June 1998

Methylene Chloride

White Paper

Executive Summary

The health effects of methylene chloride (dichloromethane) have been studied extensively. Laboratory studies have shown an increased incidence of lung and liver cancer in mice, but not in rats or hamsters. Results of extensive pharmacokinetic and mechanistic research indicate that rats, hamsters, and humans metabolize methylene chloride to a far lesser extent by the metabolic pathway associated with tumor formation than do mice. Further, the tissue effects associated with tumor formation in mice are not likely to occur to a significant degree in humans. In addition, epidemiology studies of five separate worker cohorts exposed to the chemical over extended periods of time have, overall, shown no increased risk of cancer.

On the basis of the extensive evidence, it can be concluded that methylene chloride does not pose a significant health risk to humans under normal conditions of occupational exposure and when products are used in accordance with manufacturers instructions. It is nevertheless important that workplace activities and user operations should continue to be carried out in such a way as to keep exposure as low as is reasonably practicable.

Introduction

Methylene chloride is a widely used chemical solvent with a diverse number of applications. It was introduced as a replacement for more flammable solvents over 60 years ago. Methylene chloride is commonly used in paint removers and industrial adhesive formulations. It also is employed in the production of flexible urethane foams, pharmaceutical products, and plastics, as a cleaning agent for fabricated metal parts, and as an extraction solvent.

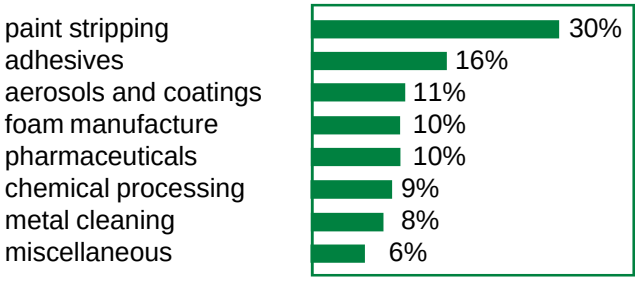
Methylene chloride is a member of a family of saturated aliphatic halogenated compounds. It is a colorless, volatile liquid, completely miscible with a variety of other solvents. It is produced in the United States by The Dow Chemical Company and Vulcan Materials Company. Total U.S. demand for the chemical in 1996 was estimated at about 285 million pounds (129,000 metric tons) of which about 20 million pounds (9000 metric tons) was imported. About 130 million pounds (59,000 metric tons) were exported.

Uses

Methylene chloride is a highly desirable chemical for many applications because of the following characteristics:

- Its aggressive solvency makes it an ideal paint remover that does not harm wood in the removal process.
- It has no flash point under normal use conditions and can be used to reduce the flammability of other substances, decreasing the chance of in-plant fire or explosion.
- It is an effective vapor pressure depressant in aerosols.
- It does not contribute significantly to atmospheric pollution through the formation of smog, to the depletion of the stratospheric ozone layer, or to global warming.

For 1996, the use of methylene chloride in its various applications is estimated to be:



Paint Stripping

Methylene chloride is the active ingredient in many formulations of paint removers including industrial paint and commercial furniture strippers, home paint removers, and products used for aircraft maintenance. The chemical has a unique ability to penetrate, blister, and lift a wide variety of paint coatings. Formulations of the chemical are used extensively in both flow-over and immersion (dip) tanks in furniture refinishing operations. For the maintenance of military and commercial aircraft, a me-

thylene chloride-based product has commonly been used to inspect the surface for damage.

Adhesives

Since the mid 1990s methylene chloride has replaced 1,1,1-trichloroethane in nonflammable adhesive formulations for industrial applications, including fabrication of upholstery foam. It provides adhesive formulations with strong, instant bonding characteristics and efficacy under extremes of temperature and humidity. In foam applications, use of methylene chloride eliminates the possibility of hard seams and allows for ready compliance with flammability requirements for upholstered furniture.

Aerosols and Coatings

Methylene chloride is used in aerosols as a strong solvent, a flammability suppressant, vapor pressure depressant, and viscosity thinner. Current aerosol uses of methylene chloride include spray paints and lubricants.

Foam Manufacture

Methylene chloride is a leading auxiliary blowing agent used in the production of slabstock flexible polyurethane foams for the furniture and bedding industries. Evaporation of the solvent during production of the urethane polymer expands the cells of the foam, reducing its density without making it stiff or rigid. The auxiliary blowing agent also helps to control the reaction temperature, which otherwise could get sufficiently high to burn or scorch the foam interior.

Pharmaceuticals

Methylene chloride is used as an effective reaction and recrystallization solvent in the extraction of several pharmaceutical compounds and in the production of many antibiotics and vitamins. The chemical also has been used as a carrier for pharmaceutical tablet coatings. In these applications, essentially no methylene chloride is left in the coating of the tablet. Residue tolerances have been established by the Food and Drug Administration (FDA) for this particular use.

Chemical Processing

Methylene chloride is employed in the manufacture of polycarbonate resin used for the production of thermoplastics. It is used as a solvent in the production of cellulose triacetate which serves as a base for photographic film. Other applications include its use in the solvent welding of plastic parts, and as a releasing agent to prevent the manufactured part from permanently bonding to the mold.

Metal Cleaning

It is often necessary to remove grease, oil, or similar substances used as lubricants or temporary protective coatings during metal fabrication. Methylene chloride is used extensively for this purpose, both for cold (room temperature) cleaning and vapor degreasing of metal parts.

Miscellaneous

Methylene chloride is used as an extractant in the recovery and purification of a wide variety of materials including oils, fats, and waxes. The chemical is used for the decaffeination of coffee and tea, oleoresin extraction from a variety of spices, and for the extraction of hops. As with tablet coatings, little or none of the chemical remains in the finished product.

Health Effects

General

Methylene chloride is painful and irritating if splashed into the eyes or held in contact with the skin. Overexposure to methylene chloride vapor may cause central nervous system depression (anesthesia) and irritation to the skin, eyes, mucous membranes, and respiratory tract. These effects become more pronounced as the vapor concentration increases, but generally are not observed below 200 parts per million (ppm). Visible symptoms of anesthesia have been reported in several animal species during exposure to methylene chloride concentrations of approximately 4000 ppm and greater.

Carbon monoxide is an end product of metabolism of methylene chloride. Studies in man have demonstrated that 8-hour exposures to concentrations of 100 to 200 ppm of methylene chloride vapor produce carboxyhemoglobin (COHb) concentrations of about 3 to 7 percent, approximating those produced by CO at 50 ppm and well below COHb levels generally required to produce symptoms. The metabolic pathway becomes saturated in man at concentrations from 300 to 500 ppm, thus limiting the production of CO in man and preventing excessive buildup of COHb.

A potential concern linked with elevated COHb levels is that they may exacerbate heart disease. An epidemiology study of Eastman Kodak workers occupationally exposed to methylene chloride (discussed below) showed no increase in deaths due to cardiovascular disease, suggesting that carboxyhemoglobin- induced cardiac effects have not been, and are unlikely to be, a problem at occupational exposure levels. Methylene chloride produces cardiac sensitization at very high exposure levels (24,000 ppm) in dogs, but this effect is unlikely to lead to human problems when methylene chloride is correctly used.

Liver effects have not been reported in man, but liver changes have been observed in several long-term (six months or longer) studies with laboratory animals. Inhalation of 500 to 3500 ppm methylene chloride for 2 years produced only minimal, nonproliferative changes in the liver of Sprague-Dawley rats (the no observed-effect level was equal to 200 ppm) and no liver effects in hamsters. Nonproliferative changes were noted in rats in another study after exposure to 1000 to 4000 ppm. Liver enlargement has been observed in mice exposed to 2000 and 4000 ppm of methylene chloride for 11 days. The slight liver toxicity observed in laboratory rodents after exposure to high concentrations of methylene chloride is not particularly striking. The human experience indicates the liver is not adversely affected by methylene chloride, particularly when used in accordance with current exposure guidelines and labeled instructions.

Genotoxicity

In a wide variety of tests for genotoxicity, only one - the Ames bacterial mutagenicity test - has given consistently positive results across laboratories. In tests using mammalian systems (cells in culture or whole animals), the observed responses have generally been negative or, in a few instances, equivocal. Research sponsored by HSIA has shown, both in vivo and in vitro, that metabolites of the primary pathway by which methylene chloride is metabolized (see below) interact with DNA in mouse liver and lung tissue. This effect, responsible for the tumors observed in mice, is not detectable in human cells in vitro even under extreme conditions.

Reproductive and Developmental Toxicity

Several studies of the potential reproductive and developmental effects of methylene chloride have been carried out on mice and rats. A two-generation inhalation study of methylene chloride, sponsored by HSIA and published in 1988, showed no adverse reproductive effects in Fischer 344 rats exposed to as much as 1500 ppm of methylene chloride for 14 weeks. In studies of female Sprague-Dawley rats and Swiss-Webster mice exposed by inhalation to 1250 ppm methylene chloride during gestation, no significant developmental effects were observed. A similar result was observed in Long-Evans rats exposed to 4500 ppm before and during gestation.

In 1996, HSIA reported to the Agency for Toxic Substances and Disease Registry (ATSDR) the results of a physiologically-based pharmacokinetic (PB-PK) modeling project to convert the inhalation results from the developmental study to comparable drinking water exposures. This work signified the first cooperative effort between government and industry to use PB-PK modeling to avoid unnecessary animal testing.

Neurotoxicity

HSIA has sponsored extensive testing in rats of methylene chloride for potential neurotoxic effects. The results indicate no significant neurotoxic effects after exposure to concentrations up to 2000 ppm for 90 days. As noted above, no neurotoxic effects have been observed in humans at typical occupational exposures.

Carcinogenicity

Laboratory Animal Studies

Administration of the methylene chloride in the drinking water of mice and rats at concentrations up to 250 milligrams per kilogram body weight per day did not induce tumors. Similarly, methylene chloride administered to hamsters via inhalation at concentrations up to 3500 ppm for two years was not tumorigenic.

In inhalation studies conducted on rats, an increase in the number of benign mammary tumors was found upon exposure to concentrations of 500 to 3500 ppm methylene chloride. At lower concentrations of 50 to 200 ppm, no significant increase in these tumors was observed. Importantly, no progression toward malignancy was observed in these studies. A small increase in ventral neck region tumors in and around the salivary glands was observed among male (but not female) rats exposed to 1500 to 3500 ppm of methylene chloride in one study. This increase was not seen in subsequent studies and was not thought by the Environmental Protection Agency's (EPA) Science Advisory Board to have relevant human health implications.

In 1986 the National Toxicology Program (NTP) reported the results of inhalation bioassays in mice (2000 and 4000 ppm) and rats (1000, 2000, and 4000 ppm). There was an increase in the spontaneous incidence of benign mammary tumors in male and female Fischer 344 rats (with no progression towards malignancy), and an increase in the incidence of malignant liver and lung tumors in B6C3Fl mice. NTP concluded that these data demonstrated "clear evidence" of carcinogenicity in mice and female rats and "some evidence" of carcinogenicity in male rats.

Significance of Animal Data

Benign mammary tumors occur spontaneously at a relatively high rate in the strains of rats tested, and the frequency of occurrence in the NTP study was within, or only slightly above, historical control frequency data. A subsequent study found the inhalation of 3500 ppm of methylene chloride to increase the plasma concentration of the hormone prolactin in female rats. The elevated prolactin concentrations observed after exposure to a high concentration of methylene chloride may be

associated with stimulation of the mammary gland, resulting in the enhancement of a normal, spontaneous response. EPA's Science Advisory Board concluded that the increase in benign mammary tumors was not sufficient evidence for a finding of carcinogenicity in rats.

HSIA and its counterparts in Europe and Japan have supported a research program to investigate species differences in the metabolism of methylene chloride and the mechanism responsible for its induction of lung and liver tumors in laboratory mice. This research, which has resulted in 30 separate publications and reports shows that mice are uniquely sensitive at high exposure levels to methylene chloride-induced lung and liver cancer. Other species, including humans, are not at similar risk.

The first phase of the research, completed by 1992, established that methylene chloride is metabolized by two pathways. At low dose levels in mice, rats, and humans, it is metabolized primarily by the cytochrome P450 pathway at rates that do not differ markedly between species. The second pathway involves metabolism by a specific member of the theta glutathione-S-transferase (GST) class of enzymes. The GST enzyme that is capable of metabolizing methylene chloride, glutathione-S-transferase T1-1 (GSTT1-1) is found in the mouse, rat, and human. However, the GST pathway is a major metabolic pathway only in mice and then only at high dose levels after saturation of the P450 pathway.

As a result of this species difference in metabolism, application of a PB-PK model to assess the potential carcinogenic risk of methylene chloride has been widely supported, the GST pathway being accepted as the dose surrogate. Such a PB-PK model can provide risk estimates based on the concentrations of GST metabolites in the target organs of the species of interest.

Despite the excellent correlation between metabolism of methylene chloride by the GST pathway and the occurrence of tumors in different species, the mechanism by which metabolites of the GST pathway induced tumors remained unclear. HSIA and its counterparts thus initiated a second phase of research, intended to ascertain the mechanism whereby methylene chloride causes lung and liver tumors in mice but not other species. This phase concluded in 1995.

Sophisticated studies of enzyme distribution in mouse, rat, and human liver and lung now provide strong biochemical support for the conclusion that the increases in lung and liver tumors seen in mice exposed in two-year bioassays to high levels of methylene chloride are unique to that species. The basis for this conclusion may be summarized as follows:

- Both the liver and lung tumors in mice are caused by a genotoxic mechanism involving metabolites of the GST pathway. The glutathione conjugate which is a principal metabolite of this pathway is reactive but highly unstable. Because of its instability, this conjugate must be generated in close proximity to DNA to produce a genotoxic effect. This can occur only where enzyme activity, specifically that of GSTT1-1, is present in the nucleus of mammalian cells.

- Very high concentrations of GSTT1-1 have been identified in mouse liver and lung samples and found to be localized in the nucleus of liver cells and present in the nucleus of cells in the lung. This enzyme, which is necessary to metabolize methylene chloride by the GST pathway, accounts for the unique sensitivity of the mouse to the genotoxic effects of the solvent. In the absence of such enzyme activity, no effect on DNA is detectable even when extraordinarily high concentrations of methylene chloride are used.

- High concentrations of GSTT1-1 were not identified in rat or human liver tissue. Similarly, transferase l-l was not concentrated in rat lung tissue and has only been detectable at very low levels in the lung of one human subject to date.

- Liver growth and cellular damage and increases in cell division in the lung that may contribute to tumor development are seen only in the mouse.

Epidemiology

The conclusions regarding inter-species differences are supported by the available occupational epidemiology studies which show no association between increased cancer risk and exposure to relatively high concentrations of methylene chloride. Studies of five occupational cohorts are available for the assessment of mortality effects in methylene chloride-exposed populations. These studies include two cohorts of photographic film base manufacturing workers at a Eastman Kodak facility in New York state, two cohorts of fiber production employees at plants in Maryland and South Carolina owned by Hoechst Celanese, and a cohort at an ICI fiber production facility in the United Kingdom.

The epidemiology studies have many features that make them useful for evaluating potential health effects associated with methylene chloride, including: (1) relatively large study groups with significant numbers of long-term employees; (2) large numbers of workers with career mean & hour time-weighted average (TWA) exposures above the currently recommended levels; and (3) lengthy intervals between first exposure and end of follow-up. In addition, the Eastman Kodak studies contains a detailed exposure characterization allowing dose-response analyses.

Considered as a whole, the available epidemiological evidence does not indicate a carcinogenic risk associated with occupational exposures to methylene chloride. The studies consistently demonstrate no excess mortality for all causes of death, total cancer, and the cancers that were observed in the NTP mouse bioassay (lung and liver cancers). In addition, no positive dose-response relationships have been observed. The small number of excess deaths from biliary tract tumors observed in the first Celanese study has not been replicated in the other investigations. Similarly, findings of excess prostate and cervical cancer in the second Celanese study were not replicated in the other studies.

The five epidemiology studies also do not support an association between methylene chloride exposure and astrocytic brain cancer. Such an association was suggested in a recent report which used a statistical treatment based on job codes to estimate whether, and to what extent, solvent exposure had occurred. Among several methodological concerns, the job codes selected for this analysis do not relate well to methylene chloride use.

Carcinogenicity Classification

Methylene chloride is considered a "probable human carcinogen" (Category B2) under EPA's 1986 Guidelines for Carcinogen Risk Assessment. EPA's Science Advisory Board has stated, however, that the level of uncertainty is greater and that the hazard may be less than that expressed by EPA's classification of methylene chloride. An interagency recharacterization of the potential carcinogenicity of methylene chloride completed in 1998 has led EPA to initiate a reassessment of methylene chloride under its proposed revised Guidelines for Carcinogen Risk Assessment.

Methylene chloride is considered "possibly carcinogenic to humans" (Group 2B) by the International Agency for Research on Cancer (IARC) and is considered a potential human carcinogen by the Occupational Safety and Health Administration (OSHA). The American Conference of Government Industrial Hygienists (ACGIH), however, classifies methylene chloride in Category A3 ("animal carcinogen"):

> The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are not considered relevant to worker exposure. Available epidemiological studies do not confirm an increased risk of cancer in exposed humans. Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure.

Regulation

Environmental Exposure

The Clean Air Act Amendments of 1990 significantly revised the provisions of Section 112 relating to the regulation of emissions of hazardous air pollutants. Under the new law, EPA is required to develop national emission standards based on maximum achievable control technology, or MACT, for sources of methylene chloride and nearly 200 other substances within 10 years. The revised Section 112 also requires EPA to review the need for additional control of regulated sources within 8 years of the implementation of the MACT standard. Methylene chloride is also regulated as a toxic air pollutant by some states.

A standard for halogenated solvent cleaning (degreasing) with methylene chloride and other chlorinated solvents became effective for existing sources in December 1997. As a result, degreasing sources using methylene chloride may be required to obtain an operating permit from the state regulatory agency. In some states, permitting for small degreasing sources has been deferred until 1999.

EPA has also developed MACT standards that apply to methylene chloride use in aircraft depainting, wood furniture manufacturing, and polyurethane foam blowing. MACT standards are being developed for polyurethane foam fabrication, pharmaceutical manufacturing, paint stripping, and other uses. A detailed discussion of the requirements of these standards, which generally apply to major sources that emit at least 20,000 pounds of methylene chloride per year, is beyond the scope of this paper.

EPA has determined that methylene chloride is an acceptable alternative in many applications for methyl chloroform and chlorofluorocarbon (CFC) 113, solvents whose production has been phased out because of their potential to deplete stratospheric ozone. Because methylene chloride does not contribute appreciably to smog formation, EPA has indicated that it is exempt from regulation as a volatile organic compound (VOC) under state regulations implementing the national ambient air quality standard for ozone. Methylene chloride is exempt in almost all of the states with VOC regulations, in accordance with federal guidelines.

EPA has established national drinking water regulations setting a maximum contaminant level of 5 micrograms per liter (ug/l), equal to 5 parts per billion (ppb), for methylene chloride. The maximum contaminant level goal (MCLG) for methylene chloride is zero. EPA has indicated that "[t]he establishment of an MCLG at zero does not imply that actual harm necessarily occurs to humans at a level somewhat above zero,

but rather that zero is an aspirational goal which includes a margin of safety, within the context of the Safe Drinking Water Act." Various states also have drinking water regulations that apply to methylene chloride. For various industry categories, EPA has established effluent limitation guidelines, which may contain effluent limits for methylene chloride. EPA also has published ambient water quality criteria for the halomethane class, including methylene chloride, for use by states in developing water quality standards.

Methylene chloride waste is considered hazardous under the federal Resource Conservation and Recovery Act (RCRA) and many state laws. The waste must be stored, transported, and disposed of in accordance with applicable RCRA and state requirements.

The reportable quantity (RQ) for releases of methylene chloride under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or Superfund) is 1000 pounds. Methylene chloride is one of several hundred chemicals subject to the material safety data sheet (MSDS), inventory, and release reporting requirements of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986).

Occupational and Consumer Exposure

The Occupational Safety and Health Administration (OSHA) in January 1997 adopted a comprehensive standard for workplace exposure to methylene chloride. The standard establishes permissible exposure limits (PELs) of 25 ppm as an 8-hour time-weighted average (TWA) and 125 ppm as a short-term exposure limit (STEL). The compliance dates vary by industry sector and size of business; all companies must be in compliance by April 2000 at the latest. The standard also requires medical surveillance and contains a number of other ancillary provisions. The ACGIH threshold limit value (TLV) is 50 ppm for an 8-hour TWA exposure.

In 1987, the Consumer Product Safety Commission (CPSC) published a Statement of Interpretation and Enforcement Policy for household products containing methylene chloride. This policy statement establishes labeling guidance for these products under the Federal Hazardous Substances Act. In addition, the use of methylene chloride in cosmetic products is restricted by the Food and Drug Administration (FDA), which also regulates its use as a decaffeinating agent for coffee and tea.

Regulatory and Other Information for Methylene Chloride

Chemical Formula	CH_2Cl_2
Molecular Formula	84.9
CAS Number	75-09-2
Flammable limits (at 25°C)	14 % - 22 % solvent in air
OSHA PEL	
8-hour TWA	25 ppm
15-minute STEL	125 ppm
ACGIH TLV	
8-hour TWA	50 ppm
15-minute STEL	--
IARC Classification	2B ("possibly carcinogenic to humans")
CERCLA Reportable Quantity (RQ)	1000 pounds
Maximum Contaminant Level (Drinking Water)	5 micrograms/liter (5 parts per billion)
RCRA Hazardous Waste Number	U 080
DOT Hazard Classification	6.1 (packing group III)
DOT ID Number	UN 1593

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