Methyl chloride; CASRN 74-87-3 (07/17/2001)

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Methyl chloride

File First On-Line 07/17/2001

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	07/17/2001
Inhalation RfC (I.B.)	yes	07/17/2001
Carcinogenicity Assessment (II.)	yes	07/17/2001

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Methyl chloride
CASRN — 74-87-3
Last Revised — 07/17/2001

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.1. Oral RfD Summary

Not applicable. Methyl chloride exists primarily as a gas. No adequate oral exposure studies exist from which an oral RfD may be derived.

I.A.2. Principal and Supporting Studies (Oral RfD)

Not applicable.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

Not applicable.

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

Not applicable.

I.A.5. Confidence in the Oral RfD

Not applicable.

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

Source Document — U.S. EPA, 2001

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Methyl chloride
CASRN — 74-87-3
Last Revised — 07/17/2001

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 generally expressed in units of mg/m^3. 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.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Cerebellar lesions **Mouse 11-day continuous inhalation study** **Landry et al., 1983, 1985**	NOAEL: 50 ppm (103.2 mg/m^3) NOAEL(ADJ): 94.6 mg/m^3 NOAEL(HEC): 94.6 mg/m^3 LOAEL: 100 ppm (206.4 mg/m^3) LOAEL(ADJ): 189.2 mg/m^3 LOAEL(HEC): 189.2 mg/m^3	1,000	1	9E-2 mg/m^3

*Conversion Factors and Assumptions: MW = 50.49. Assuming 25° and 760 mmHg: NOAEL (no-observed-adverse-effect level) (mg/m^3) = 50 ppm × 50.49/24.45 = 103.2 mg/m^3; LOAEL(ADJ) (lowest-observed-adverse-effect level) =103.2 mg/m^3 × 22 hours/24 hours × 7 days/7 days = 94.6 mg/m^3. Methyl chloride is a Category 2 gas (U.S. EPA, 1994) for which

periodicity was assumed to be attained for systemic effects and for which the blood:gas partition coefficients for humans (Nolan et al., 1985) and rats (Gargas et al., 1989) yield an approximate 1:1 ratio. The assumption is that the partition coefficient for the mouse would be similar to that for the rat on the basis of the tabulation of Gargas et al. (1989), who reported that blood:gas partition coefficients for 6/7 chemicals are similar for both the rat and mouse. In addition, it is a defensible assumption that is within the range of current modeling practice. Thus, a regional gas dose ratio (RGDR) of 1.0 was applied to calculate a human equivalent concentration (HEC) for the NOAEL, resulting in an HEC of 94.6 mg/m^3. Note: ADJ = duration-adjusted concentration.

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

Dysfunction of the central nervous system (CNS) is a hallmark for toxicity due to methyl chloride both in human case reports and in short- and long-term studies in laboratory animals. The 2-year CIIT study (1981), which is the only long-term intermittent (6 hours/day, 5 days/week) inhalation study currently available, would typically have been chosen for identification of the critical effect (e.g., cerebellar lesions) because it satisfies the criteria set forth in U.S. EPA (1994) in spite of several procedural errors (e.g., some misidentification of mice, pregnancy of some mice, and an exposure error early in the study). However, the continuous (22-22.5 hr/day) 11-day exposure of the female C57BL/6 mouse (Landry et al., 1983, 1985) is considered more appropriate in the context of protecting public health for the following reasons:

1. The study was well conducted.

2. Cerebellar lesions (considered the most critical effect in the context of known CNS deficits from human case reports) occurred at continuous exposure levels (100 ppm) and at intermittent levels (400 ppm) far below those in the $B6C3F_1$ strain exposed chronically (1,000 ppm) in the 1981 CIIT study.

3. No cerebellar lesions were observed in the 90-day pilot study in the $B6C3F_1$ mouse (Mitchell et al., 1979) at levels up to 1,500 ppm.

4. Continuous exposure of C57BL/6 mice resulted in mortality at 200 ppm, whereas intermittent 2-year exposure of the $B6C3F_1$ mouse did not cause mortality below 1,000 ppm.

Landry, TD; Quast, JF; Gushow, TS; et al. (1983) Methyl chloride: inhalation toxicity in female C57BL/6 mice continuously or intermittently exposed for 11 days. EPA/OTS Doc #878213687, NTIS/OTS0206357.

Landry, TD; Quast, JF; Gushow, TS; et al. (1985) Neurotoxicity of methyl chloride in continuously versus intermittently exposed female C57BL/6 mice. Fundam Appl Toxicol 5(1): 87-98.

Continuous exposure of female C57BL/6 mice (12/group) to 100 ppm and higher (22 hours/day for 11 days) caused degenerative changes (slight in all 12 at 100 ppm and moderate to severe in 100% of animals at higher levels) in granule cells of the cerebellum; higher exposure levels (150 ppm and above) also led to a moribund condition and death. There were no cerebellar lesions or mortality at 15 and 50 ppm. No histopathological evidence of damage in the spinal cord area or to peripheral nerves was reported at any exposure level. Decrements in neurofunctional testing (ability to stay on an accelerating rod after 4, 8, and 11 days of exposure) were observed at 150 ppm. Decreased glycogen content in 100- to 200-ppm mice was the principal significant change observed in the liver, although focal periportal hepatocellular degeneration and/or necrosis was noted in the 400 ppm group. There was no histological evidence of kidney lesions. Duration-dependency of cerebellar lesions was observed upon serial necropsy of 150-ppm animals (5/time period except on day 11 when 12/time period were sacrificed), with moderate degeneration and neurofunctional deficits on day 4 (not days 1 and 2) and a moribund condition by day 10.5.

Mice were also exposed intermittently (5.5 hours/day) for 11 days to 0, 150, 400, 800, 1,600, or 2,400 ppm. A concentration-related increase in the cerebellar incidence of granule-cell pyknosis and karyorrhexis (slight) was observed in the 400-ppm and higher groups. Decreased hepatocyte size, without degeneration or necrosis, was variably seen in mice from the 400- through 2,400-ppm groups. Decreases in mean absolute and relative thymus weights were statistically significant and considered exposure-related (reflecting decreased body weights and stress) for the 2,400 and 1,600 ppm groups; the latter group evidenced a decrease in the size of the thymus. Evidence of kidney toxicity was found only in the 2,400-ppm group and consisted of slight multifocal tubular degeneration and regeneration, and eosinophilic-staining tubular casts. Inanition was apparent in the 2,400-ppm group, as was thin, watery blood from the heart, a finding supported by low blood packed cell volume. The spleens of this group were considerably enlarged, suggestive of extramedullary hematopoiesis, which was microscopically confirmed. The in-life observation of red urine in the 2,400-ppm group was determined to result from hemoglobinuria consistent with intravascular hemolysis. These animals deteriorated (e.g., hind limb extensor rigidity) and were sacrificed moribund on days 8-9.

Based upon cerebellar damage, this study identifies a NOAEL and LOAEL of 50 and 100 ppm, respectively, for continuous exposure. For intermittent exposure, the NOAEL and LOAEL are 150 and 400 ppm, respectively.

CIIT. 1981. Final report on a chronic inhalation toxicology study in rats and mice exposed to methyl chloride, conducted by the Battelle Columbus Laboratories for the Chemical Industry Institute of Toxicology. EPA/OTS Doc #878212061, NTIS/OTS0205952.

Groups of F-344 rats and B6C3F1 mice (117-120/sex/species/concentration) were exposed 6 hr/day, 5 days/wk, for up to 24 months to concentrations of 0, 50, 225, or 1,000 ppm (0, 103, 465, or 2,065 mg/m^3) of 99.97% pure methyl chloride. Duration-adjusted exposure levels were 0, 8.9, 40.2, or 178.6 ppm (18.4, 83.0, or 368.8 mg/m^3).

Mouse: Mouse mortality was significantly increased in females (beginning at 10 months) at 1,000 ppm compared with controls, but was unaffected at 50 and 225 ppm. Signs suggestive of CNS toxicity (e.g., tremor, paralysis) were noted only in 1,000-ppm mice. Neurofunctional impairment (clutch response) was found in nearly all 1,000-ppm mice of either sex after 18-22 months of exposure. This finding was supported by the histopathological observation of cerebellar lesions (degeneration and atrophy of the granular layer) that first appeared in 1,000-ppm male and female mice at the 18-month sacrifice. It did not occur in the 0, 50, or 225 ppm groups.

At the 24-month end-of-study sacrifice, there was no difference in incidence of spinal cord axonal swelling and degeneration between exposed and control mice. Hepatocellular lesions (vacuolization, karyomegaly, cytomegaly, multinucleation, degeneration), first noted at 6 months in 1,000 ppm male mice, were found with increasing frequency at 12 and 18 months and were seen in the majority of males suffering unscheduled deaths. Renal tubuloepithelial hyperplasia and karyomegaly were first apparent in 1,000-ppm male mice at 12 months, subsequently increasing in incidence and severity until the last males in this group were sacrificed at 21 months. Seminiferous tubule atrophy and degeneration were also statistically significant and considered exposure-related in 1,000-ppm males. Finally, 1,000-ppm mice developed splenic atrophy and lymphoid depletion during months 6-22 that was considered related to methyl chloride exposure. In mice, 1,000 ppm was identified as an FEL on the basis of high mortality.

Rat: There was no treatment-related mortality in the rat. The testes were the only target organs examined in the rat that were considered to have significant gross or histopathological lesions (bilateral, diffuse degeneration and atrophy of the seminiferous tubules) related to methyl chloride exposure (1,000 ppm). At the 18-month period, age-related interstitial hyperplasia and/or adenomas were present in controls and the 225-ppm group; these lesions exhibited an increasing incidence with level of exposure.The testicular results in rats are consistent with a LOAEL of 1,000 ppm, based on early signs of seminiferous tubule degeneration and atrophy in the absence of age-related degeneration. A NOAEL of 225 ppm appears reasonable because

tubule degeneration and atrophy at this exposure level occurred upon onset of age-related hyperplasia and compressive adenomas.

A shortcoming of this study relates to some incorrect sexing (periodic pregnancies were observed in the mouse population) and misplacement of specific mice. The investigators considered the problem serious but not one that threatened the validity of interpretation of the experimental results. This conclusion appears reasonable considering that the types of effects and the levels at which they occurred were confirmed in several shorter term studies.

McKenna, MJ; Burek, JD; Henck, JW; et al. (1981a) Methyl chloride: a 72-hour continuous (23-1/2 hr/day) inhalation toxicity study in dogs and cats. EPA/OTS #878210220, NTIS/OTS0206129.

Three groups of three male beagle dogs (ages 7-8 mo) and three male cats (ages 8-9 mo) were exposed for approximately 23.5 hr/day for 3 days (i.e., 72-hr treatment regimen) to methyl chloride concentrations of 0, 200, or 500 ppm. After 48 hr of treatment, 500-ppm dogs appeared more tranquil, with one exhibiting intermittent tremor and slight excess salivation, but all were judged alert and responsive. Immediately after 72 hr of treatment, control and 200-ppm dogs were comparable. However, all 500-ppm dogs appeared weak and displayed a range of adverse effects that varied in severity from animal to animal. These included hind and fore limb stiffness and incoordination, occasional slipping and falling, inability to sit up or walk, limb tremor, and excessive salivation. Improvement was noted in all 500-ppm dogs by postexposure day 10, which continued until termination on day 27.

Neurological evaluations and gross and histopathology revealed no treatment-related abnormalities in control or 200-ppm dogs, whereas each of the three 500-ppm dogs exhibited various clinical deficiencies (posterior paresis, opisthotonus, extensor tonus, and intention tremors). By 26 days postexposure, spinal reflexes and postural reactions were normal, balance was maintained normally, and walking with intermittent ataxia was observed. All three 500-ppm dogs displayed lesions in the brain and spinal cord (vacuolization, swollen eosinophilic axons, axon loss, demyelinization, and microglial cells that contained phagocytosed debris), which were characterized as generally very slight to slight and multifocal in nature. The lesions were localized to the brain stem and the lateral and ventral funiculi of the spinal column, and were not observed in the cerebrum, cerebellum, or peripheral nerves. During the first 48 hr of exposure, the 200- and 500-ppm cats evidenced a decline in appetite that then recovered, and after 24 hr they appeared less active than controls, but always were alert and displayed no signs of inactivity or sluggishness upon removal from the exposure chamber. Throughout the 2-week recovery period, 200 and 500 ppm cats were comparable to controls. Brain and/or spinal cord lesions were found in control (1/3), 200-ppm (1/3), and 500-ppm (3/3) cats. Several characteristics of these lesions led the authors to

speculate that they were likely the result of a postvaccinal reaction, a viral infection, or both; however, it was recognized that exposure to 500 ppm methyl chloride could possibly have exacerbated such a disease process. The findings of this study indicate a NOAEL of 200 ppm for a continuous (nearly) 72 hr exposure to methyl chloride, and a LOAEL of 500 ppm based principally upon a spectrum of clinically and histopathologically observable neurological effects seen in male beagle dogs. In a second study by the same investigators, there was no evidence of brain or spinal cord lesions in male beagle dogs exposed for 6 hr/day, 5 days/week for a total of 64-66 exposures to concentrations of 0, 50, 150, or 400 ppm (McKenna et al., 1981b).

These histopathological effects (e.g., cerebellar lesions), as well as other testicular effects (e.g., decreased sperm count sperm granulomas), were also seen in shorter term studies (Burak et al., 1981; Morgan et al., 1982; Chapin et al., 1984; Working et al., 1985a,b) at levels of 500 ppm and greater. Thus, the results of these shorter-term studies lend support to the NOAEL and LOAEL from the Landry et al. (1983) study.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 1,000.

A factor of 10 is used to protect sensitive human subpopulations (intraspecies variability). It is clearly established that in rodents (probably in humans as well), methyl chloride is principally metabolized in the liver via a GSH-conjugation mediated pathway. The unknown susceptibility of the two human subpopulations identified in several studies on the basis of differences in their rates of metabolism of methyl chloride in erythrocytes is considered sufficient justification for the intraspecies uncertainty factor of 10. In vivo pretreatment of laboratory animals with a specific inhibitor of g-glutamate-cysteine ligase resulted in the elimination of lethality and cerebellar lesions, clearly indicating that reaction (metabolism) products of GSH with methyl chloride play a key role in the manifestation of cerebellar and other target organ lesions (Chellman, 1986a,b). Whether there is susceptibility on the basis of gender is another concern because there is limited, but not convincing, evidence that female C57BL/6 mice have a higher incidence (and severity) of cerebellar lesions than males or other mouse strains and rats at intermittent short-term exposure concentrations >500 ppm (Morgan et al., 1982).

A factor of 10 is used to extrapolate from an 11-day continuous study to a lifetime inhalation study. In the typical situation in which only a subchronic intermittent rodent inhalation exposure study is available, a full factor of 10 is generally applied to account for the lack of chronic intermittent exposure results. Although the 11-day study is not fully equivalent in duration to a subchronic study, it is a valuable continuous inhalation study supported by the

conclusions of a chronic study. A factor of 10 is thus considered protective to account for using a less-than-chronic study for the derivation of the RfC.

A factor of 3 ($10^{1/2}$) is used to account for interspecies variability in extrapolating from animals to humans considering that a dosimetric adjustment accounts for the pharmacokinetic portion of the interspecies uncertainty factor. Only the C57BL/6 female mouse was examined under continuous exposure conditions; therefore, it is unknown how the male or B6C3F_1 mice would react upon similar exposure conditions. The only strain comparisons that were made were those of Morgan et al. (1982), and they were under intermittent exposure conditions at relatively high concentrations; thus, a factor of 3 is considered prudent.

A database uncertainty factor of 3 ($10^{1/2}$) is used for lack of brain histopathology in F_1 generation mice. The effect of exposure on in utero development of the brain in mice has not been examined and remains an important data gap.

The product of the two factors of 3 ($10^{1/2}$) coalesces to a 10.

MF = 1.

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

In humans, methyl chloride acts principally as a depressant of the CNS. Typical signs and symptoms of intoxication have been described as appearing within 2-3 hr of exposure, including headache, nausea, vomiting, painful neck, loss of appetite, diarrhea, dizziness, giddiness, blurred vision, ataxia, confusion, slurred speech, diplopia (double vision), tremors of the hands and lips, drooping eyelids and eye twitch, muscle spasms, convulsions and opisthotonus (body spasms), cold and clammy skin, loss of memory, hallucinations, respiratory depression, unconsciousness, coma, and death (ATSDR, 1998; Ellenhorn and Barceloux, 1988; Farber and Torkelson, 1989; IPCS, 1999; Sittig, 1991). Effects of longer term, low-level exposure are thought to be generally, although not always, mild and reversible after a recovery period of days to months, and include fatigue or malaise, loss of appetite, headache, disequilibrium, blurred vision, confusion, anxiety, personality changes, short-term memory loss, vertigo, loss of coordination, weakness, pale skin, nausea, and vomiting. Evidence suggests that in persons exposed to doses of methyl chloride sufficient to cause serious CNS effects, other organ systems including the heart, gastrointestinal tract, liver, kidneys, and lungs can be adversely affected, although the cardiovascular and gastrointestinal effects may largely be secondary to CNS toxicity (ATSDR, 1998; IPCS, 1999; Farber and Torkelson, 1989).

In a two-generation reproduction study in F-344 rats exposed intermittently (10-week exposure periods followed by 10-week recovery periods) to 0, 150, 475, or 1,500 ppm methyl chloride, degeneration and atrophy of the seminiferous tubules in all 1,500 ppm F_0 males (10/10) were observed, in addition to increased incidences of epididymal sperm granulomas (3/10) and decreased testes size in these latter three animals (Hamm et al., 1985). This study identified a two-generation reproductive LOAEL based on statistically significant reduced male fertility at 475 ppm (fertility returned to control levels after 10 weeks of recovery), with a corresponding NOAEL of 150 ppm. There was no clear effect of exposure on fertility of the F_1 generation (no histopathology was performed) other than a reduced percentage of male offspring in the 475-ppm group compared with controls and the 150-ppm group.

In a study of female F-344 rats and female C57B/6 mice (bred to C3H males) exposed to concentrations up to 1,500 ppm during gestation, the mouse progeny ($B6C3F_1$) exhibited a small but statistically significant increase in the incidence of a heart anomaly in the 500-ppm group only (Wolkowski-Tyl, 1983a). No such effects were seen in rats. In a further extension of this work, female C57BL/6 mice bred to C3H males were exposed to 0, 250, 500, or 750-ppm (Wolkowski-Tyl et al., 1983b). The 750-ppm level was maternally toxic and heart malformations were observed in both male and female progeny at 500 and 750 ppm, but not at 250 ppm. Because this lesion was not observed in another laboratory (John-Greene et al., 1985) under a different exposure protocol, some uncertainty exists regarding the exposure conditions under which this lesion occurs, although it is prudent to regard methyl chloride as a mouse teratogen.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium
RfC — Medium

The overall confidence in the RfC assessment is medium. Although the confidence in the principal and supporting studies is high, overall confidence in the database is medium because of the lack of brain histopathology on F_1 generation mice, particularly female C57BL/6, a strain that may be particularly sensitive to the effects of methyl chloride. There is suggestive evidence that methyl chloride may cross the placenta (Bus et al., 1980) and, given the known effects of methyl chloride on the cerebellum, is cause for concern about the lack of histopathological data in offspring of exposed laboratory animals. A reproduction/teratology

study in the rat through the F_1 generation has been performed and provides some support for effects on the male reproductive system, but no brain histopathology was performed.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2001

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Methyl Chloride. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Agency Consensus Date 6/26/2001

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Methyl chloride conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Methyl chloride
CASRN — 74-87-3
Last Revised — 07/17/2001

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 µg/L drinking water or risk per $\mu g/m^3$ air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with 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/600/887/045) 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.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Methyl chloride is found ubiquitously in nature and exists primarily as a gas, with inhalation as the predominant route of exposure. However, it is moderately soluble in water, which suggests that ingestion of drinking water containing methyl chloride can be a secondary route of exposure.

Applying the criteria for evaluating the overall weight-of-evidence for carcinogenicity to humans outlined in EPA's guidelines for carcinogen risk assessment (U.S. EPA, 1986), methyl chloride is most appropriately designated a Group D - Not classifiable as to its human carcinogenicity. Using the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), the available data suggest that methyl chloride would be classified as an agent whose carcinogenic potential *cannot be determined*.

Limited human epidemiology studies show no suggestive evidence that methyl chloride exposure was associated with a carcinogenic response. However, weak to moderate mutagenicity has been demonstrated in *S. typhimurium* (albeit at high concentrations), and an increased incidence of tumor formation (benign and malignant) in male mouse kidneys does provide some suggestive information of carcinogenic risk, although no renal tumors were found in female mice or in either sex of rats tested in the same study. In addition, induction of sister chromatid exchanges (SCE) by methyl chloride has been observed in human lymphoblasts, and by a congener, methyl bromide, in lymphocytes from a human subgroup categorized as "slow metabolizers." This group is known to be genetically predisposed

(polymorphisms in glutathione transferase) to have a lower rate of metabolism compared with the majority of human populations studied.

The lack of detectable CYP2E1 protein in human kidney (in contrast to mice, which have high levels) suggests that the metabolism of methyl chloride by P450 (presumably leading to elevated formaldehyde concentrations) that could be responsible for the induction of male mouse kidney tumors may not be relevant to humans. However, the role of hepatic (and/or kidney) metabolism (leading to potential genotoxic metabolites) via the predominant GSH pathway (or even by P450 isozymes other than CYP2E1) in this regard cannot be discounted; in vivo metabolism of methyl chloride to formate in liver is GSH-dependent, via the GSH-requiring formaldehyde dehydrogenase that oxidizes formaldehyde to formate. Inasmuch as methyl chloride exposure can lower tissue nonprotein sulfhydryl concentrations, it thus has the potential to inhibit formaldehyde dehydrogenase and increase formaldehyde levels. The extent to which this may or may not take place in the human kidney is an area for further research.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Inadequate. The few studies that have examined methyl chloride's potential carcinogenicity in humans have failed to convincingly demonstrate any association, and in one instance even indicated a lower cancer incidence than expected in workers chronically exposed to methyl chloride in a butyl rubber manufacturing plant (Holmes et al., 1986). There was no conclusive evidence for an effect of acute, severe exposure to methyl chloride on mortality from all cancers or from lung cancer in a small cohort accidentally exposed to methyl chloride from a leaking refrigeration unit (Rafnsson and Gudmundsson, 1997); because of the wide confidence intervals that included unity, the data cannot be construed as suggestive of an elevated cancer mortality risk Other occupational studies involved exposure to multiple chemicals in addition to methyl chloride, making it difficult to attribute any effects specifically to methyl chloride (Dow Corning Corporation, 1992; Olsen et al., 1989).

II.A.3. Animal Carcinogenicity Data

In animals, the only evidence of carcinogenicity comes from a single 2-year bioassay, which found a statistically significant increased incidence of renal benign and malignant tumors only in male B6C3F1 mice at the high concentration (1,000 ppm), although two renal adenomas

occurring in 225-ppm males may also be treatment-related (CIIT, 1981). Neoplasia were not found at lower concentrations or at any other site in the male mouse, nor at any site or concentration in female mice or F-344 rats of either sex. Renal cortical tubuloepithelial hyperplasia and karyomegaly were also confined to 1,000-ppm male mice.

II.A.4. Supporting Data for Carcinogenicity

There is some evidence that methyl chloride is a weak genotoxin at high concentrations when tested in vitro; however, its in vivo cytotoxicity appears to dominate any potential genotoxic effects that may occur. Methyl chloride was mutagenic in *Salmonella* strain TA100 at a 5% concentration (Simmon, 1981), in strain TM677 at 5%-30% (Fostel et al., 1985), in TA1535 at 0.5%-0.8% to 20.7% (Andrews et al., 1976; Longstaff et al., 1984), and in strain TA1535 at 4% and 7% and strain TA100 at 1%, 4%, and 7% (du Pont, 1977). It has not been shown to methylate DNA (Kornbrust et al., 1982). Methyl chloride was weakly positive for the in vivo induction of unscheduled DNA synthesis (UDS) in rat liver at 15,000 ppm, but not at 3,500 ppm, nor in pachytene spermatocytes or tracheal epithelial cells at either concentration (Working et al., 1986). In vitro exposure of the spermatocytes induced UDS at 3%-10%, but not 1%, while in the tracheal cells the response was negative at 1%, negative but suggestively positive at 3%, and toxic at 5% and 10%. Primary cultures of human hepatocytes from three individuals were collectively negative at 0.1%-0.3%, negative or weakly positive at 1%, and toxic at 2%-10% (Butterworth et al., 1989). A high concentration (20%) of methyl chloride was found to be a potent inducer of sex-linked recessive lethal mutations in *Drosophila* (University of Wisconsin, 1982), and 6,000-25,000 ppm (but not 3,000 ppm) enhanced viral transformation in cultured Syrian hamster embryo (SHE) cells (Hatch et al., 1983). An increase in the frequency of SCE in human lymphoblasts was induced by 0.3%-5% methyl chloride, although there was no evidence of DNA damage (Fostel et al., 1985). Finally, 2,000-3,000 ppm (but not 1,000 ppm) produced dominant lethal effects in Sprague-Dawley rats (SRI, 1984) and F-344 rats (Working et al., 1985a). This dominant lethality appears attributable to cytotoxic effects on sperm in the testes rather than to direct genotoxicity, and to the effects of genotoxic oxidative metabolites resulting from an induced inflammatory response in the epididymides (Chellman et al., 1986a,b, 1987; Working et al., 1985b; Working and Bus, 1986; Working and Chellman, 1989). Thus, methyl chloride has mutagenic potential, but does not appear to methylate DNA. On the other hand, both methyl chloride and methyl bromide induce SCEs in human lymphocytes in vitro; methyl bromide induced SCE in lymphocytes from a human subgroup characterized as "slow metabolizers" in terms of glutathione transferase polymorphisms, but not in "fast metabolizers." It remains to be established whether methyl chloride behaves similarly.

Renal tumors in the male mouse may be related to the production of formaldehyde during methyl chloride metabolism. Generation of formaldehyde has been demonstrated in renal

microsomes of male CD-1 mice (Dekant et al., 1995) that exceeds that of naive (androgen-untreated) female mice, whereas kidney microsomes from the rat did not generate formaldehyde. The P-450 isozyme believed to be responsible, CYP2E1, is present in male mouse kidney and is androgen-dependent; female mice had levels only 20%-25% of those in males (Dekant et al., 1995); in the rat, renal activity of CYP2E1 was very low. The findings of Hu et al. (1990) show that there is a specific cellular localization of CYP2E1 in mouse kidney. Cell-type-specific localization was confirmed by Cummings et al. (1999), who found that CYP2E1 in F-344 kidney was produced by both proximal and distal tubular cells, with the level of certain P-450 isozymes being cell-type-specific. On the other hand, no CYP2E1 activity was detected in human kidney microsomal samples (Amet et al., 1977; de Waziers et al., 1990; Lasker et al., 2000), nor was it detected in freshly isolated proximal tubular cells from human kidney (Cummings et al., 2000). CYP4A11 was detected in human kidney (Cummings et al., 2000), but its ability to metabolize methyl chloride is unknown. The only P-450 enzymes found at significant levels in human renal microsomes are, in addition to CYP4A11, CYP4F2 (Lasker et al., 2000) and CYP3A isoforms (Kharasch et al., 1995). According to the P-450 review by Parkinson (1996), no commonly known environmental chemicals appear to be metabolized by the CYP4A family.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2001

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Methyl Chloride. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date 6/26/2001

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Methyl chloride conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676(phone), (202)566-1749 (Fax), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Methyl chloride
CASRN — 74-87-3

VI.A. Oral RfD References

Not applicable.

VI.B. Inhalation RfC References

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VII. Revision History

Substance Name — Methyl chloride
CASRN — 74-87-3

Date	Section	Description
07/17/2001	I.B., II., VI	RfC, carcinogenicity assessment, and RfD discussion first on line

Date	Section	Description
10/28/2003	I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Methyl chloride
CASRN — 74-87-3
Last Revised — 07/17/2001

- 74-87-3
- CHLOROMETHANE
- MONOCHLOROMETHANE