwent a neurological examination. The exposure group was blinded to the physician giving the examination. Most of the structural fumigators used both **bromomethane** (MB) and sulfuryl fluoride (SF). The formation of the study groups was based on the estimated time devoted to **bromomethane** and sulfuryl fluoride fumigation activities, and estimated length of time in the occupation. Four groups were formed: the MB group (n=32) consisted of structural fumigators using MB 80% or more of the time and soil fumigators using the mixture MB and chloropicrin; the SF group (n=24) consisted of structural fumigators who used SF 80% or more of the time; group COMB (n=18) consisted of workers using both MB and SF 40-60% of the time, the reference group (Group R, n=29) consisted of those workers who were not directly exposed to fumigants, but worked in the fumigation industry. The workers in the exposed groups had been in the profession for 1 or more years and had fumigated a house or field within the last 50 days. More symptoms were reported in the exposed groups than in the reference population: 78-83% and 41% respectively showed symptoms. The difference was significant for the MB and COMB groups when compared to Group R. The MB group did not perform as well as referents on several behavioral tests, including tests of cognitive function, reflexes, sensory and visual effects. Although this study suggests mild neurological effects of exposure to **methyl bromide**, it is difficult to draw any conclusions between exposure and effect because of the confounding factors. The exposed and reference groups were not well matched for age; use of prescription medication, alcohol, or illegal drugs within 2 days of the testing; education; or ethnic group. In addition, participation in the study was voluntary and no information is provided on the use of personal protective equipment in these groups.

Herzstein and Cullen (1990) reported on 4 cases of **bromomethane** toxicity at a nursery following the removal of polyethylene sheets covering soil fumigated with 98% **bromomethane** and 2% chloropicrin. Four workers involved in removing the tarp wore no respiratory protection, and had no training in the handling or Hazards of **bromomethane**. On the second day, all four workers noted fatigue and lightheadedness. After arriving home, three of the workers developed severe coughing, chest tightness, nausea, vomiting, headaches, and tremulousness during the night. Three workers were found to have either ataxia, tremor, or both. Blood bromide levels were not performed. The symptoms continued to improve without treatment. Upper- and lower-extremity paresthesias and reduced hand dexterity were reported in two workers at 3 weeks post-exposure. There were no long-term adverse effects after 18 months of follow-up.

The first reported study on the effects of short-term and repeated exposure to **bromomethane** in experimental animals was conducted by Irish et al. (1940). In the first set of experiments, rats and rabbits were exposed once to 420-50,000 mg/cu.m **bromomethane** for varying lengths of time. Concentrations of **bromomethane** greater than or equal to 10,000 mg/cu.m were lethal to 100% of the animals within 6-132 minutes. Deaths also occurred at 6-36 hours after exposure to concentrations less than 10,000 mg/cu.m. Clinical signs observed in rats exposed to less than 10,000 mg/cu.m included roughening of the fur, hunching of the back, drowsiness, heavy breathing, and lacrimation. Nasal irritation and lacrimation were observed, in addition to the signs mentioned above, at higher concentrations. Rabbits did not exhibit these signs. However, in rats exposed to greater than

1000 mg/cu.m for 20 hours, a hyperexcitable state was observed, whereas rabbits exposed to the same concentration exhibited paralysis. Evidence of pulmonary irritation (congestion and edema) was found (predominantly in the rat) following exposures to 1,000-20,000 mg/cu.m.

In subsequent studies, rats (n=135), rabbits (n=104), guinea pigs (n=98) and female rhesus monkeys (n=13) were exposed to 0, 17, 33, 66, 100, or 220 ppm (0, 66, 128, 256, 388, or 853 mg/cu.m, respectively) 7-8 hours/day, 5 days/week for 6 months or until the majority exhibited severe reactions or died. The frank-effect-levels (increased mortality) were 100 ppm for rats, guinea pigs, and monkeys and 133 ppm for rabbits (Irish et al., 1940). Rabbits and monkeys exhibited paralysis after exposure to 66 ppm whereas rats and guinea pigs exhibited no adverse effects. Pulmonary damage was still seen in rabbits exposed to 33 ppm, but the monkeys appeared normal. None of the species exhibited adverse effects following repeated exposure to 17 ppm (66 mg/cu.m; Irish et al. 1940).

The **brain** and heart also appeared to be target organs following inhalation exposure to **bromomethane** in a study conducted by Kato et al. (1986). Male Sprague-Dawley rats (10-12/group) were exposed to 150 ppm (583 mg/cu.m) **bromomethane** (purity unspecified) 4 hours/day, 5 days/week for 11 weeks (duration-adjusted to 69.3 mg/cu.m). Focal necrosis and fibrosis of coronary ventricles and papillary muscle disorders were observed in the exposed animals. In the same study, male Sprague-Dawley rats (10-12/group) were exposed to 0, 200, 300, or 400 ppm (0, 777, 1,165, or 1,553 mg/cu.m) 4 hours/day, 5 days/week for 6 weeks (duration-adjusted concentrations are 0, 92.5, 139, and 185 mg/cu.m, respectively). Focal necrosis and fibrosis of coronary ventricles and papillary muscle were observed in all exposed animals. Neurological dysfunction (ataxia, paralysis) were reported at levels at and exceeding 300 ppm; necrosis in the bilateral regions of the dorso-external cortex of the cerebral hemisphere was observed in animals exposed at 400 ppm. Testicular atrophy with suppression of spermatogenesis was apparent in 6 of the 8 the animals exposed to 400 ppm. Although the lungs appeared to be one of the tissues examined histopathologically, respiratory effects were not addressed in the descriptions of either experiment.

Neurobehavioral effects of **bromomethane** inhalation were studied in rats and rabbits by Anger et al. (1981). In one set of experiments, Sprague-Dawley rats and New Zealand white rabbits were exposed to 0 (n=2) or 65 ppm (252 mg/cu.m, n=6) 7.5 hours/day, 4 days/week for 4 weeks. Neurobehavioral testing, consisting of conduction velocity in the sciatic and ulnar nerves (rats and rabbits), eye-blink reflex (rabbits), open field activity (rats), and grip/coordination (rats) were conducted weekly. Exposed rabbits exhibited depressed body weight gain as compared with the controls, and signs of hind limb paralysis were evident during the last week of exposure. Statistically significant decreases in the eyeblink reflex magnitude and in nerve conduction velocity were also observed in the exposed rabbits. In contrast, no effects on weight gain, grip/coordination, or nerve conduction velocity were observed in the rats exposed to 65 ppm for 4 weeks. The LOAEL for neurological effects in rabbits and the NOAEL for rats is 65 ppm. In another experiment that was performed as part of this study, Sprague-Dawley rats were exposed to 0 or 55 ppm (214 mg/cu.m) **bromomethane** 6 hour/day, 5 day/week for 36 weeks. Neurobehavioral tests (conduction velocity in the sciatic and ulnar nerves, open-field activity, and grip/coordination) conducted at 25- to 30-day intervals did not reveal any exposure-related effects.

In a subsequent study performed by this group (Russo et al., 1984) that was designed to assess the neurotoxic effects of **bromomethane** in rabbits following longer-term exposure at lower concentration, male New Zealand white rabbits were exposed to 0 (n=2) or 26.6 ppm (103 mg/cu.m, n=6) 99% pure **bromomethane** 7.5 hours/day, 4 days/week for 8 months (Russo et al., 1984). Exposure concentrations were monitored every 12 minutes by an infrared analyzer. Neurobehavioral

tests examined the latency rates of the sciatic and ulnar nerves and the amplitude of the reflex of the orbicularis oculi muscle. No other parameters, including respiratory effects, were monitored. No exposure-related neurological effects were observed [NOAEL(HEC) = 23 mg/cu.m]. As part of this study, the animals exposed to 252 mg/cu.m **bromomethane** for 4 weeks (previously discussed; Anger et al., 1981) were allowed to recover for 6-8 weeks and the neurological tests were repeated. The animals demonstrated partial, but not complete recovery within the 6-week period. Therefore rabbits, which are sensitive to the neurotoxic effects of high-level exposure to **bromomethane**, can tolerate long-term low-level exposure to **bromomethane**, and appear to be able to recover from severe neurological effects after cessation of exposure.

Morrissey et al. (1988), using data obtained from the 13-week NTP (1990) study in rats and mice, evaluated testis, epididymis, and cauda epididymis weights; caudal sperm motility and count; sperm head morphology; average estrous cycle length; and relative frequency of different estrous stages to assess the potential reproductive effects of **bromomethane**. In mice, they found that inhalation exposure to **bromomethane** resulted in an increase in the relative weights of the epididymis and testis, a decrease in sperm density, and an increase in the percentage of abnormal sperm. In the rats, a decrease in absolute cauda epididymis and absolute and relative epididymis weights, an increase in relative testis weight, and a decrease in sperm motility occurred as a result of subchronic inhalation exposure to **bromomethane**. No effects on estrous cycle length were noted. This study is an evaluation of a screening method for reproductive toxicants and was applied to 50 subchronic studies carried out by the NTP. The exposure levels at which these effects were found were not specified.

Male Fischer 344 rats (75/group) were exposed to 0 or 200 ppm **bromomethane** (777 mg/cu.m) 6 hours/day for 5 consecutive days and sacrificed on various days beginning on day 1 of exposure through 68 days after termination of exposure. Plasma testosterone and testicular glutathione levels were depressed, but returned to control levels within 3 days after exposure had ended. No effects on spermatogenesis, sperm quality, or testicular weight or histology were noted (Hurtt and Working, 1988).

Female Wistar rats (n=39-45) were exposed to 0, 20, or 70 ppm (0, 78, or 272 mg/cu.m, respectively) **bromomethane** 7 hours/day, 5 days/week for 3 weeks, mated and exposed during gestational days 1-19. The study design included groups at each exposure level exposed pregestationally, during gestation, and both, as well as a control. At gestational day 21, litters were evaluated for fetotoxicity and live fetuses were examined for external, visceral (about 1/2 of fetuses), and skeletal abnormalities. Maternal organ weights for liver, kidney, and lung, and histopathology on 8 animals/group on ovaries, uterus, kidney, lung, and trachea were performed. No mortality or change in organ weights were observed and body weight was decreased during gestation but was not different than controls at full term. Histological effects observed in the lung and kidney were not clearly exposure-related due to the small sample size and high control incidence. There was no effect on pregnancy rate or fetal size. There were 31-38 litters/group examined and no effect on embryotoxicity, fetal viability, or fecundity measures was observed. There was no increase in malformations. The NOAEL for reproductive toxicity (changes in fertility rate) and maternal and fetal toxicity in rats is 70 ppm (Sikov et al., 1981; Hardin et al., 1981).

Female New Zealand white rabbits (25/group) were exposed to 0, 20, or 70 ppm (0, 78, or 272 mg/cu.m, respectively) **bromomethane** 7 hours/day, 5 days/week for 3 weeks during gestational days 1-24. Evaluation of developmental effects was the same as in the rat study except that all fetuses were evaluated for visceral abnormalities. In the 70-ppm group, severe neurotoxic effects occurred and 24/25 animals died. No effects on body weight, organ weight, or histology were observed in maternal

animals exposed to 20 ppm. There was no effect on pregnancy rate or fetal size. There were 13 litters in the group exposed to 20 ppm examined and no effect on embryotoxicity, fetal viability, or fecundity measures was observed. There was no increase in malformations. The NOAEL for maternal and fetal toxicity in rabbits is 20 ppm (Sikov et al., 1981; Hardin et al., 1981).

Breslin et al. (1990) performed a developmental study in rabbits in which New Zealand rabbits (26/group) were exposed to 0, 20, 40, or 80 ppm (0, 78, 155, or 311 mg/cu.m, respectively) **methyl bromide** 6 hours/day on gestation days 6-19. Maternal toxicity at 80 ppm included reduced body weight and weight gain. Clinical signs of central nervous system toxicity were observed at 80 ppm. There was no effect on pre- or postimplantation loss, litter size, or fetal body weights. There was an increase in agenesis of the gall bladder and fused sternbrae at 80 ppm. The NOAEL for maternal toxicity and developmental effects in this study is 40 ppm [NOAEL(HEC) = 155 mg/cu.m].

American Biogenics Corporation (1986) conducted a two-generation reproduction study in Sprague-Dawley rats. Groups of 25 rats/sex/dose were exposed by inhalation to **methyl bromide** vapor at 0, 3, 30, or 90 ppm (0, 12, 117, or 350 mg/cu.m) 6 hours/day, 5 days/week during the pre-mating, gestation, and lactation periods for 2 generations. In F0 male rats, exposure at 90 ppm caused statistically significant decreases in body weight gain during the pre-mating period, final body weight, and total weight gain. No treatment-related changes in reproductive organs were noted. Also, no adverse effects were found on the progeny and reproductive parameters examined. In second generation (F1) animals, no adverse effects were found on body weights, histopathology of reproductive organs, or reproductive parameters measured. However, a statistically significant concentration-related reduction in body weights at 28 days was noted in F2 males and females at 30 ppm and 90 ppm. Although significant changes were seen in some of the mean organ weights and organ-to-body weight ratios in F0, F1, and F2 generation animals, no histopathology changes were seen in these organs. Therefore, the biological significance of these findings if any is not clear. Under the conditions of the study, exposure to **methyl bromide** did not affect fertility in rats but decreased the body weights of parental rats and reduced the growth of neonatal rats. The NOAEL and LOAEL for these effects were 30 and 90 ppm for adult rats and 3 and 30 ppm for neonates, respectively.

Medinsky et al. (1985) and Bond et al. (1985) conducted a series of experiments to assess the uptake, distribution, and excretion of **bromomethane** in rats following inhalation exposure. In one experiment, F344 rats were exposed to 1.6, 9, 170, or 310 ppm (6, 35, 660, or 1,203 mg/cu.m) radiolabeled **bromomethane** (nose-only) for 6 hours (Medinsky et al., 1985), and in the other, F344 rats were exposed to 9 ppm radiolabeled **bromomethane** for 6 hours (Bond et al., 1985). The percentage of total volume of inhaled radiolabeled **bromomethane** that was absorbed decreased in a concentration-related manner from 48+/-2% at the two lower concentrations to 27+/-4% at the highest concentration, which indicates that uptake of **bromomethane** is a saturable process. In both studies, inhaled **bromomethane** was distributed quickly throughout the body, and the highest concentrations were found in the lung, adrenal, kidney, liver, and nasal turbinates. By 65-66 hours after exposure, 75% of the radiolabel had been eliminated. The amount of **bromomethane** eliminated was linearly related to the amount absorbed (Medinsky et al., 1985). Excretion of **bromomethane** and its metabolites does not appear to be a concentration dependent (i.e., saturable) process, once absorbed.

I.B.2. Principal and Supporting Studies (Inhalation RfC):

Principal and Supporting Studies (Inhalation RfC)

Reuzel, P.G.J., C.F. Kuper, H.C. Dreef-van der Meulen and V.M.H. Hollanders. 1987. Chronic (29-month) inhalation toxicity and carcinogenicity study of **methyl bromide** in rats. Report No. V86.469/221044. Netherlands Organization for Applied Scientific Research, Division for Nutrition and Food Research, TNO. EPA/OTS Document No. 86-8700001202.

Reuzel, P.G.J., H.C. Dreef-van der Meulen, V.M.H. Hollanders, C.F. Kuper, V.J. Feron and C.A. van der Heijden. 1991. Chronic inhalation toxicity and carcinogenicity study of **methyl bromide** in Wistar rats. *Fd. Chem. Toxic.* 29(1): 31-39.

A series of inhalation toxicity studies of **bromomethane** were conducted under the sponsorship of the National Institute of Public Health and Environmental Hygiene of the Netherlands. In a chronic inhalation study conducted by Reuzel et al. (1987, 1991), 50 male and 60 female Wistar rats were exposed to 0, 3, 30, or 90 ppm (0, 11.7, 117, or 350 mg/cu.m, respectively) 98.8 % pure **bromomethane** 6 hours/day, 5 days/week (duration-adjusted concentrations are 0, 2.08, 20.9, or 62.5 mg/cu.m, respectively) for up to 29 months. Three satellite groups of 10 animals/sex/exposure level were sacrificed at 14, 53, and 105 weeks of exposure. Animals were observed daily, and body weight was recorded weekly for the first 12 weeks and monthly thereafter. Hematology, clinical chemistry, and urinalyses were conducted at 12-14 weeks and 52-53 weeks in the satellite groups. Eleven organs were weighed at necropsy, and approximately 36 tissues, including the lungs with trachea and larynx; 6 cross-sections of the nose; heart; **brain**; and adrenal glands were examined histopathologically. The test atmosphere was measured by gas chromatography every 30 minutes during exposure.

Males and females exposed to 90 ppm exhibited decreased body weight gains; no treatment-related changes in hematological, biochemical, or urine parameters were observed. A significant concentration-related decrease in relative kidney weights was reported in the 30- and 90-ppm males. A decrease in mean absolute **brain** weight was reported to occur in the 90-ppm females at weeks 53 and 105, but there was no change in relative **brain** weight or in **brain** histology. Microscopic evaluation revealed that the nose, the heart, and the esophagus and forestomach were the principle targets of **bromomethane** toxicity in this study. Very slight to moderate hyperplastic changes in the basal cells accompanied by degeneration in the olfactory epithelium in the dorso-medial part of the nasal cavity were observed in all exposed groups of both sexes at 29 months of exposure. At the lowest concentration, the lesion is described as very slight. These changes were concentration-related in both incidence and severity and were statistically significant at 29 months. Incidence of basal cell hyperplasia in control, 3-, 30-, and 90-ppm groups were 4/46, 13/48, 23/49, and 31/48 in males and 9/58, 19/58, 25/59, and 42/59 in females, respectively. Slight increases in incidence of basal cell hyperplasia in the 30- and 90-ppm groups (n=7-10) at 53 and 105 weeks were not statistically significant. Lesions in the heart were statistically significant in the males (cartilaginous metaplasia and thrombus), and the females (myocardial degeneration and thrombus) exposed to 90 ppm. The authors attributed part of the increased mortality in the high-concentration animals to the cardiac lesions. A statistically significant increase in hyperkeratosis of the esophagus was observed in the 90-ppm males after 29 months of exposure. Slight increases in forestomach lesions were not statistically significant. No effects were observed in the tracheobronchial or pulmonary regions of the respiratory tract. No other exposure-related effects were noted. Based on these results, a LOAEL of 3 ppm (HEC = 0.48 mg/cu.m) for nasal effects is established.

II.A.3. Animal Carcinogenicity Data:

Animal Carcinogenicity Data

Inadequate. **Bromomethane** was administered by gavage to groups of 10 male and female Wistar rats (Danse et al., 1984). Animals were administered doses of 0, 0.4, 2, 10, or 50 mg/kg/day **bromomethane** in arachis oil 5 days/week for 13 weeks, at which time the experiment was terminated. There was an apparent dose-related increase in diffuse hyperplasia of the forestomach. The authors reported a forestomach papilloma incidence of 2/10 in the high-dose males and forestomach carcinoma incidences of 7/10 and 6/10 in the high-dose males and females, respectively. These results were subsequently questioned (U.S. EPA, 1985; Schatzow, 1984). A panel of NTP scientists reevaluated the histological slides and concluded that the lesions were hyperplasia and inflammation rather than neoplasia.

Rosenblum et al. (1960) reported a 1-year study in which beagle dogs (4/treatment group, 6/control) were provided diets fumigated to residue levels of 0, 35, 75, or 150 ppm **bromomethane**. No **tumors** were observed at any dose level; however, there was no indication that the dogs were examined for **tumors**. In addition, 1-year observation is considered to be inadequate by the EPA for **tumor** induction in dogs.

In an earlier study (Irish et al., 1940) small numbers of rats, guinea pigs, rabbits and monkeys were exposed by inhalation to **bromomethane** at doses ranging from 0.065 to 0.85 mg/L air. Exposures were for 7.5 to 8 hours/day, 5 days/week for up to 6 months. The authors reported that the highest dose produced acutely toxic effects in all species, but no **tumors** were observed at any dose level. The short duration of exposure and observation are considered inadequate by the EPA.

Bromomethane is currently on test at NTP.

VI.B. Inhalation RfC References:

Inhalation RfC References

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I.A.4. Additional Studies/Comments (Oral RfD):

Additional Studies/Comments (Oral RfD)

The current RfD is based on the Danse et al. (1984) study, which uses the preferred oral route of exposure for deriving an oral RfD. The previous oral RfD (4E-4 mg/kg/day) was based on the inhalation studies by Irish et al. (1940). Inhalation studies are inappropriate for oral risk assessment extrapolation for **bromomethane** because portal-of-entry effects are observed for both the inhalation route (lung pathology) and oral route (stomach hyperplasia). In addition, neurological effects reported after inhalation exposures have not been reported after oral exposures.

Beagle dogs of either sex were fed **methyl bromide** fumigated food ad libitum for 1 year so that groups of four dogs each ingested approximately 35, 75, or 150 mg/kg/day of bromide, or adjusting for molecular weight, 41.6, 89.1, or 178.2 mg/kg/day of **methyl bromide**, assuming all the bromide was present as **methyl bromide** (Rosenblum et al., 1960). The control group consisted of three male and three female dogs fed only dog chow, ad libitum. The dogs ingesting 178.2 mg/kg/day **methyl**

bromide gained more weight than the controls or the two lower treatment groups; they also became lethargic and displayed excessive salivation and occasional diarrhea. **Methyl bromide** was reported to have no effect on hematological values, urinalysis, blood chemistry (including BUN levels) or mortality rate. Mild chronic renal inflammation was reported in two dogs in the high-dose group and in one dog in the control group. Mild hepatic focal inflammation was reported in three dogs in the high-dose group, two dogs in the low-dose group and one dog in the control group. No other histological lesions were reported.

No adverse developmental effects were observed in the fetuses of Wistar rats exposed to 20 ppm (78 mg/cu.m) or 70 ppm (272 mg/cu.m) of **bromomethane** for 7 hours/day on days 1-19 of gestation (Hardin et al., 1981; Sikov et al., 1980). Exposure to 20 ppm (78 mg/cu.m) or 70 ppm (272 mg/cu.m) for 7 hours/day, 5 days/week for 3 weeks prior to mating, and gestation, did not result in developmental toxicity in the offspring. No maternal toxic effects were observed.

Bromomethane was highly toxic to pregnant New Zealand White rabbits exposed to 70 ppm (272 mg/cu.m) for 7 hours/day, 5 days/week on days 1 to 15 of gestation; 24/25 rabbits died by day 30 of gestation (Hardin et al., 1981; Sikov et al., 1980). No adverse developmental effects were observed in the one remaining litter or in a group of rabbits exposed to 20 ppm (78 mg/cu.m) of **bromomethane** for 7 hours/day, 5 days/week on days 1 to 30 of gestation.

VI.A. Oral RfD References:

Oral RfD References

Danse, L.H.J.C., F.L. van Velsen and C.A. van der Heijden. 1984. Methylbromide: Carcinogenic effects in the rat forestomach. *Toxicol. Appl. Pharmacol.* 72: 262-271.

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. *Scand. J. Work Environ. Health.* 7: 66-75.

Irish, D.D., E.M. Adams, H.C. Spencer and V.K. Rowe. 1940. The response attending exposure of laboratory animals to vapors of **methyl bromide**. *J. Ind. Hyg. Toxicol.* 22: 218-230.

Rosenblum, I., A.A. Stein, and G. Eisinger. 1960. Chronic ingestion by dogs of **methyl bromide**-fumigated food. *Arch. Environ. Health.* 1: 316-323.

Sikov, M.R., W.C. Cannon, D.B. Carr, R.A. Miller, L.F. Montgomery and D.W. Phelps. 1980. Teratologic assessment of butylene oxide, styrene oxide and **methyl bromide**. NTIS PB 81-16851. 87 p.

U.S. EPA. 1986. Health and Environmental Effects Profile for **Methyl Bromide**. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington DC.

U.S. EPA. 1987. Drinking Water Health Advisory for **Bromomethane**. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington DC.

Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- **Bromomethane**
 CASRN -- 74-83-9
 Primary Synonym -- **Methyl bromide**
 Last Revised -- 07/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.6. EPA Documentation and Review of the Oral RfD:

EPA Documentation and Review of the Oral RfD

U.S. EPA. 1986. Health and Environmental Effects Profile for **Methyl Bromide**. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington DC.

U.S. EPA. 1987. Drinking Water Health Advisory for **Bromomethane**. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington DC.

Agency Work Group Review -- 12/02/1985, 02/05/1986, 09/29/1986, 04/15/1987, 05/26/1988

Verification Date -- 05/26/1988

Screening-Level Literature Review Findings -- A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for **Bromomethane** conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 301-345-2870.

Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- **Bromomethane**
 CASRN -- 74-83-9
 Primary Synonym -- **Methyl bromide**
 Last Revised -- 10/01/1992

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- **Bromomethane**

CASRN -- 74-83-9

Primary Synonym -- **Methyl bromide**

Last Revised -- 08/01/1990

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

Revision History

Substance Name -- **Bromomethane**

CASRN -- 74-83-9

Primary Synonym -- **Methyl bromide**

Date	Section	Description
09/30/1987	I.A.1.	MF changed to UF -- no change in RfD
09/30/1987	I.A.2.	Text changes
09/30/1987	I.A.3.	Text changes
09/30/1987	I.A.4.	Study descriptions added
09/30/1987	I.A.5.	Text change
09/30/1987	I.A.6.	Secondary contact changed
03/01/1988	I.A.1.	Critical effect added
06/30/1988	I.A.	Withdrawn; new RfD verified (in preparation)
09/26/1998	I.A.	Oral RfD summary replaced
05/01/1989	II.	Carcinogen assessment now under review
06/01/1989	II.	Carcinogen summary on-line
06/01/1989	VI.	Bibliography on-line
08/01/1989	VI.A.	Oral RfD references added
10/01/1989	I.B.	Inhalation RfC now under review
06/01/1990	I.A.2.	Dosing clarified
06/01/1990	IV.F.1.	EPA contact changed
08/01/1990	I.A.	Text edited
08/01/1990	II.	Text edited
08/01/1990	III.A.	Health Advisory on-line
08/01/1990	VI.D.	Health Advisory references added
07/01/1991	I.A.7.	Secondary contact changed
01/01/1992	IV.	Regulatory actions updated
04/01/1992	I.B.	Inhalation RfC summary on-line
04/01/1992	VI.B.	Inhalation RfC references added
05/01/1992	I.B.6.	Deleted incorrect work group review date
10/01/1992	I.B.1.	'NOAEL' corrected to LOAEL
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
12/03/2002	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

II.D.1. EPA Documentation:

<http://to...:iia4~0,ib4~0,ib2~0,iia3~0,vib~0,vic~0,ia4~0,ia~0,ia~0,ia6~0,ib~0,ii~0,vii~0,iid1~0> 6/22/03

EPA Documentation

Source Document -- U.S. EPA, 1985, 1986, 1987

The Health and Environmental Effects Profile for Methyl Bromide and the Health Effects Assessment for Bromoethane received Agency review.

ETHYL CHLORIDE

CASRN: 75-00-3

*For other data, click on the Table of Contents***Best Sections****Non-Human Toxicity Excerpts :**

A two hr LC50 of 152 mg/l (57600 ppm) has been reported in rodents. Deaths were anesthetic in nature but hyperemia, edema, and hemorrhages were reported in the internal organs, **brain**, and lung. Repeated 2 hr exposures for 60 days to 14 mg/l (5300 ppm) caused a decr in the phagocytic activity of the leukocytes, lowered hippuric acid formation in the liver, and resulted in histological or pathological changes in the liver, **brain**, and lung. ...

[Clayton, G.D., F.E. Clayton (eds.) Patty's Industrial Hygiene and Toxicology. Volumes 2A, 2B, 2C, 2D, 2E, 2F: Toxicology. 4th ed. New York, NY: John Wiley & Sons Inc., 1993-1994. 4083]**PEER REVIEWED**

National Toxicology Program Studies :

Toxicology and carcinogenesis studies of **chloroethane** (99.5% pure), ... were conducted by exposing groups of F344/N rats and B6C3F1 mice of each sex to **chloroethane** by whole-body inhalation once for 4 hours or for 6 hours per day, 5 days per week for ... 2 years. The survival of the exposed groups of both male (after day 330) and female (after day 574) mice was significantly lower than that of controls (final survival male: 28/50; 11/50; female: 32/50; 2/50). The majority of exposed female mice died as a result of uterine carcinomas. Male mice, and particularly exposed mice, died early as a result of an ascending urinary tract infection. ... There was equivocal evidence of carcinogenic activity of **chloroethane** for male F344/N rats, as indicated by benign and malignant epithelial neoplasms of the skin. For female F344/N rats, there was equivocal evidence of carcinogenic activity, as indicated by three uncommon malignant astrocytomas of the **brain** in the exposed group. The study in male B6C3F1 mice was considered to be an inadequate study of carcinogenicity because of reduced survival in the exposed group. However, there was an increased incidence of alveolar/bronchiolar neoplasms of the lung. There was clear evidence of carcinogenic activity for female B6C3F1 mice, as indicated by carcinomas of the uterus. A marginally increased incidence of hepatocellular neoplasms was observed in the exposed group.

[NTP; Toxicology and Carcinogenesis Studies of Chloroethane in F344/N Rats and B6C3F1 Mice (Inhalation Studies) p.3-4 Report # 346 (1989) NIH Pub# 90-2801]

PEER REVIEWED

Emergency Medical Treatment :**EMT Copyright Disclaimer:**

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The following Overview, *** **ETHYL CHLORIDE** ***, is relevant for this HSDB record
<http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAMNa4ST:1:BASIC>

6/22/03

chemical.

Life Support:

- o This overview assumes that basic life support measures have been instituted.

Clinical Effects:

SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

o WITH POISONING/EXPOSURE

1. **Ethyl chloride** vapors may be irritating to the eyes, skin, and mucous membranes. Exposure may produce headache, blurred vision, dizziness, incoordination, inebriation, CNS depression, nausea, vomiting, abdominal cramps, and liver or kidney damage. In animals, **ethyl chloride** increases myocardial sensitivity to catecholamines.
2. The liquid is harmful to the eyes, and may cause frostbite injury if spilled on the skin. It is the least toxic of the chlorinated hydrocarbons.
3. When heated to decomposition, hydrogen chloride, phosgene, chlorine, and carbon monoxide gases may be released.

HEENT

0.2.4.1 ACUTE EXPOSURE

o WITH POISONING/EXPOSURE

1. Eye irritation occurred when humans were exposed to airborne concentrations of 40,000 ppm. Liquid **ethyl chloride** evaporates rapidly and may cause thermal damage to the eyes. Vapors are mildly irritating to mucous membranes and the respiratory tract.

CARDIOVASCULAR

0.2.5.1 ACUTE EXPOSURE

o WITH POISONING/EXPOSURE

1. Sudden, unforeseen fatalities have occurred from **ethyl chloride** inhalation at significant concentrations, possibly due to a decrease in the myocardial threshold to the dysrhythmogenic effects of endogenous epinephrine.

RESPIRATORY

0.2.6.1 ACUTE EXPOSURE

- o ANIMAL STUDIES - Lung damage has not been reported in humans, but occurred with exposure to high concentrations in experimental animals.

NEUROLOGIC

0.2.7.1 ACUTE EXPOSURE

o WITH POISONING/EXPOSURE

1. CNS depression and coma have occurred with exposure to airborne concentrations of tens of thousands of ppm. Stupor and lack of coordination may occur with exposure to airborne concentrations greater than 13,000 ppm.

GASTROINTESTINAL

0.2.8.1 ACUTE EXPOSURE

o WITH POISONING/EXPOSURE

1. Abdominal cramps developed in humans exposed to airborne levels of 40,000 ppm for two short intervals.

DERMATOLOGIC

0.2.14.1 ACUTE EXPOSURE

o WITH POISONING/EXPOSURE

1. Frostbite may occur if the compressed liquid is spilled on the skin due to rapid evaporation.

o WITH THERAPEUTIC USE

1. Eczema and allergic contact dermatitis have been reported.

GENOTOXICITY

- o Ethyl chloride has caused bacterial mutations, but was inactive in a cancer cell transformation study.

Laboratory:

- o No toxic serum or blood concentrations have been established. Liver, blood, and kidney functions have not been significantly altered in human poisonings. Monitor ECG in patients with significant exposure.

Treatment Overview:

INHALATION EXPOSURE

- o INHALATION: Move patient to fresh air. Monitor for respiratory distress. If cough or difficulty breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer oxygen and assist ventilation as required. Treat bronchospasm with beta2 agonist and corticosteroid aerosols.
- o SEIZURES: Administer a benzodiazepine IV; DIAZEPAM (ADULT: 5 to 10 mg, repeat every 10 to 15 min as needed. CHILD: 0.2 to 0.5 mg/kg, repeat every 5 min as needed) or LORAZEPAM (ADULT: 2 to 4 mg; CHILD: 0.05 to 0.1 mg/kg).
 1. Consider phenobarbital if seizures recur after diazepam 30 mg (adults) or 10 mg (children > 5 years).
 2. Monitor for hypotension, dysrhythmias, respiratory depression, and need for endotracheal intubation. Evaluate for hypoglycemia, electrolyte disturbances, hypoxia.
- o Monitor ECG and adequacy of respirations and oxygenation.
- o CNS depression is common and in most cases responds to supportive measures.
- o There have been a few reported cases of sudden, unpredictable death possibly due to cardiac dysrhythmias from a lowering of the myocardial threshold to the arrhythmogenic effects of endogenous epinephrine. Monitor ECG in patients with significant exposure.

EYE EXPOSURE

- o DECONTAMINATION: Irrigate exposed eyes with copious amounts of tepid water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist, the patient should be seen in a health care facility.

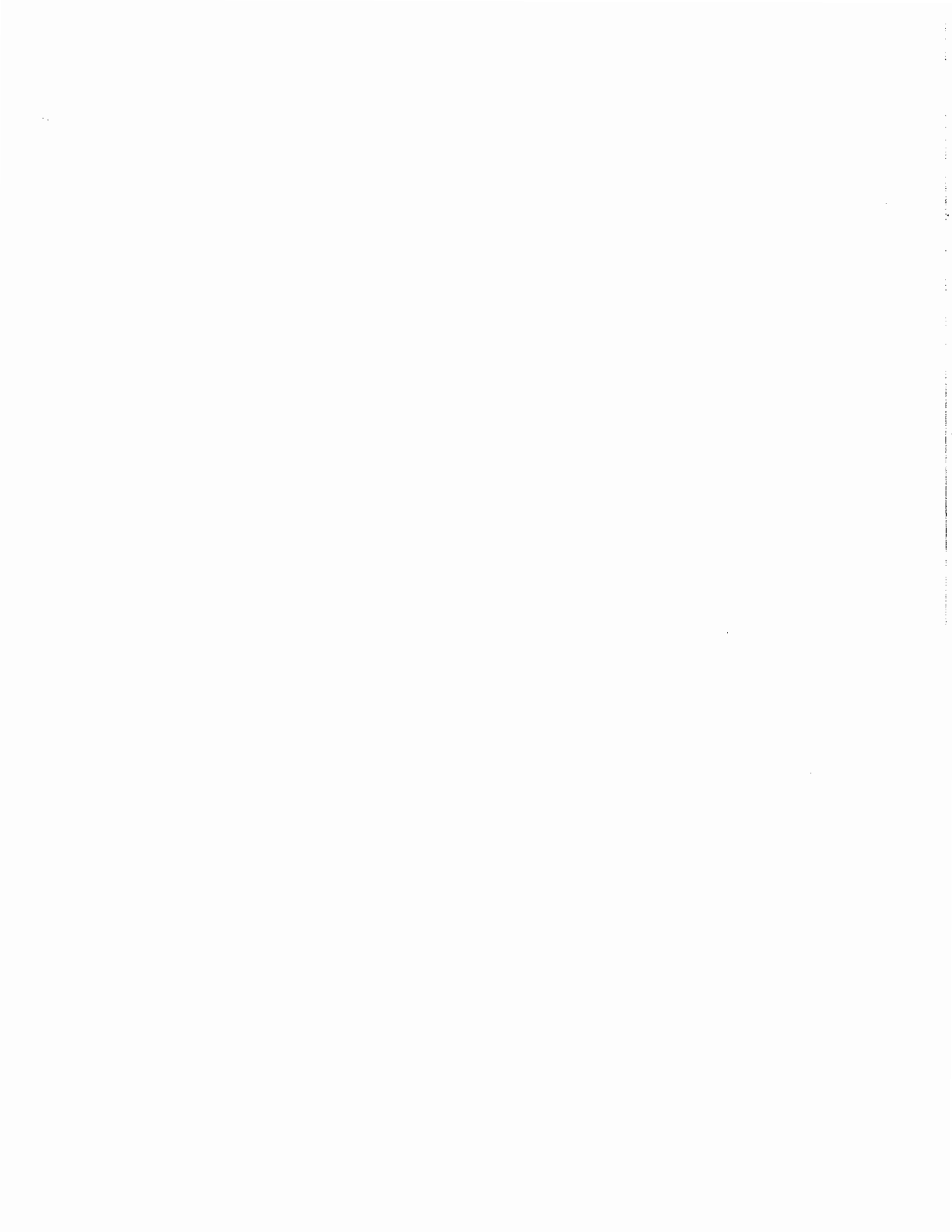
DERMAL EXPOSURE

- o DECONTAMINATION: Remove contaminated clothing and wash exposed area thoroughly with soap and water. A physician may need to examine the area if irritation or pain persists.
- o Treat dermal irritation or burns with standard topical therapy. Patients developing dermal hypersensitivity reactions may require treatment with systemic or topical corticosteroids or antihistamines.

Range of Toxicity:

- o A CNS depressant airborne concentration is estimated to be in the tens of thousands of ppm. Exposure to airborne concentrations of 40,000 ppm resulted in stupor, eye irritation, and abdominal cramps, while exposure to 25,000 ppm caused lack of coordination, and exposure to 19,000 ppm produced weak analgesia.

[Rumack BH: POISINDEX(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003. Hall AH & Rumack BH (Eds): TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003.]**PEER REVIEWED**



FORMALDEHYDE

CASRN: 50-00-0

*For other data, click on the Table of Contents***Best Sections****Human Toxicity Excerpts :**

A study was conducted to determine if pathologists with exposure to formaldehyde demonstrate an excess risk of **cancer**, particularly **cancers** of the nasopharyngeal and pharyngeal areas. A population of 6411 physicians with occupational formaldehyde exposure participated in the study. The occurrence of these types of **cancers** was 4.7 times higher in these persons than in a comparable sized group of psychiatrists, but even so it is difficult to determine the importance of this increased risk as being directly tied to formaldehyde exposure. Pathologists and other members of the study group were exposed to other chemicals and infectious agents as well as formaldehyde. There was an apparent excess of mortality from **pancreatic cancer** and **brain cancers** as well as leukemia.

[Matanoski GM; Risks of Pathologists Exposed to Formaldehyde School of Hygiene and Public Health, Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, Grant No. RO1-OH-01511 (1989)]**PEER REVIEWED**

Human Toxicity Excerpts :

The finding of nasal tumors in rodents exposed to high levels of airborne formaldehyde in the early 1980s ... led to a concern for **cancer** effect in occupationally exposed workers. There are now more than 40 epidemiology studies examining the potential for occupational formaldehyde exposure to cause **cancer** in humans. The studies include cohort mortality studies of formaldehyde-exposed industrial workers, cohort mortality studies of formaldehyde-exposed professionals or medical specialists, & case-control studies that looked for assoc between occupational exposure to formaldehyde & **cancers** of the nose, pharynx, or lung. ... Although some of the epidemiological studies have found some scattered evidence for extra-respiratory site **cancers** in groups of formaldehyde-exposed workers, the data are not consistent across studies & adjustment for potential confounding **cancer** risk factors has not often been possible. Most, if not all reviewers, have agreed that **cancer** of the respiratory tract, particularly the upper respiratory tract, is more biologically plausible than formaldehyde-induced **cancer** at distant sites given the reactivity of formaldehyde, the capacity of tissues to metabolize formaldehyde, & the results from chronic rodent inhalation studies showing that formaldehyde-induced nonneoplastic & neoplastic effects are restricted to the upper respiratory tract with exposures to concn below 5-10 ppm. Accordingly, the meta-analyses of the human data have focused on the findings for respiratory **cancer** deaths in occupationally exposed humans.

[DHHS/ATSDR; Toxicological Profile for Formaldehyde p. 89 (1999)]**PEER REVIEWED**

Human Toxicity Excerpts :

The National **Cancer** Institute study on the relationship between exposure to formaldehyde & mortality from nasopharyngeal **cancer** was evaluated. The study had indicated little evidence of a link between formaldehyde at concns normally encountered in the workplace & risk of nasopharyngeal **cancer**. Although the overall standardized mortality ration was significantly elevated in subjects exposed to formaldehyde, the overall risk did not incr with increasing intensity of exposure. A

N-METHYL-N'-NITRO-N-NITROSOGUANIDINE

CASRN: 70-25-7

*For other data, click on the Table of Contents***Best Sections****Human Toxicity Excerpts :**

Description and analysis of 3 cases of **glioblastoma** in laboratory workers whose work involved physical and chemical mutagenesis techniques. Literature survey of the epidemiology of glioblastoma in the general population and in various workplaces, and of animal and in-vitro experiments on the mutagenic and carcinogenic effects of nitroso compounds. Detailed study of 1-methyl-3-nitro-1-nitrosoguanidine, a substance handled by the 3 victims of the disease, which could therefore be one of its important causing agents.

[Pleven C et al; Journal de Toxicologie Medicale 4 (3): 249-56 (1984)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

Cells derived from rainbow trout gonad (RTG-2) and bluegill fry tissues (BF-2) were used as model cell systems to measure cytotoxicity and genotoxicity following exposure to Puget Sound sediment extracts, benzo(a)pyrene and MNNG (N-methyl-N'-nitro-N-nitrosoguanidine). Sediment was collected from several sites within Puget Sound (Washington USA) known to be contaminated with compounds such as **polycyclic aromatic hydrocarbons**, polychlorinated biphenyls, chlorinated hydrocarbons and heavy metals. Each of the sediment samples was extracted with organic solvents and added to cultures of the 2 model cell systems in DMSO (dimethyl sulfoxide). Following exposure the cultures were evaluated for cell death, mitotic inhibition, stimulatory effects and chromosomal damage. These cell cultures responded to the sediment extracts much as they did to known mutagenic/carcinogenic chemicals which were used as model compounds.

[Kocan RM et al; Aquat Toxicol 6 (3): 165-78 (1985)]**PEER REVIEWED**

TETRAETHYL LEAD

CASRN: 78-00-2

*For other data, click on the Table of Contents***Best Sections****Human Toxicity Excerpts :**

A study of workers manufacturing **tetraethyllead** /in an East TX chemical plant/ revealed excesses of respiratory **cancer** (15 observed, 11.2 expected) & **brain cancer** (3 observed, 1.6 expected).

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. S7 230 (1987)]**PEER REVIEWED**

Human Toxicity Excerpts :

... INFORMATION /COMPARED/ ON HEALTH VARIABLES FOR 153 WHITE MALE 'WAGE ROLL' EMPLOYEES WHO HAD HAD OCCUPATIONAL EXPOSURE TO **TETRAETHYLLEAD** FOR 20 OR MORE YEARS WITH THOSE FOR A SIMILAR GROUP OF WORKERS MATCHED INDIVIDUALLY FOR AGE & YEARS OF SERVICE WHO HAD NO RECOGNIZED OCCUPATIONAL EXPOSURE TO **TETRAETHYLLEAD** OR TO ANY OTHER LEAD COMPOUNDS. ... INFORMATION ON HEALTH WAS OBTAINED RETROSPECTIVELY, FROM RESULTS OF PERIODIC PHYSICAL EXAMINATIONS & LABORATORY STUDIES, MEDICAL RECORDS OF ABSENCE FROM WORK DUE TO ILLNESS, & LONG TERM MEDICAL HISTORIES IN FORM OF CUMULATIVE DIAGNOSES. THE PREVALENCE OF SKIN **CANCER** AMONG EXPOSED WORKERS WAS 7/139 (5%), NOT SIGNIFICANTLY DIFFERENT FROM THAT OF NON-EXPOSED WORKERS (4/139, 2.9%). THERE WERE NO CASES OF **CANCER** OTHER THAN OF THE SKIN IN EITHER GROUP. (THE WORKING GROUP NOTED THAT WORKERS WHO LEFT EMPLOYMENT FOR REASON, INCL ILLNESS OR RETIREMENT, WERE NOT INCLUDED; THIS STUDY WAS THEREFORE CONSIDERED INADEQUATE TO DETERMINE THE CARCINOGENIC RISK OF EXPOSURE TO **TETRAETHYLLEAD**.)

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V23 386 (1980)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

The transplacental effect of **tetraethyl lead** or lead acetate on the activity of inorganic pyrophosphatase in **brain**, liver and kidneys of newborn rats varied with the organ, the lead compound, the dose, and the route and time of administration. Enzyme activity was usually decreased in **brain** and liver, suggesting adverse effects of lead on metabolism in these organs. The inorganic pyrophosphatase activity was generally increased in kidneys.

[Tsafaris F, Alexaki E; Vet Hum Toxicol 34 (6): 510-2 (1992)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

TISSUE DISTRIBUTION STUDIES OF LEAD IN RATS & DOGS EXPOSED TO LETHAL INHALATION DOSES OF **TETRAETHYL LEAD** (TEL) OR **TETRAMETHYL LEAD** (TML) &

IN MEN FATALLY POISONED BY TEL REVEALED LEAD (PB) LEVELS OF 0.7-13.0 MG/100 G TISSUE IN LUNG, **BRAIN**, LIVER & KIDNEY IN THREE SPECIES. HUMAN PB LEVELS IN **BRAIN**, LIVER & KIDNEY RESEMBLED THOSE SEEN IN CORRESPONDING RAT & DOG TISSUES.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V2 158 (1973)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

Organic lead accumulates in the human **brain**. After acute **tetraethyl lead** poisoning, however, the lead concentrations are highest in the human liver (24 to 41 ug/g), followed by those in the kidney (8 to 19 ug/g) > pancreas (13 ug/g) > **brain** (7 to 11 ug/g) > cardiac and skeletal muscle (8 to 9 ug/g) > spleen and adrenal (3 to 6 ug/g).

[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991.1514]**PEER REVIEWED**

Absorption, Distribution & Excretion :

WITHIN 24 HR OF IV ADMIN OF **TETRAETHYL LEAD (TEL)** TO RATS 50% OF TOTAL LEAD IN SOFT ORGANS WAS IN THE FORM OF TRIETHYLLEAD, & 70% OF MUSCLE LEAD APPEARED AS TRIETHYLLEAD; HIGHEST LEVELS WERE FOUND IN LIVER, BLOOD, KIDNEY & **BRAIN**. AFTER 1 WK 90-100% OF TOTAL LEAD IN ORGANS WAS IN FORM OF TRIETHYLLEAD.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V2 155 (1973)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

REPEATED ORAL DOSES OF 0.0017-0.17 MG/KG BODY WT OF **TETRAETHYL LEAD (TEL)** & 0.001-1.08 MG/KG BODY WT TETRAMETHYLLEAD TO RATS 5 TIMES/WK FOR 20 WK RESULTED IN DEPOSITION OF LEAD IN LIVER, KIDNEY, **BRAIN**, TESTES & OTHER ORGANS. DISTRIBUTION OF LEAD IN TISSUES DIFFERED BETWEEN TEL & TETRAMETHYLLEAD & VARIED WITH DOSE, DOSE SCHEDULE & SEX OF EXPOSED ANIMALS.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V2 155 (1973)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

RATS GIVEN DERMAL APPLICATIONS OF 0.1 ML **TETRAETHYL LEAD (TEL)** (106 MG LEAD)/RAT SHOWED HIGHEST LEAD LEVELS IN BLOOD, KIDNEY, LIVER, LUNG & **BRAIN** IN THAT ORDER; ABOUT 6.5% OF DOSE APPLIED WAS ACCOUNTED FOR BY TISSUES, CARCASS & TREATED SKIN. THUS, SUBSTANTIAL PROPORTION OF THE DOSE APPLIED APPEARED TO BE LOST BY EVAPORATION FROM THE SKIN. WHEN RABBITS RECEIVED DERMAL APPLICATION OF 0.75 MG TEL FOR 4 HR & WERE KILLED FROM 6 HR TO 205 DAYS LATER, TISSUE LEAD LEVELS REACHED PEAK AFTER 18 HR EXCEPT IN SPLEEN & BONE, WHERE HIGHEST LEVELS WERE ATTAINED AFTER 7 & 30 DAYS, RESPECTIVELY.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V2 156 (1973)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

IN CASES OF ACCIDENTAL POISONING WITH **TETRAETHYL LEAD (TEL)**, LIVER, KIDNEY, PANCREAS, **BRAIN & HEART ACCUMULATE TRIETHYLLEAD**, & TOTAL TISSUE LEAD (PB) CONCEN CORRELATE WITH TRIETHYLLEAD CONCEN IN CORRESPONDING TISSUES.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V2 157 (1973)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

AFTER SINGLE DOSES WITHIN THE LETHAL RANGE WITHIN RANGE OF ... (17 MG/KG BODY WT OF **TETRAETHYL LEAD (TEL)** ...) RATS SHOWED IRRITABILITY, HYPERMOBILITY, TREMORS & SPASTICITY. AFTER SINGLE DOSES OF 1.7 MG/KG BODY WT OF TEL ... NO BEHAVIORAL CHANGES WERE SEEN. REPEATED EXPOSURE AT THESE LOWER LEVELS, HOWEVER, WAS ASSOCIATED WITH BEHAVIORAL CHANGES, PERIPHERAL HYPEREMIA & EXCESSIVE BODY WEIGHT GAIN. ... CARDIAC HYPERTROPHY, HYPEREMIA & EDEMA OF **BRAIN**, & CHANGES IN LIVER, PANCREAS, THYROID, LUNG & THYMUS WERE SEEN IN A FEW RATS. MICROSCOPICALLY, CHANGES ATTRIBUTABLE TO EXPOSURE TO TEL ... WERE NOTED IN THE CENTRAL NERVOUS SYSTEM & LIVER.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V2 156 (1973)]**PEER REVIEWED**

Interactions :

THE INCORPORATION OF LABEL FROM U(14)C-LABELED GLUCOSE IN GLUTAMIC ACID & GABA WAS AFFECTED BY **TETRAETHYLLEAD** IN A CHARACTERISTIC MANNER IN DIFFERENT REGIONS OF THE **BRAIN**. GLUCOSE UPTAKE, HOWEVER, WAS NOT INFLUENCED. PYRIDOXAL PHOSPHATE REVERSED THE EFFECT OF **TETRAETHYLLEAD** ON THE INCORPORATION, ESPECIALLY IN THE CEREBELLUM & BRAINSTEM, BUT WITH LITTLE EFFECT IN THE CEREBRAL CORTEX.

[REGUNATHAN S, SUNDARESAN R; LIFE SCI 33 (23): 2277-82 (1983)]**PEER REVIEWED**

Metabolism/Metabolites :

DEALKYLATION OF **TETRAETHYL LEAD** OCCURS IN MICROSOMES & REQUIRES OXYGEN & NADPH, & HAS BEEN OBSERVED IN HOMOGENATES OF LIVER, KIDNEY, & **BRAIN OF RAT & RABBIT**.

[The Chemical Society. Foreign Compound Metabolism in Mammals. Volume 2: A Review of the Literature Published Between 1970 and 1971. London: The Chemical Society, 1972. 334]**PEER REVIEWED**

Absorption, Distribution & Excretion :

TETRAETHYL LEAD (12 MG/KG) WAS ADMIN IP TO RABBITS TO DETERMINE

CLEARANCE RATES. 24 HR AFTER ADMIN, HIGHEST TOTAL LEAD & TRIETHYLLEAD LEVELS WERE FOUND IN LIVER, FOLLOWED BY KIDNEY, **BRAIN**, SKELETAL MUSCLE, CARDIAC MUSCLE, SPINAL CORD & BLOOD. APPROX 58% OF THE **TETRAETHYLLEAD** ADMIN WAS EXCRETED WITHIN 4 DAYS AFTER TREATMENT.

[YAMAMURA Y ET AL; SEI MARIANNA IKA DAIGAKU ZASSHI 7 (1): 10-20 (1979)]**PEER REVIEWED**

Absorption, Distribution & Excretion :

TETRAETHYL LEAD (TEL) IS READILY ABSORBED FROM DIGESTIVE & RESPIRATORY TRACTS & THROUGH THE SKIN, OWING TO THE SOLUBILITY OF TEL IN LIPIDS & TO ITS DIFFUSIBILITY. ... ALTHOUGH PART OF TEL IS METABOLIZED & THE RELEASED INORGANIC LEAD (PB) IS DISTRIBUTED IN OTHER SOFT TISSUES, THE MAJOR PORTION ACCUMULATES IN THE **BRAIN** OWING TO A SPECIAL AFFINITY BETWEEN THE ORGANIC PB & THE LIPIDS OF NERVE TISSUES.

[Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978. 189]**PEER REVIEWED**

TSCA Test Submissions :

Tetraethyl lead (CAS # 78-00-2) was evaluated for inhalation toxicity and tissue affinity in 4 male Charles River CD rats administered repeated whole-body exposures to 1.1 mg/l **tetraethyl lead** vapor (0.7 mg/l Pb), 1 hour/day for 5 days. The undiluted test material infused into a glass bubbler was vaporized and supplied as a dried metered airstream at 2.1 L/min into the bell jar containing the rats. Necropsy 3 days following the 5th and final exposure revealed pulmonary edema and congestion in the 1 decedent rat and congestion of the **brain** in all. Select harvested tissues were dried in a hot air oven at 100 degrees C to a constant weight, ashed and burned with nitric acid, and then heated to burn off the nitrates. The residue in hydrochloric acid was then analyzed for Pb content according to a method of W.W. Woessner and J. Cholak. A group average for 4 rats revealed that lead constituted 0.44, 1.0, 0.82, 7.4, 8.6, 5.14, and 13.0 mg respectively of 100 g bone, **brain**, fat, kidney, liver, lung, and spleen tissue.

[E I Dupont De Nemours & Co; Preliminary Comparative Toxicity Studies with Tetramethyl Lead & Tetraethyl Lead; 07/15/59; EPA Document No. 88-920010199; Fiche No. OTS0555601]**UNREVIEWED**

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[E I Dupont De Nemours & Co; Preliminary Comparative Toxicity Studies with Tetramethyl Lead & Tetraethyl Lead; 07/15/59; EPA Document No. 88-920010199; Fiche No. OTS0555601]**UNREVIEWED**

Emergency Medical Treatment :

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The following Overview, ***** TETRAETHYL LEAD *****, is relevant for this HSDB record chemical.

Life Support:

- o This overview assumes that basic life support measures have been instituted.

Clinical Effects:

SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

- o **Tetraethyl lead** is moderately to highly toxic. Acute or chronic EXPOSURE ROUTES include inhalation, ingestion or skin absorption. Exposure to **tetraethyl lead** often occurs through deliberate inhalation of leaded gasoline (substance abuse). Recent accidental exposure case reports have come from developing countries, such as China.
- o The central nervous system is the main target organ affected. The effects of **tetraethyl lead** may be mixed with the effects of the solvent. The exposure-onset interval varies inversely with the dose; symptoms can begin within hours to days (usually within 1 to 5 days, up to as long as 14 days after exposure). Symptoms that begin within 24 hours usually indicate serious exposure or reflect intoxication due to the hydrocarbon (gasoline).
 1. Early exposure effects are generally those of hydrocarbon abuse. These include anorexia, nausea, vomiting, diarrhea, delirium, nervous irritability, headache, restlessness, pallor, tremor, euphoria, lethargy, insomnia, slurred speech and blurred vision.
 2. After the initial effects of asthenia, weakness, fatigue, headache, nausea, vomiting, diarrhea, anorexia and insomnia, the "**tetraethyl lead triad**" of central nervous system involvement (including ataxia, tremor and hypotonia), bradycardia and decreased body temperature may be noted.
- o Mild exposure results in anxiety, lassitude, irritability, insomnia, excitement, confusion, lurid (violent or frightening) dreams, anorexia, nausea, vomiting, metallic taste, pallor, mild diarrhea, dizziness, tremulousness, lack of coordination and truncal ataxia.
- o Moderate exposure can produce disorientation, hyperexcitability, tremors, twitching, chorea, increased reflexes, spasticity, fatigue, muscle pain, bradycardia, hypotension, hypothermia, limited upward gaze and rotary or horizontal nystagmus.
- o Severe exposure leads to delusions, hallucinations, mania, psychotic behavior, seizures (maniacal, violent

convulsions), intense hyperactivity, facial contortions, cerebral edema, coma and death. ENCEPHALOPATHY and vomiting result from severe intoxication; the effects of **tetraethyl lead** differ from those of inorganic lead poisoning in that metallic taste and hematologic abnormalities are unusual and encephalopathy predominates.

- o Absorption of as little as 1 gm can be fatal within 3 to 30 days (as the compound slowly degrades to triethyl lead); acute intoxication can have a mortality rate as high as 20 percent.
- o Effects unrelated to the central nervous system include irritation of the skin, eyes and mucous membranes. Dermal contact can result in dermatitis and burns. Eye exposure produces pain, burns, blurred vision and conjunctivitis. A metallic taste, sneezing, bronchitis and pneumonia have also been noted.

VITAL SIGNS

0.2.3.1 ACUTE EXPOSURE

- o Hypothermia, fever, bradycardia, hypotension and irregular respirations have been reported following acute exposure.

CARDIOVASCULAR

0.2.5.1 ACUTE EXPOSURE

- o Hypotension and bradycardia have been reported.

RESPIRATORY

0.2.6.1 ACUTE EXPOSURE

- o Inhalation of TEL vapors can be fatal. Upper respiratory tract irritation and sneezing may follow dust exposure. Irregular respirations are a non-specific finding.

NEUROLOGIC

0.2.7.1 ACUTE EXPOSURE

- o Clinical neurologic effects of TEL intoxication can be divided into MILD, MODERATE, and SEVERE. They usually occur within 1 to 5 days, or as long as 14 days post exposure.
- o MILD - Anxiety, irritability, insomnia, lurid dreams, anorexia, metallic taste, dizziness, pallor, lassitude, tremor, incoordination, and cerebellar ataxia.
- o MODERATE - Disorientation, hyperexcitability, hyperreflexia, and lurid dreams, tremors, and chorea.
- o SEVERE - Delusions, hallucinations, mania, seizures, cerebral edema, coma, and death.

GASTROINTESTINAL

0.2.8.1 ACUTE EXPOSURE

- o TEL intoxication usually lacks the common GI manifestations of inorganic lead intoxication. Anorexia, nausea, vomiting, diarrhea and weight loss have been seen after acute exposure.

HEPATIC

0.2.9.1 ACUTE EXPOSURE

- o Elevated liver enzymes may occur.

GENITOURINARY

0.2.10.1 ACUTE EXPOSURE

- o Renal damage has been reported following acute exposure; urinary retention has occurred infrequently.

HEMATOLOGIC

0.2.13.1 ACUTE EXPOSURE

- o Anemia, basophilic stippling, and neutrophilia may occur.

DERMATOLOGIC

0.2.14.1 ACUTE EXPOSURE

- o Skin absorption of TEL can occur. Pallor may be

observed following acute exposure.

MUSCULOSKELETAL

0.2.15.1 ACUTE EXPOSURE

- o Elevated CPK has been reported in severe cases of chronic exposure.

METABOLISM

0.2.17.1 ACUTE EXPOSURE

- o ALAD enzyme levels are depressed by TEL.

REPRODUCTIVE HAZARDS

- o In contrast to inorganic lead, which is a known human reproductive hazard and also has many reproductive effects in animals, the effect of TEL on human and animal reproduction, if any, is much less clear.

CARCINOGENICITY

0.2.21.1 IARC CATEGORY

- o Group 3 (Animal Evidence: Inadequate evidence)

0.2.21.2 HUMAN OVERVIEW

- o Not known to be a human carcinogen. TEL has been implicated, but not proven as a carcinogen.

Laboratory:

- o The blood lead level provides one measure of INORGANIC lead burden which does not necessarily reflect organic lead burden. The normal upper limit is 10 mcg/dL. Inorganic lead levels correlate with CNS signs after chronic exposure.
- o Metabolic substrates in heme synthesis (ALAD, EP or ZnPP, coproporphyrin) may or may not rise after prolonged exposure and are not a reliable test in diagnosis or assessment of severity.
- o Monitor liver function tests, renal function tests, and hematologic parameters.
- o The ability to penetrate skin makes reliance on airborne concentrations impractical (Hathaway et al, 1996).
- o An analysis of the urinary concentration of lead is helpful in evaluating the amount of TEL absorbed during chronic exposure (Hathaway et al, 1996). Urinary lead concentrations are not helpful after acute exposures (He, 1999).

Treatment Overview:

ORAL EXPOSURE

- o Emesis is not recommended following ingestion of leaded gasoline or other products containing organolead compounds because of the potential for CNS depression, seizures, and aspiration of the hydrocarbon vehicle.
- o Gastric lavage should be preceded by endotracheal intubation in cases of ingestion of large amounts when CNS depression is present.
- 1. GASTRIC LAVAGE: Consider after ingestion of a potentially life-threatening amount of poison if it can be performed soon after ingestion (generally within 1 hour). Protect airway by placement in Trendelenburg and left lateral decubitus position or by endotracheal intubation. Control any seizures first.
 - a. CONTRAINDICATIONS: Loss of airway protective reflexes or decreased level of consciousness in unintubated patients; following ingestion of corrosives; hydrocarbons (high aspiration potential); patients at risk of hemorrhage or gastrointestinal perforation; and trivial or non-toxic ingestion.
- o ACTIVATED CHARCOAL: Administer charcoal as a slurry

(240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years), and 1 g/kg in infants less than 1 year old.

INHALATION EXPOSURE

- o INHALATION: Move patient to fresh air. Monitor for respiratory distress. If cough or difficulty breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer oxygen and assist ventilation as required. Treat bronchospasm with beta2 agonist and corticosteroid aerosols.
- o Organolead compounds can be absorbed via inhalation.
- o Consider chelation therapy in patients with blood lead greater than 45 mcg/dL and where symptoms of lead encephalopathy are noted.
 1. BAL (dimercaprol) - 3 to 5 mg/kg/dose deep IM every 4 hours for 2 days; then every 4 to 6 hours for 2 more days; then every 4 to 12 hours up to an additional 7 days.
 2. CALCIUM EDTA - 50 to 75 mg/kg/day deep IM in 3 to 6 divided doses for up to 5 days. EDTA should only be administered after BAL in patients with encephalopathy or children with levels >69 mcg/dL.
 3. DMSA - Initial pediatric dose is 10 mg/kg or 350 mg/m² orally every 8 hours for 5 days; reduced to every 12 hours for an additional 2 weeks.
 4. D-PENICILLAMINE - 250 mg 4 times a day PO for up to 5 days. Do not exceed 40 mg/kg/day. OSHA prohibits prophylactic chelation therapy in workers occupationally exposed to lead.
- o SEIZURES: Administer a benzodiazepine IV; DIAZEPAM (ADULT: 5 to 10 mg, repeat every 10 to 15 min as needed. CHILD: 0.2 to 0.5 mg/kg, repeat every 5 min as needed) or LORAZEPAM (ADULT: 2 to 4 mg; CHILD: 0.05 to 0.1 mg/kg).
 1. Consider phenobarbital if seizures recur after diazepam 30 mg (adults) or 10 mg (children > 5 years).
 2. Monitor for hypotension, dysrhythmias, respiratory depression, and need for endotracheal intubation. Evaluate for hypoglycemia, electrolyte disturbances, hypoxia.
- o CEREBRAL EDEMA
 1. HYPERVENTILATION: Is the most effective early method of reducing **brain** swelling and should be the first-line modality in all patients.
 2. DIURETICS: Mannitol lowers CSF pressure and reduces **brain** bulk; it is a drug of choice when there is an immediate need to reduce ICP. Furosemide is an alternative, especially in children; unlike mannitol, there is no rebound effect, hypernatremia, nor serum osmolarity fluctuation.
 - a. MANNITOL DOSE: 0.25 to 2 g/kg/dose IV slowly over 10 to 15 minutes every 3 to 4 hours PRN (maximum: 1 g/kg/dose).
 - b. FUROSEMIDE DOSE: 1 mg/kg/dose intravenously every 4 to 6 hours.

EYE EXPOSURE

- o DECONTAMINATION: Irrigate exposed eyes with copious amounts of tepid water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist, the patient should be seen in a health care facility.

DERMAL EXPOSURE

- o DECONTAMINATION: Remove contaminated clothing and wash exposed area thoroughly with soap and water. A

physician may need to examine the area if irritation or pain persists.

Range of Toxicity:

- o TLV - 0.1 mg/m³
- o Exposure to 100 mg/m³ for 1 hr or longer periods at a lower rate results in an acute intoxication. Although TEL can cause toxicity through skin absorption, no reliable data exist to relate dermal dose to symptoms in humans.

[Rumack BH: POISINDEX(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003. Hall AH & Rumack BH (Eds): TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003.]**PEER REVIEWED**

VINYL CHLORIDE

CASRN: 75-01-4

*For other data, click on the Table of Contents***Best Sections****Human Toxicity Excerpts :**

An unusual distribution in the cell type of **brain cancer** was noted in vinyl chloride exposed workers. Of 10 **brain cancer** deaths identified, 9 had a histologic diagnosis of glioblastoma multiforme. The other case did not have histological confirmation.

[Waxweiler RJ et al; Ann NY Acad Sci 271: 40-8 (1976)]**PEER REVIEWED**

Human Toxicity Excerpts :

Nine retrospective mortality studies of workers exposed to vinyl chloride were reviewed to determine whether differences in their hypothesis testing results might be due to differences in statistical power. Where possible, the power of each study was calculated for **cancer** of the lung, **brain** and liver. When power was taken into consideration, the results for liver and **brain cancer** were consistent with an etiologic role for vinyl chloride. For lung **cancer**, the data were not consistent with an etiologic role, in that 2 studies with very high power yielded negative results.

[Beaumont JJ, Breslow NE; Am J Epidemiol 114 (5): 725-34 (1981)]**PEER REVIEWED**

Human Toxicity Excerpts :

The methods and results of a collaborative study, coordinated by the International Agency for Research on **Cancer** and conducted in many research centers in Europe, were examined. The study examined the **cancer** incidence and mortality among vinyl chloride workers. A total of 14,351 subjects were contributed to the combined data base. The results indicated that vinyl chloride is associated with an increase in liver **cancer** incidence. An exposure response relationship was noted for both ranked and estimated cumulative exposure. The relationship was even more evident when only liver angiosarcoma was analyzed. No significant excess of mortality was observed for the other sites suspected a-priori to be affected by vinyl chloride exposure. While the incidence of lung **cancer** was slightly increased, neither it nor lung **cancer** mortality appeared to be associated with any of the exposure variables. **Brain cancer** and lymphosarcoma mortality, while demonstrating slight increases, did not appear to be consistently associated with exposure, although the small numbers prohibited firm conclusions. An increased risk of bladder **cancer** and melanoma of the skin was detected which did not appear to be related to exposure in that the association with employment in the vinyl chloride industry was confined to one country only. No increased mortality was observed for the other main causes of death.

[Simonato L et al; Scandinavian Journal of Work, Environment and Health 17 (3): 159-69 (1991)]**PEER REVIEWED**

Human Toxicity Excerpts :

The cohort consisted of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride prior to 1 January 1973. These men were employed at 37 plants in the U.S., belonging to 17 companies. Observation of the mortality experience of the cohort was updated from

31 December 1972 to 31 December 1982 (the study now covering 1942-1982). A total of 1,536 cohort members were identified as having died. The observed mortality, by cause, was compared with the expected based on U.S. mortality rates, standardized for age, race, and calendar time. Analyses by length of exposure, latency, age at first exposure, calendar year of first exposure, and type of products were performed. The study confirmed that the vinyl chloride workers experience a significant mortality excesses in angiosarcoma (15 deaths), **cancer** of the liver and biliary tract (SMR = 641), and **cancer** of the **brain** and other CNS (SMR = 180). In addition, the study also found a significant mortality excess in emphysema/chronic obstructive pulmonary disease (SMR = 179). On the other hand, the study did not find any excess in either respiratory **cancer** or lymphatic and hematopoietic **cancer**. This study also found an increase in biliary tract **cancers**, independent from liver **cancer**.

[Wong O et al; Am J Ind Med 20 (3): 317-34 (1991)]**PEER REVIEWED**

Human Toxicity Excerpts :

Epidemiological evidence of an occupational risk of **brain cancer** has been reported in four industries where chemical exposures are likely, most recently in a series of prospective studies in the petrochemical industry. However, only in the case of vinyl chloride exposure has an occupational central nervous system carcinogen been identified. This report reviews the convergence of epidemiological and laboratory evidence that established the occupational carcinogenicity of vinyl chloride, and discusses in detail the current evidence for an occupational risk of **brain** tumors in the petrochemical industry.

[Moss AR; J Toxicol Environ Health 16 (5): 703-11 (1985)]**PEER REVIEWED**

Human Toxicity Excerpts :

... MORTALITY STUDY OF 8384 MEN ... /WITH/ @ LEAST 1 YR ... EXPOSURE ... BEFORE DEC 31, 1972, DEMONSTRATED THAT **CANCERS** OF DIGESTIVE SYSTEM (PRIMARILY ANGIOSARCOMA), RESP SYSTEM, **BRAIN**, & **CANCERS** OF UNKNOWN SITE, AS WELL AS LYMPHOMAS OCCURRED MORE OFTEN THAN EXPECTED IN ... STUDY POPULATION WITH GREATEST ESTIMATED EXPOSURE.

[American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1986.625]**PEER REVIEWED**

Human Toxicity Excerpts :

In 1974, vinyl chloride (VC) was first reported in the open scientific literature to induce angiosarcoma of the liver both in humans and in animals. Additional research has now demonstrated the carcinogenicity of VC to other organs and at lower concentrations. The target organs for VC now clearly include the liver, **brain** and the lung, and probably the lymphohematopoietic system. The evidence for a carcinogenic risk has been extended to jobs associated with poly (vinyl chloride) exposure. Cases of liver angiosarcoma have been reported among individuals employed in poly vinyl chloride fabrication facilities and an epidemiological study has demonstrated a significant association between exposure to poly vinyl chloride dust and the risk of lung **cancer** mortality. Cases of angiosarcoma of the liver also have been reported among individuals living in near proximity to vinyl chloride-poly vinyl chloride plants. An association between poly vinyl chloride dust and pneumoconiosis also has been demonstrated. On the basis of findings, prudent control of poly vinyl chloride dust in the industrial setting is indicated.

[Wagoner JK; Environ Health Perspect 52: 61-6 (1983)]**PEER REVIEWED**

Analytic Laboratory Methods :

EPA Method 5030. Purge and Trap extraction procedure for the analysis of volatile organics. Such compounds include low-molecular weight halogenated **hydrocarbons**, aromatics, ketones, nitriles, acetates, acrylates, ethers and sulfides. An inert gas is bubbled through the solution at ambient temperature, and the volatile components are efficiently transferred from the aqueous phase to the vapor phase. After purging is complete, the sorbent column is heated and backflushed with inert gas to desorb the components onto a GC column. Water samples can be analyzed directly, while preparation is necessary for water-miscible liquids, solids, wastes and soil/sediments.

[USEPA; Test Methods for Evaluating Solid Waste SW-846 (1986)]**PEER REVIEWED**

Impurities :

Specifications for a typical commercial product call for maxima in mg/kg by weight of the following impurities: unsaturated **hydrocarbons** - 10; acetaldehyde - 2; dichloro compounds - 16; water - 15; hydrogen chloride - 2; nonvolatiles - 200; iron - 0.4. Phenol at levels of 25-50 mg/kg by weight is used as a stabilizer to prevent polymerization.

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V7 292 (1972)]**PEER REVIEWED**

Solubilities :

Soluble in **hydrocarbons**, oil, chlorinated solvents, and most common organic solvents.

[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present.,p. V24 (97) 852]**PEER REVIEWED**

Human Toxicity Excerpts :

A review was undertaken of the deaths of 253 workers in seven facilities in Italy manufacturing vinyl chloride monomer and polyvinyl chloride and at one facility for extruding polyvinyl chloride. Thirty nine of the deaths resulted from liver disease, 14 of which were primary liver **cancers**. Of these 14, seven were angiosarcoma (primary liver **cancer-A**), and two were hepatocellular carcinoma. Histological data were not available for the other five, but clinical data would suggest angiosarcoma of the liver. Mean age at death was 48 years for primary liver **cancer-A**, 53 years for primary nonangiosarcoma liver **cancer** (primary liver **cancer-non-A**) and 60 years for liver cirrhosis and other chronic liver diseases. Mean duration of exposure was 16 years for primary liver **cancer-A**, 18 years for primary liver **cancer-non-A**, and 12 years for other pathological entities. Mean latency was 19, 20, and 20 years, respectively. The list of longest held jobs for the afflicted individuals included PVC loader, dryer operator, and maintenance worker for primary liver **cancer-A** and primary liver **cancer-non-A**. It was concluded that vinyl chloride may have a broader carcinogenicity spectrum on the liver than known before and that exposure lower than that occurring in autoclave cleaning can cause primary liver **cancers**.

[Pirastu R et al; American Journal of Industrial Medicine 17 (2): 155-61 (1990)]
PEER REVIEWED

Human Toxicity Excerpts :

Based on results from two previous studies where an excess of melanomas was found in a cohort of workers exposed to vinyl chloride (VCM), a follow up of the incidence of **cancer** in the same cohort

of 428 workers was carried out to scrutinize whether or not the excess could be confirmed by new cases. The total number of deaths in the study group from 1953 to the end of 1993 was 132 v 141 expected, & the total number of incident **cancer** cases was 56 v 57 expected. There were 11 cases of lung **cancer** v eight expected, seven cases of melanomas v 2.07 expected, & 2 cases of thyroid **cancer** v 0.34 expected. 5 of the 7 melanoma cases had occurred in the group that had been most heavily exposed to VCM v 0.7 expected. In the present follow up we also found 5 cases of the spinocellular **cancer** of the skin v 1.7 expected. Out of these 5 cases 4 were diagnosed after 1984. 2 of the 5 cases v 0.7 expected had occurred in the most heavily exposed group. The total number of skin **cancers** (melanomas & spinocellular **cancers**) were 12 v 3.7 expected. There was 1 new case of melanoma between 1985 & 1993 v 0.7 expected. Hence, the strength of the relation between the observed & expected number of cases was reduced compared with the last follow up, & does not strengthen the previously indicated causal relation between exposure to VCM & development of malignant melanoma. There was no excess of testicular **cancers** in this study. The present results may indicate that occurrence of spinocellular skin **cancer** could bear some relation to work in the manufacture of polyvinyl chloride.

[Langard S et al; Occup Environ Med 57 (1): 65-68 (2000)]**PEER REVIEWED**

Human Toxicity Excerpts :

OBJECTIVES: To determine if there is an increased risk of admission to hospital for various diseases among vinyl chloride monomer (VCM) workers. **METHODS:** 2224 workers with occupational exposure to VCM were identified for occurrence of disease based on a search of hospital computer files on labour insurance. These data were compared with those of workers manufacturing optical equipment & motorcycles from 1 Jan 1985 to 31 March 1994. Cardiovascular & cerebrovascular diseases were used as reference diseases, & the age adjusted morbidity odds ratio (MOR) was calculated. **RESULTS:** A significantly increased risk of admission to hospital among VCM workers due to primary liver **cancer** (MOR 4.5-6.5), cirrhosis of the liver (MOR 1.7-2.1), & other chronic diseases (MOR 1.5-2.0) was found. There were 8 cases of primary liver **cancer**, all with heavy previous exposure to VCM. Another 4 cases of hepatoma in polyvinyl chloride (PVC) workers were found in the death registry. 10 of 11 cases of hepatoma, with detailed medical information, were carriers of hepatitis B virus. The average latent period (20 yr) was not different from other studies. Alternative agents of primary liver **cancer** were largely ruled out, suggesting that the combination of hepatitis B & VCM may lead to primary liver **cancer**. **CONCLUSION:** There is an increased risk of primary liver **cancer** in workers exposed to VCM...

[Du CL et al; Occup Environ Med 55 (8): 528-532 (1998)]**PEER REVIEWED**

Human Toxicity Excerpts :

A retrospective mortality study of 454 male workers exposed to chloroethene during its production and polymerization to polyvinyl chloride was conducted. The cohort consisted of men working for at least 1 year during 1950-1969 and the group was followed during 1953-1979. A total of 23 **cancer** deaths were observed (20.2 expected) with 1 case of liver angiosarcoma, 5 lung **cancers** (2.8 expected), 3 colon **cancers** (1.4 expected), 2 thyroid **cancers** (0.16 expected) and 4 malignant melanomas of the skin (0.8 expected) ... "the increased incidence of **cancer** is accounted for almost entirely by the high exposure group" ... The high level of malignant melanoma among this group of workers is unique and warrants further attention.

[Heldaas SS et al; Br J Ind Med 41 (1): 25-30 (1984) as cited in USEPA; Health and Environmental Effects Profile for Chloroethene; p.59 (1985) ECAO-CIN-P155]
PEER REVIEWED

Human Toxicity Excerpts :

A standardized mortality ratio of 1.49 for respiratory system **cancer** (42 observed deaths versus 28.2 expected, $p < 0.01$) was observed among a cohort of 4806 males employed at a synthetic chemicals plant since its startup in 1942. Upon review of pathologic material, the excess was found to be limited to adenocarcinoma and large cell undifferentiated lung **cancer**. Many of the workers had been exposed to vinyl chloride, as well as to chlorinated solvents, polyvinyl chloride (PVC) dust, acrylates and acrylonitrile. To evaluate the association between lung **cancer** and occupational chemical exposures, detailed work histories for each cohort member were combined with exposure ratings for each of 19 chemicals for each job for each calendar year since 1942. A serially additive expected dose model was then constructed which compared the doses of the chemicals observed for the lung **cancer** cases to the doses expected based on subcohorts without lung **cancer** individually matched to the cases. Poly vinyl chloride dust appeared to be the most likely etiologic agent ($p = 0.037$). Time trends of poly vinyl chloride dust exposure indicated a potential latent period of 5-16 years before death.

[Waxweiler RJ et al; Environ Health Perspect 41: 159-65 (1981)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

Vinyl chloride, a hepatocarcinogen in humans & rodents, can form promutagenic etheno bases in DNA after metabolic activation. The formation of 1,N6-ethenoadenine (epsilon A) & 3,N4-ethenocytosine (epsilon C) was measured in adult Sprague Dawley rats by immunoaffinity purification & (32)P-postlabelling. A highly variable background was found in all tissues from untreated animals: the mean molar ratios of epsilon A:A & epsilon C:C in DNA ranged from 0.043×10^{-8} to 31.2×10^{-8} & from 0.062×10^{-8} to 20.4×10^{-8} , respectively. After exposure to 500 ppm vinyl chloride by inhalation (4 hr/day, 5 days/wk for 8 wk), increased levels of epsilon A were found in the liver, lung, circulating lymphocytes & testis, the mean (+/- SD) of induced levels (treated-control values) being $(4.1 \pm 1.5) \times 10^{-8}$ for these tissues. No incr in the epsilon A:A ratio was observed in kidney, **brain** or spleen. The levels of epsilon C increased in all the tissues examined except the **brain**. The mean value of the induced epsilon C:C ratios was $(7.8 \pm 1.2) \times 10^{-8}$ for the liver, kidney, lymphocytes & spleen, & these ratios were higher in the lung (28×10^{-8}) & testis (19×10^{-8}). The results suggest a variable repair capacity for epsilon A or epsilon C in different tissues. The results are discussed in relation to published studies on the accumulation & persistence of etheno bases in the liver during & after exposure to vinyl chloride & on mutation spectra in the ras & p53 genes in liver tumours induced by vinyl chloride. In addn, /studies/ show that the linear relationship established for monofunctional alkylating agents between their carcinogenic potency in rodents & their covalent binding index for promutagenic bases in hepatic DNA holds for vinyl chloride. It is concluded that etheno bases are critical lesions in hepatocarcinogenesis induced by vinyl chloride. ... Further work is needed on the role of DNA repair pathways & of endogenous lipid peroxidation products in the formation & persistence of etheno bases in vivo.

[Barbin A; IARC 150: 303-13 (1999)]**PEER REVIEWED**

Human Toxicity Excerpts :

A mortality and **cancer** morbidity study was conducted to investigate whether there was an increased risk for **cancer** among employees in the polyvinyl chloride processing industry and whether such risks could be associated with special chemical exposures, including exposure to vinyl chloride monomer. The main products manufactured at the company included thick film floor sheeting, floor tiles, homogenous mats, thin film, and extruded pipes. The group of workers studied included 2031 male workers employed at this facility for at least 3 mo from 1945 through 1980. Total mortality was

almost significantly increased, and deaths by violence or intoxication were significantly increased. Deaths from ischemic heart disease were not significantly increased. There was a significant increase in total **cancer** morbidity, and respiratory **cancers**. Liver hemangiosarcoma was not observed. No significant dose response associations were found associated with exposure to vinyl chloride monomer, asbestos, or plasticizers.

[Hagmar L et al; American Journal of Industrial Medicine 17 (5): 553-565 (1990)]
PEER REVIEWED

Human Toxicity Excerpts :

... The mortality in a cohort of 451 workers exposed to vinyl chloride monomer for more than 5 yr was compared with that of 870 workers from the same company ... not exposed to vinyl chloride. The relative risk for digestive **cancer** was significantly higher than 1 (6.25, confidence interval 2.69-14.52) in the exposed group. The standardized mortality ratio for digestive **cancer** was also higher (standardized mortality ratio 259.26 $p < 0.01$) than that of the general population. No other **cancer** was in excess. Since the exposed workers are known to have had a cigarette smoking experience similar to that of those who were not exposed, it is concluded that the association between lung **cancer** and vinyl chloride monomer exposure ... is ... rather small.

[Th'eriault G, Allard P; J Occup Med 23 (10): 671-6 (1981)]**PEER REVIEWED**

Human Toxicity Excerpts :

... The nervous system and bioelectric functioning of the **brain** (EEG) /were evaluated/ in 114 workers aged 20-62, employed in significant exposed to vinyl chloride for 1-28 yr on avg 7.5 + or - 4.0 years. Clinical symptoms of the nervous system occurred in the form of peripheral-vegetative syndrome with accompanying vasomotor disturbances of Raynaud syndrome type. EEG yielded 39 (34.2%) correct and 75 (65.8%) incorrect records. Among incorrect records most frequent (32.5%) were low-voltage and flat records; those with fast spindled activity and frequent changes typical for reduced wakefulness. The nature of clinical symptoms and EEG disturbances may point to the contribution of the hypothalamus in the pathomechanism of changes in those chronically exposed to vinyl chloride.

[Si'nczuk-Walczak H, Gluszcz M; Med Pr 33 (5-6): 349-54 (1982)]**PEER REVIEWED**

Human Toxicity Excerpts :

A population of 10,173 men employed in 37 plants, /were/ identified as having worked for at least one yr in jobs involving probable exposure to vinyl chloride monomer (VCM). Of the 9677 men whose vital status was determined, 707 were known to have died. For 699, death certificates were obtained.

... The only type of malignancy found in significant excess was ... malignant neoplasms of the **brain** and other parts of the nervous system. ... There were slight but inconclusive upward trends for malignancies of the respiratory tract, digestive tract, and central nervous system associated with reported levels of maximum exposure to vinyl chloride.

[Cooper WC; Environ Health Perspect 41: 101-6 (1981)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

Recent results of the long term carcinogenicity bioassay in which vinyl chloride was administered prenatally and postnatally to Sprague-Dawley rats were presented. The animals were exposed to 2500 parts per million through inhalation over 4 to 7 hours a day, 5 days a week, or through the transplacental route (by exposure of the parents) and then by inhalation. The parental rats and some

offspring were exposed for 104 weeks; the remainder of the offspring were exposed for 15 weeks. Mortality was higher in exposed rats; in rats exposed both transplacentally and by inhalation, mortality was related to the length of exposure. The percentage of rats bearing benign or malignant tumors was found to be increased in rats exposed for 15 or 104 wk. Benign mammary tumors, leukemias, pheochromocytomas, and pheochromoblastomas were found at a lower rate in exposed rats, possibly due to the early death of these animals. Vinyl chloride monomer produced unexpectedly high numbers of liver angiosarcomas, hepatocarcinomas and **brain** neuroblastomas in exposed rats. The onset of neuroblastoma was affected by the length of treatment. The onset of hepatocarcinoma was affected by the age at the start of treatment. The onset of angiosarcoma was affected by both the treatment and age.

[Maltoni C, Cotti G; Annals of the New York Academy of Sciences 534: 145-59 (1988)]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

... DEGENERATION OF BONE & CONNECTIVE TISSUE IN MALE WISTAR RATS EXPOSED TO CONCEN OF 30,000 PPM ... 4 HR/DAY ON 5 DAYS/WK FOR UP TO 12 MO. DEGENERATIVE CHANGES WERE OBSERVED IN LIVER (INTERSTITIAL HEPATITIS, NECROSIS, PROLIFERATION OF KUPFER CELLS AND FIBROSIS), KIDNEY (TUBULAR NEPHROSIS & INTERSTITIAL NEPHRITIS), **BRAIN** (NEURONAL AND GLIAL CELL DEGENERATION).

[IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work).p. V7 302 (1979)]**PEER REVIEWED**

Human Toxicity Excerpts :

The results of a mortality study of British vinyl chloride monomer workers between the years 1940 and 1974 were described. The data included the personnel records of nine chemical plants that manufactured or polymerized vinyl chloride. Individuals included in the study had been employed in a job involving vinyl chloride monomer exposure for 25 percent of the work week for a minimum of 1 year. Deaths were followed from 1940 through 1984 and coded according to the categories defined in the International Classification of Diseases. A total of 5,498 male workers were included in the cohort, and 780 deaths were identified. The exposed workers showed significantly fewer deaths from circulatory disease, diseases of the digestive tract, peptic ulcer, diseases of the genitourinary system, and pulmonary disorders relative to the general male population. A significant increase in mortality due to nonsecondary liver **cancer** was noted. Mortality from malignant diseases where an association with exposure to vinyl chloride monomer was previously suggested included malignant neoplasms of the liver, lymphosarcoma, and reticulocyte sarcoma. Autoclave workers experienced the greatest exposure to vinyl chloride monomer and showed the highest mortality rate due to liver **cancer** with a latency period ranging from 8 to 33 years. No significant increase in respiratory disease was determined for baggers and driers exposed to increased amounts of polyvinyl chloride dust.

[Jones RD et al; Scandinavian Journal of Work, Environment, and Health 14 (3): 153-60 (1988)]**PEER REVIEWED**

Special Reports :

Dogliotti E et al; Recent Results **Cancer Res** 154: 97-124 (1998). Mutation spectra resulting from carcinogenic exposure: from model systems to **cancer**-related genes.

Storage Conditions :

early indicator of carcinogenic risk in exposed individuals.

[LI Y et al; BIOMARKERS 3 (6): 433-439 (1998)]**PEER REVIEWED**

Prior History of Accidents :

Travelling from Belgium to the BUNA works in Schkopau, ten of eighteen tank wagons filled with vinyl chloride (VC) derailed on the Magdeburg-Halle railway line just outside Schonebeck station. One wagon exploded & 4 others went up in flames. Buildings & trees in gardens located in the immediate vicinity of the track caught fire & burned. 4 owners of garden plots suffered burns. A total of 28 people received inpatient treatment in a nearby hospital, another 268 people were treated as outpatients. The typical symptoms of fume poisoning such as headache, nausea, irritations of respiratory tract & eyes were the primarily diagnosed problems. The vegetation was damaged by flue gases & developing HCl causing fire & caustic burns. Fire brigades & special task forces succeeded to control the looming danger of health & environmental hazards by cooling the burning wagons & pumping the liquid gases from the tank wagons. Vinyl chloride which was released over several days was measured in residential areas to be 0.06-8 ml/m³ air. Vinyl chloride is a gas which is heavier than air. When exposed to light it will be degraded within a few days. A technical guide concn of 3 ml/m³ air has been adopted for its cancerogenic potential. Dioxin values measured in soils & plants were in the natural range of 20 ng I-TE/kg DS. These values increased to 8300 ng at the very seat of the fire only. With the water used for fire fighting vinyl chloride penetrated into the groundwater revealing values of up to 73 mg/litre. A total of 292 urine samples taken from patients & members of the rescue forces, residents & a control group were tested for their contents of the VC metabolite thiodiacetic acid. However, this number does not allow to draw any conclusions with regard to a potential incr in the risk of cancer. With 0.27, 0.43 and 0.37 mg/litre of urine, the mean values are in the normal range for unexposed people. Only 3 cases showing values of up to 3.1 mg/litre indicated that a real exposure had taken place. The environmental & health authorities have evaluated the results of the measurements at site.

[Thriene B et al; Gesundheitswesen 62 (1): 34-38 (2000)]**PEER REVIEWED**

Evidence for Carcinogenicity :

WEIGHT-OF-EVIDENCE CHARACTERIZATION: On the basis of sufficient evidence for carcinogenicity in human epidemiology studies, vinyl chloride is considered to best fit the weight-of-evidence characterization Category A, according to current EPA Risk Assessment Guidelines (USEPA, 1986). Agents classified into this category are considered known human carcinogens. This classification is supported by positive evidence for carcinogenicity in animal bioassays including several species and strains, and strong evidence for genotoxicity. Under the Proposed Guidelines for Carcinogen Risk Assessment (USEPA, 1996), it is concluded that vinyl chloride is a known human carcinogen by the inhalation route of exposure, based on human epidemiological data, and by analogy the oral route because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes. Vinyl chloride is also considered highly likely to be carcinogenic by the dermal route because it is well absorbed and acts systemically. The weight of evidence for human carcinogenicity is based on 1) consistent epidemiologic evidence of a causal association between occupational exposure to vinyl chloride via inhalation and the development of angiosarcoma, an extremely rare tumor; 2) consistent evidence of carcinogenicity in rats, mice, and hamsters by both the oral and inhalation routes; 3) mutagenicity and DNA adduct formation by vinyl chloride and its metabolites in numerous in vivo and in vitro test systems; and 4) efficient vinyl chloride absorption via all routes of exposure tested, followed by rapid distribution throughout the body. In light of the very high percentage of angiosarcoma worldwide that are associated with vinyl chloride exposure, the evidence for its carcinogenicity is considered strong. The International Agency for Research on

Cancer (IARC) has also concluded that sufficient evidence for carcinogenicity in humans exists and has placed vinyl chloride in carcinogenicity category 1, that is, carcinogenic to humans. Vinyl chloride carcinogenicity occurs via a genotoxic pathway and is understood in some detail. Vinyl chloride is metabolized to a reactive metabolite, probably chloroethylene oxide, which is believed to be the ultimate carcinogenic metabolite of vinyl chloride. The reactive metabolite then binds to DNA, forming DNA adducts that, if not repaired, ultimately lead to mutations and tumor formation. Therefore, a linear extrapolation was used in the dose-response assessment. Because of uncertainty regarding exposure levels in the occupationally exposed cohorts, recommended potency estimates are based on animal bioassay data. **HUMAN CARCINOGENICITY DATA: Sufficient. ANIMAL CARCINOGENICITY DATA: Sufficient.**

[U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS) on Vinyl Chloride (75-01-4) Available from: <http://www.epa.gov/ngispgm3/iris> on the Substance File List as of August 8, 2000]**PEER REVIEWED**

Metabolism/Metabolites :

The first step in biotransformation of ... vinyl chloride ... has been proposed to involve microsomal oxidation leading to epoxide formation across the double bond. ... /It has been/ suggested that the resulting oxiranes are highly reactive and therefore can covalently bind to nucleic acids with the eventual end result of mutations and **cancer**.

[Klaassen, C.D., M.O. Amdur, Doull J. (eds.). Casarett and Doull's Toxicology. The Basic Science of Poisons. 5th ed. New York, NY: McGraw-Hill, 1995. 750]**PEER REVIEWED**

Non-Human Toxicity Excerpts :

Ethenobases are exocyclic adducts formed with DNA by some environmental carcinogens such as vinyl chloride or urethane. ... Increased levels of DNA etheno adducts have been measured in target tissues from rodents exposed to vinyl chloride or urethane. Hepatic tumours caused by exposure to vinyl chloride in humans & in rats & lung tumours induced by urethane in mice exhibit base pair substitution mutations in the ras & p53 genes which seem to be exposure-specific & consistent with the promutagenic properties of etheno bases. Background levels of etheno adducts have been detected in DNA from non-exposed humans or animals, pointing to an alternative, endogenous pathway of formation. This background may be affected by dietary factors. It could arise from the reaction of trans-4-hydroxy-2-nonenal (or its epoxide 2,3-epoxy-4-hydroxynonanal), a lipid peroxidation product, with nucleic acid bases. Elevated levels of etheno adducts are found in hepatic DNA from humans & rodents with genetic predisposition to oxidative stress and lipid peroxidation in the liver, & with an associated increased risk of liver **cancer**. These data suggest that DNA etheno bases could serve as new biomarkers of oxidative stress/lipid peroxidation.

[Barbin A; Acta Biochim Pol 45 (1): 145-161 (1998)]**PEER REVIEWED**

Human Toxicity Excerpts :

The production of mutations in cellular tumor suppressor genes such as p53 is involved in the development of many human **cancers**. These mutations result in the expression of mutant forms of the encoded p53 protein which can potentially serve as a biomarker for this carcinogenic process.

Workers exposed to vinyl chloride who are at risk for the development of the sentinel neoplasm angiosarcoma of the liver represent a model population for the study of such a mutant p53 biomarker, since vinyl chloride is known to cause specific p53 mutations in persons with angiosarcoma of the liver. To determine the relation between vinyl chloride exposure & this p53 biomarker, the authors examined serum samples collected between 1987 & 1992 from a cohort of 225 French vinyl chloride

workers & 111 unexposed controls (matched according to age, sex, race, smoking, & alcohol drinking) for the presence of mutant p53 protein, using an enzyme-linked immunosorbent assay. Stratification of the exposed workers by quartile of vinyl chloride exposure (in estimated ppm-yr) yielded a statistically significant trend of increasing odds ratios for p53 biomarker seropositivity with increasing exposure. These results suggest that this serum biomarker for mutant p53 protein is related to vinyl chloride exposure & may be an early indicator of carcinogenic risk in exposed individuals. [Smith SJ et al; Am J Epidemiol 147 (3): 302-308 (1998)]**PEER REVIEWED**

Human Toxicity Excerpts :

Vinyl chloride (VC) workers are known to be at risk for development of angiosarcoma of the liver (ASL), a rare tumor. Previously, a study of p53 gene mutations in tumors of VC-exposed workers found that 50% of liver angiosarcomas contained such mutations. Mutant p53 oncoprotein & anti-p53 antibodies can also be found in the sera of ASL patients & VC-exposed workers without cancer. ... In this study, we used enzyme-linked immunosorbent assays to detect mutant p53 protein & anti-p53 antibodies in the plasma of VC-exposed workers in Taiwan. Thirty-three of 251 (13.2%) VC-workers tested positive for the p53 overexpression (10% with positive mutant p53 protein & 3.6% with positive anti-p53) in their plasma, but only 2 of 36 controls (5.6%) tested positive (2.8% with positive mutant p53 protein & 2.8% with positive anti-p53). There was a significant association between cumulative VC exposure concn & positive p53 expression ... among VC workers after we adjusted for age, hepatitis, drinking, & smoking status. In summary, P53 overexpression (mutant p53 protein or anti-p53 antibody) can be found in the plasma of VC workers in Taiwan, & a significant dose-response relationship exists between plasma p53 overexpression & VC cumulative exposure concn. [Luo JC et al; J Occup Environ Med 41 (6): 521-526 (1999)]**PEER REVIEWED**

Human Toxicity Excerpts :

The carcinogenicity of vinyl chloride and polyvinyl chloride is reviewed with specific attention to the gaps in knowledge for risk estimation and epidemiological presentation of the available data. Although experimental studies have demonstrated the carcinogenicity and mutagenicity of vinyl chloride/polyvinyl chloride in general, the epidemiologic studies available for review do not include an assessment of carcinogenic risk among humans exposed to these chemicals. This conclusion is based on the observation that the majority of cohort studies reviewed lacked sufficient statistical power because of small sample sizes. Further, in epidemiological studies, individuals were not followed over an adequate period of time during which cancer could become clinically manifest.

[Kalmaz EE, Kalmaz GD; Regul Toxicol Pharmacol 4 (1): 13-27 (1984)]**PEER REVIEWED**

Mechanism of Action :

The first step in biotransformation of ... vinyl chloride ... has been proposed to involve microsomal oxidation leading to epoxide formation across the double bond. ... /It has been/ suggested that the resulting oxiranes are highly reactive and therefore can covalently bind to nucleic acids with the eventual end result of mutations and cancer.

[Klaassen, C.D., M.O. Amdur, Doull J. (eds.). Casarett and Doull's Toxicology. The Basic Science of Poisons. 5th ed. New York, NY: McGraw-Hill, 1995. 750]**PEER REVIEWED**

Medical Surveillance :

Chest Radiography: This test is widely used for assessing pulmonary disease. Chest radiographs have
<http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~AAAn7aGjq:1:BASIC>

been found to be useful for detection of early lung **cancer** in asymptomatic people, especially for detection of peripheral tumors such as adenocarcinomas. However, even though OSHA mandates this test for exposure to some toxicants such as asbestos, there are conflicting views on its efficacy in detection of pulmonary disease.

[Ryan, R.P., C.E. Terry (eds.). Toxicology Desk Reference 4th ed. Volumes 1-3. Taylor & Francis, Washington, D.C. 1997. 2282]**PEER REVIEWED**

Medical Surveillance :

PRECAUTIONS FOR "CARCINOGENS": ... In relation specifically to **cancer** hazards, there are at present no health monitoring methods that may ensure the early detection of preneoplastic lesions or lesions which may preclude them. Whenever medical surveillance is indicated, in particular when exposure to a carcinogen has occurred, ad hoc decisions should be taken concerning additional tests that might become useful or mandatory. /Chemical Carcinogens/

[Montesano, R., H. Bartsch, E. Boyland, G. Della Porta, L. Fishbein, R. A. Griesemer, A.B. Swan, L. Tomatis, and W. Davis (eds.). Handling Chemical Carcinogens in the Laboratory: Problems of Safety. IARC Scientific Publications No. 33. Lyon, France: International Agency for Research on Cancer, 1979.23]**PEER REVIEWED**

Emergency Medical Treatment :

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The following Overview, *** VINYL CHLORIDE ***, is relevant for this HSDB record chemical.

Life Support:

- o This overview assumes that basic life support measures have been instituted.

Clinical Effects:

SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

- o GENERAL - In acute exposure, deaths are most often due to CNS and respiratory depression. The primary toxic hazard is exposure to vinyl chloride monomer (VCM) gas rather than to PVC products (except during pyrolysis). There may be a long latent period between exposure and symptom onset.
- o ACUTE - The nervous system is the primary target of acute vinyl chloride exposure. Signs and symptoms include nausea; abdominal pain; GI bleeding; weakness; ataxia; inebriation; headache; fatigue; numbness; tingling and pallor or cyanosis of the extremities; visual disturbances; cardiac dysrhythmias; narcosis and death. Vinyl chloride is a severe irritant of the eyes, skin, and mucous membranes.
- o CHRONIC - Enhanced collagen deposition and thickening of the subepidermal layer of the skin, Raynaud's

- o Decreased libido and sperm count have occurred following chronic exposures in men.

HEMATOLOGIC

0.2.13.1 ACUTE EXPOSURE

- o Thrombocytopenia, porphyrinuria, and capillary abnormalities have also been reported.

DERMATOLOGIC

0.2.14.1 ACUTE EXPOSURE

- o Scleroderma, frostbite, irritation and cyanosis have been reported. Vinyl chloride may be absorbed through the skin.
- o Contact dermatitis has been associated with VCM or its plasticizers or additives.

MUSCULOSKELETAL

0.2.15.1 ACUTE EXPOSURE

- o Acro-osteolysis, arthralgias, and cold extremities have been reported in workers exposed to VCM.

REPRODUCTIVE HAZARDS

- o Fetotoxicity and congenital malformations have been seen in animals. Human birth defects have not been substantiated.

CARCINOGENICITY

0.2.21.1 IARC CATEGORY

- o Vinyl chloride is in IARC Group 1 (carcinogenic to humans), based on sufficient evidence in humans and experimental animals (IARC, 1998). It is classified as A1 by ACGIH (confirmed human carcinogen) (ACGIH, 2001).

0.2.21.2 HUMAN OVERVIEW

- o Vinyl chloride is a HUMAN CARCINOGEN and can induce angiosarcoma, a rare form of liver **cancer**. **Cancers** of the **brain**, lungs, blood and digestive systems, and melanoma have also been associated with VCM exposure.

0.2.21.3 ANIMAL OVERVIEW

- o Vinyl chloride has produced gastrointestinal, liver (including angiosarcoma), and kidney tumors and skin and appendage tumors in rats; respiratory system, liver, vascular and/or skin/appendage tumors in mice; and lymphomas and skin/appendage tumors in hamsters.

GENOTOXICITY

- o Chromosomal aberrations have been found in workers exposed to vinyl chloride. It has induced DNA damage, unscheduled DNA synthesis, DNA inhibition, mutations, chromosome aberrations, sister chromatid exchanges, micronuclei, and oncogenic transformation in a variety of in vivo and in vitro assays.
- o A specific ras mutation was found to be linked with occupational vinyl chloride exposure.

Laboratory:

- o No toxic serum or blood level has been established.

Treatment Overview:

INHALATION EXPOSURE

- o Monitor for CNS and respiratory depression after acute exposure.
- o VCM and PVC dust may cause various respiratory abnormalities and respiratory **cancers**. Workers exposed to dust should have periodic chest x-rays.
- o There is no specific test to detect VCM hepatic toxicity. Periodic monitoring of liver function tests

in exposed workers is recommended, although there is disagreement about its utility.

EYE EXPOSURE

- o **DECONTAMINATION:** Irrigate exposed eyes with copious amounts of tepid water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist, the patient should be seen in a health care facility.

DERMAL EXPOSURE

- o **DECONTAMINATION:** Remove contaminated clothing and wash exposed area thoroughly with soap and water. A physician may need to examine the area if irritation or pain persists.

Range of Toxicity:

- o Airborne vinyl chloride may be narcotic in concentrations as low as 7 to 10 percent. Twelve percent may be dangerous. Concentrations greater than 10,000 ppm to 20,000 ppm may cause significant symptoms.

[Rumack BH: POISINDEX(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003. Hall AH & Rumack BH (Eds): TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003.]**PEER REVIEWED**

VINYL CHLORIDE

CASRN: 75-01-4

For other data, click on the Table of Contents

Best Sections

Human Toxicity Excerpts :

An unusual distribution in the cell type of **brain cancer** was noted in vinyl chloride exposed workers. Of 10 **brain cancer** deaths identified, 9 had a histologic diagnosis of glioblastoma multiforme. The other case did not have histological confirmation.

[Waxweiler RJ et al; Ann NY Acad Sci 271: 40-8 (1976)]**PEER REVIEWED**

Human Toxicity Excerpts :

Nine retrospective mortality studies of workers exposed to vinyl chloride were reviewed to determine whether differences in their hypothesis testing results might be due to differences in statistical power. Where possible, the power of each study was calculated for **cancer** of the lung, **brain** and liver. When power was taken into consideration, the results for liver and **brain cancer** were consistent with an etiologic role for vinyl chloride. For lung **cancer**, the data were not consistent with an etiologic role, in that 2 studies with very high power yielded negative results.

[Beaumont JJ, Breslow NE; Am J Epidemiol 114 (5): 725-34 (1981)]**PEER REVIEWED**

Human Toxicity Excerpts :

The methods and results of a collaborative study, coordinated by the International Agency for Research on **Cancer** and conducted in many research centers in Europe, were examined. The study examined the **cancer** incidence and mortality among vinyl chloride workers. A total of 14,351 subjects were contributed to the combined data base. The results indicated that vinyl chloride is associated with an increase in liver **cancer** incidence. An exposure response relationship was noted for both ranked and estimated cumulative exposure. The relationship was even more evident when only liver angiosarcoma was analyzed. No significant excess of mortality was observed for the other sites suspected a-priori to be affected by vinyl chloride exposure. While the incidence of lung **cancer** was slightly increased, neither it nor lung **cancer** mortality appeared to be associated with any of the exposure variables. **Brain cancer** and lymphosarcoma mortality, while demonstrating slight increases, did not appear to be consistently associated with exposure, although the small numbers prohibited firm conclusions. An increased risk of bladder **cancer** and melanoma of the skin was detected which did not appear to be related to exposure in that the association with employment in the vinyl chloride industry was confined to one country only. No increased mortality was observed for the other main causes of death.

[Simonato L et al; Scandinavian Journal of Work, Environment and Health 17 (3): 159-69 (1991)]**PEER REVIEWED**

Human Toxicity Excerpts :

The cohort consisted of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride prior to 1 January 1973. These men were employed at 37 plants in the U.S., belonging to 17 companies. Observation of the mortality experience of the cohort was updated from

31 December 1972 to 31 December 1982 (the study now covering 1942-1982). A total of 1,536 cohort members were identified as having died. The observed mortality, by cause, was compared with the expected based on U.S. mortality rates, standardized for age, race, and calendar time. Analyses by length of exposure, latency, age at first exposure, calendar year of first exposure, and type of products were performed. The study confirmed that the vinyl chloride workers experience a significant mortality excesses in angiosarcoma (15 deaths), **cancer** of the liver and biliary tract (SMR = 641), and **cancer** of the **brain** and other CNS (SMR = 180). In addition, the study also found a significant mortality excess in emphysema/chronic obstructive pulmonary disease (SMR = 179). On the other hand, the study did not find any excess in either respiratory **cancer** or lymphatic and hematopoietic **cancer**. This study also found an increase in biliary tract **cancers**, independent from liver **cancer**.

[Wong O et al; Am J Ind Med 20 (3): 317-34 (1991)]**PEER REVIEWED**

Human Toxicity Excerpts :

Epidemiological evidence of an occupational risk of **brain cancer** has been reported in four industries where chemical exposures are likely, most recently in a series of prospective studies in the petrochemical industry. However, only in the case of vinyl chloride exposure has an occupational central nervous system carcinogen been identified. This report reviews the convergence of epidemiological and laboratory evidence that established the occupational carcinogenicity of vinyl chloride, and discusses in detail the current evidence for an occupational risk of **brain** tumors in the petrochemical industry.

[Moss AR; J Toxicol Environ Health 16 (5): 703-11 (1985)]**PEER REVIEWED**

Human Toxicity Excerpts :

... MORTALITY STUDY OF 8384 MEN ... /WITH/ @ LEAST 1 YR ... EXPOSURE ... BEFORE DEC 31, 1972, DEMONSTRATED THAT **CANCERS** OF DIGESTIVE SYSTEM (PRIMARILY ANGIOSARCOMA), RESP SYSTEM, **BRAIN**, & **CANCERS** OF UNKNOWN SITE, AS WELL AS LYMPHOMAS OCCURRED MORE OFTEN THAN EXPECTED IN ... STUDY POPULATION WITH GREATEST ESTIMATED EXPOSURE.

[American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 1986.625]**PEER REVIEWED**

Human Toxicity Excerpts :

In 1974, vinyl chloride (VC) was first reported in the open scientific literature to induce angiosarcoma of the liver both in humans and in animals. Additional research has now demonstrated the carcinogenicity of VC to other organs and at lower concentrations. The target organs for VC now clearly include the liver, **brain** and the lung, and probably the lymphohematopoietic system. The evidence for a carcinogenic risk has been extended to jobs associated with poly (vinyl chloride) exposure. Cases of liver angiosarcoma have been reported among individuals employed in poly vinyl chloride fabrication facilities and an epidemiological study has demonstrated a significant association between exposure to poly vinyl chloride dust and the risk of lung **cancer** mortality. Cases of angiosarcoma of the liver also have been reported among individuals living in near proximity to vinyl chloride-poly vinyl chloride plants. An association between poly vinyl chloride dust and pneumoconiosis also has been demonstrated. On the basis of findings, prudent control of poly vinyl chloride dust in the industrial setting is indicated.

[Wagoner JK; Environ Health Perspect 52: 61-6 (1983)]**PEER REVIEWED**

Emergency Medical Treatment :**EMT Copyright Disclaimer:**

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The following Overview, ***** VINYL CHLORIDE *****, is relevant for this HSDB record chemical.

Life Support:

- o This overview assumes that basic life support measures have been instituted.

Clinical Effects:

SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

- o GENERAL - In acute exposure, deaths are most often due to CNS and respiratory depression. The primary toxic hazard is exposure to vinyl chloride monomer (VCM) gas rather than to PVC products (except during pyrolysis). There may be a long latent period between exposure and symptom onset.
- o ACUTE - The nervous system is the primary target of acute vinyl chloride exposure. Signs and symptoms include nausea; abdominal pain; GI bleeding; weakness; ataxia; inebriation; headache; fatigue; numbness; tingling and pallor or cyanosis of the extremities; visual disturbances; cardiac dysrhythmias; narcosis and death. Vinyl chloride is a severe irritant of the eyes, skin, and mucous membranes.
- o CHRONIC - Enhanced collagen deposition and thickening of the subepidermal layer of the skin, Raynaud's phenomenon, hepatomegaly, hepatic fibrosis, splenomegaly, thrombocytopenia, sensory-motor polyneuropathy, trigeminal sensory neuropathy, minor pyramidal signs, cerebellar and extrapyramidal motor disorders, degenerative bone changes, and acro-osteolysis may occur with chronic exposure to vinyl chloride. Vinyl chloride is a known human carcinogen and has caused angiosarcoma of the liver in heavily exposed workers.
- o DERMAL - Direct contact with liquid vinyl chloride or escaping gas can cause frostbite injury.
- o INHALATION - Inhalation may cause CNS and respiratory depression and seizures.

0.2.1.2 CHRONIC EXPOSURE

- o CHRONIC/SUBACUTE - Target organ is the liver. Direct hepatotoxicity, hepatomegaly, and hepatic **cancers**, including angiosarcoma, have been reported. Vinyl chloride is a human carcinogen and causes **cancer** of the hepatic, hematopoietic, central nervous, respiratory, and digestive systems.
- o VINYL CHLORIDE DISEASE is characterized by a scleroderma-like condition of the connective tissue of

the fingers, Raynaud's phenomenon followed by acro-osteolysis, liver damage, and sometimes hematologic changes and pulmonary effects. It develops after exposures from 1 month to 3 years and is reversible after cessation of exposure.

HEENT

0.2.4.1 ACUTE EXPOSURE

- o Contact with escaping, compressed gas may cause mechanical injury and frostbite. The vapor is irritating to the eyes.

CARDIOVASCULAR

0.2.5.1 ACUTE EXPOSURE

- o VCM sensitizes animal hearts to epinephrine-induced dysrhythmias. Ventricular fibrillation may be a cause of sudden death.

RESPIRATORY

0.2.6.1 ACUTE EXPOSURE

- o Various pulmonary abnormalities have occurred including dyspnea, asthma and pneumoconiosis.
- o A chronic interstitial pulmonary change is thought to be caused by vinyl chloride monomer; this change is distinct from a pneumoconiosis.

NEUROLOGIC

0.2.7.1 ACUTE EXPOSURE

- o VCM may cause CNS depression characterized by fatigue, headache, vertigo, ataxia, euphoria, visual disturbances, numbness and tingling in the extremities, narcosis, loss of consciousness, and death from respiratory failure.

GASTROINTESTINAL

0.2.8.1 ACUTE EXPOSURE

- o Nausea, vomiting, diarrhea, and severe epigastric pain can result from ingestion of the liquid.

HEPATIC

0.2.9.1 ACUTE EXPOSURE

- o Neoplasias (angiosarcoma), hepatomegaly and splenomegaly have been reported as toxic effects of this agent.
- o Portal hypertension can result from liver injury.

GENITOURINARY

0.2.10.1 ACUTE EXPOSURE

- o Decreased libido and sperm count have occurred following chronic exposures in men.

HEMATOLOGIC

0.2.13.1 ACUTE EXPOSURE

- o Thrombocytopenia, porphyrinuria, and capillary abnormalities have also been reported.

DERMATOLOGIC

0.2.14.1 ACUTE EXPOSURE

- o Scleroderma, frostbite, irritation and cyanosis have been reported. Vinyl chloride may be absorbed through the skin.
- o Contact dermatitis has been associated with VCM or its plasticizers or additives.

MUSCULOSKELETAL

0.2.15.1 ACUTE EXPOSURE

- o Acro-osteolysis, arthralgias, and cold extremities have been reported in workers exposed to VCM.

REPRODUCTIVE HAZARDS

- o Fetotoxicity and congenital malformations have been seen in animals. Human birth defects have not been substantiated.

CARCINOGENICITY

0.2.21.1 IARC CATEGORY

- o Vinyl chloride is in IARC Group 1 (carcinogenic to humans), based on sufficient evidence in humans and experimental animals (IARC, 1998). It is classified as A1 by ACGIH (confirmed human carcinogen) (ACGIH, 2001).

0.2.21.2 HUMAN OVERVIEW

- o Vinyl chloride is a HUMAN CARCINOGEN and can induce angiosarcoma, a rare form of liver **cancer**. **Cancers** of the **brain**, lungs, blood and digestive systems, and melanoma have also been associated with VCM exposure.

0.2.21.3 ANIMAL OVERVIEW

- o Vinyl chloride has produced gastrointestinal, liver (including angiosarcoma), and kidney tumors and skin and appendage tumors in rats; respiratory system, liver, vascular and/or skin/appendage tumors in mice; and lymphomas and skin/appendage tumors in hamsters.

GENOTOXICITY

- o Chromosomal aberrations have been found in workers exposed to vinyl chloride. It has induced DNA damage, unscheduled DNA synthesis, DNA inhibition, mutations, chromosome aberrations, sister chromatid exchanges, micronuclei, and oncogenic transformation in a variety of in vivo and in vitro assays.
- o A specific ras mutation was found to be linked with occupational vinyl chloride exposure.

Laboratory:

- o No toxic serum or blood level has been established.

Treatment Overview:

INHALATION EXPOSURE

- o Monitor for CNS and respiratory depression after acute exposure.
- o VCM and PVC dust may cause various respiratory abnormalities and respiratory **cancers**. Workers exposed to dust should have periodic chest x-rays.
- o There is no specific test to detect VCM hepatic toxicity. Periodic monitoring of liver function tests in exposed workers is recommended, although there is disagreement about its utility.

EYE EXPOSURE

- o DECONTAMINATION: Irrigate exposed eyes with copious amounts of tepid water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist, the patient should be seen in a health care facility.

DERMAL EXPOSURE

- o DECONTAMINATION: Remove contaminated clothing and wash exposed area thoroughly with soap and water. A physician may need to examine the area if irritation or pain persists.

Range of Toxicity:

- o Airborne vinyl chloride may be narcotic in concentrations as low as 7 to 10 percent. Twelve percent may be dangerous. Concentrations greater than 10,000 ppm to 20,000 ppm may cause significant symptoms.

[Rumack BH: POISINDEX(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003. Hall AH & Rumack BH (Eds): TOMES(R) Information System. Micromedex, Inc., Englewood, CO, 2003; CCIS Volume 116, edition exp May, 2003.]**PEER REVIEWED**

**National Coalition Against the Misuse of Pesticides
Poison Poles – A Report About Their Toxic Trail and Safer Alternatives**

What's in a Pesticide?

Normally, a pesticide is thought of as a product that can be purchased in stores and used as part of a service to kill pests—the insecticide, weed killer, fungicide or wood preservative.

Unfortunately, these chemicals are not that simple. Pesticide products, particularly wood preservatives, contain a number of different toxic materials, some of which are secret because they are considered confidential business information.

Active Active ingredients are by nature biologically and chemically active against the target pest, be it an insect or fungus. By definition, these materials kill living things.

Inert Inert ingredients are often as toxic as the active ingredient, although the law defines these materials as “secret business information.” Inerts, often petrochemicals like benzene, toluene or xylene, generally make up the largest percentage of the ingredients of a

The Chemical Actors

Three chemical mixtures are common to wood preservation — pentachlorophenol, creosote, and arsenicals (primarily copper chromium arsenate or CCA). A fourth, copper naphthenate is commonly regarded as an alternative. These chemicals all have serious adverse impacts on human health and the environment.

The chemicals and their toxicology

In order for a chemical to protect wood poles from insects and fungi for 40 years or more, it must be toxic to a wide range of organisms and very persistent to all living organisms. Unfortunately, those very characteristics make these chemicals dangerous when released into the environment.

Pentachlorophenol (penta) is a chlorinated aromatic hydrocarbon closely related to other chlorophenols, hexachlorobenzene, polychlorinated dibenzo-p-dioxins and furans. All of these elements are found in commercial grade penta, along with secret “inert” (but biologically and chemically active) ingredients.

Creosote is a complex and variable mixture consisting of approximately 75% polycyclic aromatic hydrocarbon derivatives of coal tar, including anthracene, naphthalene, phenanthrene, acenaphthene, fluorine, and pyridine.

Arsenicals are mixtures of metallic salts, including arsenic pentoxide. For example, **Copper Chromium Arsenate (CCA)** is a mixture of arsenic pentoxide, chromic acid, and copper or cupric oxide, plus secret “inert” ingredients, in proportions that vary with the particular product. The chromium in CCA occurs in the

pesticide product. They form the solution, dust, or granule in which the active ingredient is mixed.

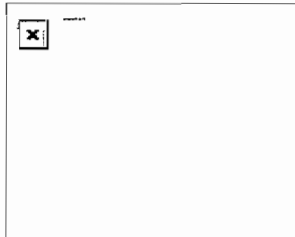
Contaminants

Contaminants and impurities are often a part of the pesticide product and are responsible for the product hazards. Dioxin is a contaminant in pentachlorophenol, created as a function of the production process.

Metabolites Metabolites, often more hazardous than the active ingredients, are breakdown products which form when the pesticide mixes with air, water, soil or living organisms.

more toxic hexavalent, or chromium (VI), form. **Copper Naphthenate** contains about 20% copper salts of naphthenic acids—which consist of an unknown mixture of certain petroleum by-products and contaminants—and about 80% unknown secret ingredients.

**Chemicals
Used for
Poles**



- Penta 45%
- Creosote 13%
- Arsenicals 42%

The chemicals’ affect on human health

Absorption

The oil-based wood preservatives, pentachlorophenol, creosote, and copper naphthenate are all easily absorbed through the skin, as well as through inhalation. The arsenicals are less easily absorbed through the skin, but are readily absorbed by inhalation of dusts or smoke from burning treated wood. Children may ingest all of the chemicals in soil contaminated by leaching from poles.

Acute health effects—Effects of short term exposures to large quantities

All wood preservatives used to treat poles have high acute toxicity. They all attack the skin and nervous system. They may all cause nausea and vomiting. They can all be fatal in single large doses.

Chronic health effects—Effects of long term exposures to small quantities

Wood preservatives are known to cause a variety of chronic health effects, though copper naphthenate is mostly untested. Some of the known health effects are:

- **Impair the immune system:** creosote, penta, arsenicals.
- **Interfere with reproduction:** creosote, arsenicals, penta.
- **Cause birth defects:** penta, arsenicals.
- **Cause cancer (EPA's cancer classification):** creosote (B1 – probable human carcinogen), penta (B2 – probable human carcinogen), arsenicals (A—known human carcinogen).
- **Cause genetic mutations:** arsenicals, penta, creosote, copper naphthenate.
- **Interfere with hormone function:** penta, creosote.

Synergism

Synergism refers to a greater-than-additive impact when a person is exposed to more than one chemical at a time. This can be thought of as teamwork among the chemical actors. If, in order to cause cancer, you need to cause a mutation in a cell and cause the mutated cell to grow fast, then a chemical that just causes mutations or one that just causes precancerous cells to grow faster won't cause many cancers alone. Together, however, they will add up to a potent carcinogen.

- This teamwork is particularly important in the case of wood preservatives, which are all complex mixtures of toxic ingredients. Some ways that wood preservative ingredients act synergistically are known:
- The toxicity of CCA to water fleas and algae has been found to be greater than what would be predicted from the toxicity of the individual metals.¹
- Several of polycyclic aromatic hydrocarbon constituents of creosote are more potent carcinogens when present together than alone.²
- The mechanism by which dioxins cause cancer is known to be one that promotes growth of cells containing a mutation.³ Therefore, it is most potent when in combination with a material that causes mutations. Among such materials are penta and its metabolites.⁴
- Creosote may be synergistic with other chemicals that cause photosensitivity.⁵
- A number of researchers have found that arsenic compounds tend to reduce the effects of selenium.⁶ Selenium plays a role in copper homeostasis and detoxification.⁷ So arsenic probably increases the toxicity of copper.
- Exposure to pentachlorophenol makes hexachlorobenzene more potent in producing porphyria (liver disease).⁸
- Hexachlorobenzene increases the potential for the thymic atrophy (immune system damage) and body weight loss (wasting) caused by dioxin.⁹

Ecological Effects

Persistence/bioaccumulation/bioconcentration potential

Persistence refers to the length of time a chemical remains in the environment before it breaks down

into other chemicals. It may break down by chemical action, with the help of the sun's energy, or through biological decomposition. Some chemicals break down into more toxic chemicals, so lack of persistence does not always mean that the toxic effects disappear. Bioconcentration refers to the way certain chemicals become more concentrated in biological tissues than in their surrounding environment. This is particularly important for aquatic organisms which live in polluted water—if they take in a chemical faster than they can excrete or metabolize it, it will concentrate in them. Bioaccumulation refers to the accumulation of a chemical in higher and higher concentrations from one step in a food chain to the next.

Although small amounts of toxic metals are excreted by organisms, doses of arsenic and associated metals that are found in some environments as a result of contamination from wood preservative are high enough to accumulate in plants and animals. Arsenic bioconcentrates in aquatic organisms—in freshwater organisms up to 17 times background levels, and in marine oysters 350 times background levels.³⁴

Some components of creosote have been found to bioaccumulate and bioconcentrate in aquatic and terrestrial systems.³⁵

The dioxin contaminants in penta are persistent and bioaccumulative. The only known process by which dioxins break down in the environment is photolysis (photodegradation).³⁶ Dioxins are strongly partitioned into the organic components of the environment. In other words, if there are living things in water contaminated with dioxin, the dioxin will be rapidly taken up by living tissue. In fact, sampling for dioxin in aquatic systems uses fish as concentrators of the toxics.³⁷

Leaching potential and environmental fate

The way a chemical moves in our environment affects the likelihood of our being exposed to it. Some chemicals attach themselves to soil particles and are more likely to be carried by heavy runoff into streams than to leach into groundwater. Some dissolve in water and leach quickly through the soil. Others may be found only in organic matter. Often the behavior of chemicals depends on certain aspects of the environment, especially acidity (pH) of the soil or water.

Studies on the movement of wood preservatives from poles have found that they move from poles into soil and from the soil into aquatic ecosystems. The mechanisms by which the various chemicals move are different. Some of the materials are water soluble and are transported as dissolved salts. Others are adsorbed onto soil particles and are carried into streams as suspended particles in heavy rainfall. Once in an aquatic setting, the soil particles provide a steady source of contaminant.³⁸

The degree to which arsenicals leach is strongly dependent on pH. Much more chemical leaches into acid water than into neutral or basic water. Therefore, we should expect arsenicals to leach more in environments high in soil humic acids or where acid precipitation has affected the pH of the soil.³⁹

Penta, on the other hand, is more mobile in neutral-to-basic soils.⁴⁰ **The Endocrine Disruptors**
Chemicals that disrupt the endocrine system wreak havoc

Hormones are chemicals made by the body that help control the body's functions. They are present in minute quantities. Certain other chemicals may be mistaken for hormones by the body, and disrupt the systems controlled by the hormones. In particular, some chemicals are mistaken for the female hormone estrogen. These estrogen mimics interfere with the reproductive system, causing infertility, malformed sexual organs, and cancer of sensitive organs. Creosote and penta interfere with hormone function. Creosote contains ingredients, benzo(a)pyrene and higher phenols, considered to be

endocrine disruptors.¹⁰

Although many chemicals, including pentachlorophenol and its contaminants—polychlorinated dibenzo-p-dioxins, dibenzofurans, and hexachlorobenzene—are considered endocrine disruptors,¹¹ evidence is rarely as strong for most chemicals as it is for penta. Exposure to penta may result in adverse reproductive effects that are associated with changes in the endocrine gland function and immunological dysfunction. A number of women with histories of spontaneous abortion, unexplained infertility and mens trual disorders had elevated levels of pentachlorophenol and/or lindane in their blood.¹²

Cancer

Some chemicals can increase the chance of cancer in humans by causing changes in cells that may lead to cancer, by facilitating the growth of cancer cells, or by inhibiting immune responses that arrest the growth of precanc erous cells. Because of the way cancer starts and progresses, any quantity of a cancer-causing substance increases the chance that the exposed person will get cancer. EPA assigns ratings to substances that cause cancer ranging from A (human carcinogen) to E (evidence of non-carcinogenicity). Creosote, penta, and the arsenicals all cause cancer. EPA's cancer classifications are as follows: creosote—B1 (probable human carcinogen), penta—B2 (probable human carcinogen), arsenicals—A (human carcinogen) .

An increased risk for cancer has been demonstrated in animals exposed to coal-tar creosote. The International Agency for Research on Cancer has determined that creosote is probably carcinogenic to humans (Group 2A).¹³ EPA has determined that cresols are p ossible human carcinogens.¹⁴ Animal studies show that cresols, a component of creosote, may increase the ability of some carcinogenic chemicals to cause tumors.¹⁵ Dermal exposure to creosote can increase the risk of cancer from other agents.¹⁶

The studies indicating that human exposure to pentachlorophenol products causes cancer go back to 1978.¹⁶ They include studies of occupational exposure in the lumber and sawmill industry linking penta with acute leukemias, Hodgkin's and non-Hodgkin? 146;s lymphomas and multiple myelomas.¹⁸

EPA classifies pentachlorophenol as a probable human carcinogen (B2). It finds the sole human study examined by the agency to be inadequate. EPA bases the B2 classification on animal studies that find that two different preparations of pentachlorophenol c ause statistically significant increases in incidences of biologically significant tumor types in both male and female mice: hepatocellular adenomas and carcinomas, adrenal medulla pheochromocytomas and malignant pheochromocytomas, hemangiosarcomas, and hemangiomas. Other animal tests and reviews by other agencies support the conclusion of carcinogenicity.¹⁹

The hexachlorobenzene and hexachlorodibenzo-p-dioxin contaminants in penta are also carcinogens. Agriculture Canada has concluded that the combined evidence from epidemiological studies on humans with mixed exposures to chlorophenols, dioxins, or pesticid es contaminated with these chemicals suggest that occupational exposure to chlorophenols or phenoxy herbicides increases the risk of three kinds of cancer: soft tissue sarcoma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma.²⁰ National Toxicolog y Program studies show the penta metabolite pentachloroanisole to be carcinogenic in rats and mice.²¹ EPA classifies arsenic as a class A, or known human carcinogen. Arsenic ingestion or inhalation has been reported to increase the risk of cancer, especially in the liver, bladder, kidney, and lung.²² Chromium (VI), found in some arsenicals (such as CCA) i s also

classified as a known human carcinogen.²³ **Effects on the Immune & Nervous System** When a chemical interferes with the body's immune system, it makes a person more susceptible to disease. Creosote, penta, and the arsenicals all interfere with the body's defenses against disease.

Laboratory studies find that technical grade penta causes immune suppression in animals, which has been linked to dioxins contained in penta.²⁴

Evidence in both animals and humans suggests that arsenic suppresses the immune system.²⁵ Neurotoxic chemicals affect the nervous system in various ways.

Both arsenic exposure and penta exposure are associated with disturbances and degeneration of nerves in the peripheral nervous system—causing, for example, numbness and a sensation of “pins and needles.”²⁶ **Reproductive Toxicity and Teratogenicity** Chemicals may interfere with reproduction in different ways—by causing infertility, death of the fetus (fetotoxicity), low birth weights, or birth defects. Creosote, penta, and the arsenicals all interfere with reproduction, and/or cause birth defects.

Mice fed benzo(a)pyrene, one of the components of coal tar creosote, during pregnancy had difficulty reproducing, and so did their offspring.²⁷

Experiments in rats and mice have shown creosote to be teratogenic.²⁸ Birth defects have been seen in livestock exposed to wood treated with coal-tar creosote.²⁹

Animal experiments indicate that chronic exposure to pure pentachlorophenol affects reproduction and induces birth defects.³⁰ EPA has concluded that penta and possibly its hexachlorodibenzo-p-dioxin (HxCDD) contaminants cause birth defects and fetotoxic effects in test animals.³¹ Reported adverse effects in fetuses from penta exposure include distorted sex ratios, increased incidences of resorbed embryos, skeletal anomalies, subcutaneous edema (excessive fluid), reduced survival, and reduced growth. Several studies of rats and mice have shown birth defects due to the penta contaminant HCB, including changes in rib development and cleft palate formation in rats. Kidney malformations and decreased body weight were also noted.³²

Spontaneous abortion rates were increased among workers exposed to arsenic, compared to controls. In rodent tests, arsenic increased fetal mortality and birth defects, and increased the ratio of males to females in mice.³³

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