APPENDIX A

External Peer Review—Summary of Comments and Disposition

Instructions to Peer Reviewers for Reviewing IRIS Summaries and Supporting Documentation for Methyl Chloride (CAS No.74-87-3)

The U.S. EPA is conducting a peer review of the scientific basis supporting the health hazard and dose response assessments for the subject chemical that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). Materials to be reviewed include the summary information that will appear on IRIS (the inhalation reference concentration [RfC], oral reference dose [RfD], and cancer assessment) and the supporting document, the Toxicological Review, which will also be made available to the public.

A listing of Agency Guidelines and Methodologies that were used in the development of these hazard and dose-response assessments included the following: The Risk Assessment Guidelines (1986), the (new) Proposed Guidelines for Carcinogen Risk Assessment (1996), Guidelines for Developmental Toxicity Risk Assessment, (proposed) Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity, (proposed) Guidelines for Neurotoxicity Risk Assessment, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, Recommendations for and Documentation of Biological Values for Use in Risk Assessment and Use of the Benchmark Dose Approach in Health Risk Assessment. Copies of these documents (and/or their relevant sections) will be made to the reviewer upon request.

Peer review is meant to ensure that science is used credibly and appropriately in derivation of these dose-response assessments. You have been chosen as an expert on the chemical under consideration, on a scientific discipline related to at least one of the assessments, or in the field of risk assessment. At least three peer reviewers per chemical are being chosen to review the scientific basis of these draft dose-response assessments before they are forwarded on to the EPA's Consensus Process for final approval and adoption by the EPA. These hazard and dose-response assessments will then appear on IRIS and become available as Agency consensus health effect information.

The primary function of the peer reviewer should be to judge whether the choice, use, and interpretation of data employed in the derivation of the assessments is appropriate and scientifically sound. This review is not of the recommended Agency risk assessment guidelines or methodologies used to derive cancer or RfD/C assessments as these have been reviewed by external scientific peers, the public, and EPA Science Advisory Boards. The reviewer's comments on the application of these guidelines/methodologies within the individual assessments is, however, welcomed and encouraged. For example, the reviewer may ascertain whether or not there is data sufficient to support use of other than default assumptions for areas such as sensitive subpopulations or linear cancer extrapolation. The reviewer may also have opinions on other areas of uncertainty such as subchronic to chronic duration (when only a subchronic study is available) or an incomplete data base but should focus on the specific area of uncertainty rather than on the magnitude of the overall estimate.

Below are two groups of questions regarding this review. The first is a set of general questions that are meant to guide you through your review. It is not imperative that you specifically answer each question of this group. The second group of questions, however, are specific for the chemical assessments and deal with areas of scientific controversy or uncertainty in which the Agency may have to make a scientific judgment. Your input to this set of questions is considered vital to the review process.

Questions for IRIS Peer Reviewers - General

1. Are you aware of any other data/studies that are relevant (i.e., useful for the hazard identification or dose-response assessment) for the assessment of the adverse health effects, both cancer and noncancer, of this chemical?

2. For the RfD and RfC, has the most appropriate critical effect been chosen (i.e., that adverse effect appearing first in a dose-response continuum)? For the cancer assessment, are the tumors observed biologically significant? relevant to human health? Points relevant to this determination include whether or not the choice follows from the dose-response assessment, whether the effect is considered adverse, and if the effect (including tumors observed in the cancer assessment) and the species in which it is observed is a valid model for humans.

3. Have the noncancer and cancer assessments been based on the most appropriate studies? These studies should present the critical effect/cancer (tumors or appropriate precursor) in the clearest dose-response relationship. If not, what other study (or studies) should be chosen and why?

4. Studies included in the RfD and RfC under the heading "Supporting/Additional studies" are meant to lend scientific justification for the designation of critical effect by including any relevant pathogenesis in humans, any applicable mechanistic information, any evidence corroborative of the critical effect, or to establish the comprehensiveness of the data base with respect to various endpoints (such as reproductive/developmental toxicity studies). Should other studies be included under the "Supporting/Additional" category? Should some studies be removed?

5. For the noncancer assessments, are there other data that should be considered in developing the uncertainty factors or the modifying factor? Do you consider that the data support use of different (default) values than those proposed?

6. Do the Confidence statements and weight-of-evidence statements present a clear rationale and accurately reflect the utility of the studies chosen, the relevancy of the effects (cancer and noncancer) to humans, and the comprehensiveness of the data base? Do these statements make sufficiently apparent all the underlying assumptions and limitations of these assessments? If not, what needs to be added?

Questions for IRIS Peer Reviewers - Chemical Specific

1. Do the results (cerebellar degeneration) of Landry et al.(1983, 1985) and particularly those of Morgan et al.(1982) support the statement in section I.B.5 of the summary that the female C57BL/6 mouse may be particularly sensitive to the neurotoxic effects of methyl chloride?

2. Histopathology of the spinal nerves apparently was not part of the CIIT (1981) protocol at the 6- and 12-month time points. Are these lack of data, the lack of a dose-response, and the exposure error (low dose group exposed to 1,000 ppm for 3 days) sufficient reasons for giving a low confidence rating to this study?

3 .Does the absence of axonal degeneration in the C57BL/6 mouse in the Landry et al. continuous study cause one to doubt the significance of the evidence of axonal degeneration in the CIIT intermittent exposure study with the $B6C3F_1$?

4. Is the lack of a developmental neurotoxicity study in the mouse sufficient justification for for the inclusion of an uncertainty factor of 3?

5. Because the mode of action may operate through modulation of prostaglandins and leukotrienes, should an additional uncertainty factor be included for a lack of immunological studies?

6. Are you aware of any links between leukotriene and prostaglandin synthesis and GSH-theta metabolism? If so, please describe.

7. Given the amount of text data reported for the CIIT (1981) study (pages 42-48), which data could better be presented in tabular form with minimal text discussion?

RECOMMENDATIONS

Based on your reading and analysis of the information provided, please identify your overall recommendation for the IRIS materials you have reviewed as

- acceptable as is
- acceptable with minor revision (as indicated)
- acceptable with major revision (as outlined)
- not acceptable

Substance code
Methyl Chloride; CASRN 74-87-3

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Methyl Chloride

File First On-Line _/_/_

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	under review	
Carcinogenicity Assessment (II.)	under review	

_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

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.

_1.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 ORAL RfD

Source Document--_____

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_____.

Other EPA Documentation --_____

Agency Consensus Date --_/_/_

_I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

_I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Methyl Chloride
CASRN -- 74-87-3

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/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.

_1.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses	UF	MF	RfC
Axonal swelling in areas of spinal cord	NOAEL: none	1,000	1	2E-2 mg/cu.m
Mouse 2-Year Inhalation Study CIIT (1981)	LOAEL: 50 ppm (103.2 mg/cu.m) LOAEL(ADJ):18.4 mg/cu.m LOAEL(HEC): 18.4 mg/cu.m			

*Conversion Factors and Assumptions: MW = 50.49. Assuming 25°C and 760 mmHg: LOAEL (mg/cu.m) = 50 ppm × 50.49/24.45 = 103.2 mg/cu.m; LOAEL(ADJ) =103.2 mg/cu.m × 6 hours/24 hours × 5 days/7 days =18.4 mg/cu.m. Methyl chloride is a Category 2 gas (U.S. EPA, 1994) for which periodicity was assumed to be attained for systemic effects and the blood:gas partition coefficients for humans (Nolan et al., 1985) and for the rat (Gargas et al., 1989) yield an approximate 1:1 ratio. Thus, a regional gas dose ratio (RGDR) of 1.0 was applied to calculate a human equivalent concentration (HEC) for the LOAEL of 18.4 mg/cu.m. There is no NOAEL.

Note: ADJ = duration-adjusted concentration

_I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

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.

The 2-year study for the CIIT (1981) is the only long-term repeated inhalation study currently available. F-344 rats and $B6C3F_1$ mice were exposed 6 hr/day, 5 days/wk, for up to 24 months to concentrations of 0, 50, 225 or 1,000 ppm of 99.97% pure methyl chloride (120/sex/species/concentration). The duration-adjusted levels are 0, 18.4, 83, or 368.8 mg/m^3, respectively. There was inadvertent exposure of the 50 ppm mice to 1,000 ppm for three successive days early in the study which may have confounded the pathology results for the spinal cord. The LOAEL in mice for chronic inhalation exposure to methyl chloride was 50 ppm, based principally on the occurrence of axonal swelling and degeneration (minimal to mild severity) in the cauda

equina and dorsal root of the spinal cord. Because of the well-known adverse CNS effects of methyl chloride both in humans and laboratory animals as well as the occurrence of spinal cord lesions in other mammalian species (see below), it is prudent to classify the spinal cord lesions in mice as a treatment-related critical effect.

The incidence of axonal swelling and degeneration at the 18-month interim necropsy was elevated in the dorsal root and cauda equina without a clear dose-response trend. The incidence at the dorsal root was elevated (particularly females) over controls (7/10 females at both 50 and 225 ppm *vs* 0/10 female controls). There were no lesions in males or females at 1,000 ppm. Results were only presented for the 1,000 ppm females at 22 months; similar effects were reported in this group although apparently only involving other areas (cervical ventral and thoracic) of the spinal cord. At terminal sacrifice (24 months), the incidence of spinal cord lesions across exposure groups was similar, suggesting that methyl chloride may have accelerated an aging process at earlier time points. The brain and spinal cord were not examined at shorter time points (6- and 12-months).

Cortical microcysts in the kidneys were observed at 24 months in mice exposed to 50 ppm only. The toxicological significance, exposure-relatedness, and relevance to human exposure for this lesion were considered by the investigators to likely represent background lesions that occur principally in aged mice.

Adverse effects were also observed in liver, brain, kidney, and spleen of mice at 1,000 ppm. Cerebellar lesions and neurobehavioral effects, as well as hepatocellular degeneration and necrosis and significantly elevated levels of serum alanine aminotransferase, kidney lesions (tubuloepithelial hyperplasia and karyomegaly), seminiferous tubule atrophy and degeneration, and splenic lesions (atrophy and lymphoid depletion) were noted in mice at this concentration level. These effects were not observed at levels below 1,000 ppm. although serum alanine aminotransferase was elevated in both males and females at 6 and 12 months

The only adverse effect attributed to exposure in the rat was seminiferous tubule degeneration and atrophy. This was first noted at the six-month interim sacrifice at 1,000 ppm and also at 12 months, in the absence of any age-related hyperplasia or adenoma formation. The latter became evident at both 18 and 24-month necropsies, in which all groups, including controls, showed evidence of age-related seminiferous tubule hyperplasia and compression, both bilateral and unilateral. These findings are consistent with a LOAEL and NOAEL of 1,000 and 225 ppm, respectively. These effects, 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., 1985 a,b) at levels of 500 ppm and greater. Thus, the results of these shorter- term studies lend support to the indicated NOAEL and LOAEL

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 3 male Beagle dogs (ages 7–8 mo) and 3 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. Neurological examinations were performed on all dogs on post-exposure day 4, and again on post-exposure day 26 on the 500 ppm dogs. These consisted of observing each dog's gait, posture, demeanor and general appearance, and evaluating cranial nerves, spinal reflexes, pain sensation, and attitudinal and postural reactions. Gross necropsy and pathology examinations were conducted on all dogs and cats, as was microscopic histopathology on most major organs and tissues of each. Limited statistical analysis was performed with the level of significance set at $p < 0.05$ (two-sided).During the first 24 hr of treatment, no differences in demeanor or condition were observed between control and methyl chloride-exposed dogs. 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, except that one dog displayed possible hind limb stiffness that was not apparent by the next day, and which likely resulted from confinement. All 500 ppm dogs appeared weak, but alert and responsive, 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 post-exposure day 10, which continued until termination on day 27. The most severely affected dog was able to get up and take several steps by post-exposure day 11, and by the study's end was able to frequently walk about and appeared alert and in good spirits, despite continued limb tremor and intermittent ataxia. 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 two week recovery period, 200 and 500 ppm cats were comparable to controls.

Neurological evaluations revealed no abnormalities in control or 200 ppm dogs, whereas each of the three 500 ppm dogs exhibited various clinical deficiencies. The most severely affected dog was alert and good-natured during the first examination (4 days post-exposure), but was unable to walk, lay in lateral recumbency, and exhibited posterior paresis, extensor tonus of all four limbs, and when excited or attempting to move, opisthotonus and intention tremors. By 26 days post-exposure, spinal reflexes and postural reactions were normal, balance was maintained normally, and walking with intermittent ataxia was observed. Thus, most neurological abnormalities had partially or fully resolved The other two dogs were similarly but less severely affected on post-exposure day 4, and appeared to be fully or nearly completely recovered on post-exposure day 26. No treatment-related alterations in gross or histopathology were observed in any 200 ppm dog. 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. They 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. Brain and/or spinal cord lesions were also found in control (1/3), 200 ppm (1/3) and 500 (3/3) ppm cats. Several characteristics of these lesions (perivascular aggregates of mononuclear cells, location in the cerebrum and cerebellum as well as the midbrain, presence in 1 of 3 cats in the control and 200 ppm groups) led the authors to speculate that they were likely the result of either a post-vaccinal reaction or 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. 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)

_I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = 1,000. A factor of 10 was used to protect sensitive human subpopulations (intrahuman variability), a factor of 3 ($10^{1/2}$) to account for interspecies variability in extrapolating from animals to humans, a factor of 10 for extrapolating from a LOAEL and a 3 ($10^{1/2}$) for an incomplete database. The data base lacks a developmental neurotoxicity study. Because two factors of 3 coalesce to a 10, a total UF of 1,000 was applied.

MF -- None

_I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

In addition to cerebellar lesions noted in the CIIT (1981) study, other shorter-term studies have reported similar findings. Continuous exposure of female C57BL/6 mice to 100 ppm and higher (22 hours/day for 11 days) caused degenerative changes in granule cells of the cerebellum (Landry et al., 1983, 1985); higher

exposure levels also led to a moribund condition and death. No histopathological evidence of damage in the spinal cord area or to peripheral nerves was reported at any exposure level. Decrements in neurofunctional testing was observed at 150 ppm. Similar effects were seen upon intermittent exposure at higher levels; degenerative lesions in the cerebellum were first seen in the 400 to 1,000 ppm groups, becoming more severe at 1,500 to 2,000 ppm.. Cerebellar degeneration was not seen in C3H mice or in $B6C3F_1$ males, was minimal in $B6C3F_1$ females at 2,000 ppm, but was moderate to severe in C57BL/6 females at 1,000 -2,000 ppm. exposed for 6 hours/day for 12 consecutive days (Morgan et al., 1982).

In a 2-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). The study authors identified a 2-generation reproductive LOAEL based on statistically-significant reduced male fertility at 475 ppm (fertility recovered 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 other than a reduced percentage of male offspring in the 475 ppm group compared to controls and the 150 ppm group.475 ppm had no effect on sex ratio in the F_0 generation.

_I.B.5. CONFIDENCE IN THE INHALATION RfC

Study –Low
Data Base –Low
RfC –Low

The overall confidence in the RfC assessment is low; the confidence in the principal study is low because (1) not all mouse tissues were examined at all time points thus compromising interpretation of the neurotoxic effects, (2) the study was not published in the peer-review literature, (3) the exposure error in the 50 ppm animals may have affected histopathological findings at later time points, and (4) a NOAEL was not identified. The overall confidence in the database is low because there are no other supporting long-term inhalation studies, particularly the C57BL/6 strain of mice which may be particularly sensitive to the effects of methyl chloride. A reproduction/teratology study in the rat through the F_1 generation has been performed and provides some support for an effect on the male reproductive system. However, there is no developmental neurotoxicity study that examined F_1 tissue for histopathological evidence of spinal cord or brain lesions. There are a few studies in humans that provide only anecdotal support for reproductive or developmental effects, but these involved poorly characterized methyl chloride exposures, and probable exposures to other chemicals.

_I.B.6. EPA DOCUMENTATION AND REVIEW OF INHALATION RfC

Source Document--_____

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_____.

Other EPA Documentation --_____

Agency Consensus Date --_/_/_

I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

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

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 µg/cu.m 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

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 “not likely” to cause cancer in humans. This conclusion rests on the lack of evidence for carcinogenicity from limited human studies, the occurrence of tumors in only one organ of one sex of a single rodent species at the highest tested concentration, and mechanistic considerations that suggest the most probable mode of action responsible for the induction of male mouse kidney tumors may not be relevant to humans under normal exposure conditions.

_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). Very weak suggestive evidence for an effect of acute, severe exposure to methyl chloride on mortality from all cancers or from lung cancer was seen in a small cohort accidentally exposed to methyl chloride from a leaking refrigeration unit (Rafnsson and Gudmundsson, 1997). 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

Limited. In animals, the only evidence of carcinogenicity comes from a single 2-year bioassay, which found a statistically significant increased incidence of renal tumors only in male $B6C3F_1$ mice at the high concentration (1,000 ppm), although two renal adenomas occurring in 225 ppm males were also considered by the investigators to be related to methyl chloride exposure (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. This effect needs to be corroborated in a peer-reviewed study, and preferably in more than one species, before its relevance to cancer assessment can be properly determined.

_II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

There is some evidence that methyl chloride may be 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). 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 SHE cells (Hatch et al., 1983). 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). However, rather than to direct genotoxicity, this dominant lethality appears attributable to cytotoxic effects on sperm in the testes, 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, there is inadequate evidence of a genotoxic effect from methyl chloride that would result in increased carcinogenic potential.

_II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

_II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

_II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

_II.D.1. EPA DOCUMENTATION

Source Document -_____

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 _____.

_II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Not available.

_II.D. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA GOV (internet address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name -- Methyl Chloride
CASRN --74-87-3

_VI.A. ORAL RfD REFERENCES

None.

_VI.B. INHALATION RfC REFERENCES

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_VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Substance Name: Methyl Chloride
CASRN --74-87-3
Last Revised -- __/__/__

_VIII. SYNONYMS

Substance Name -- Methyl Chloride
CASRN --74-87-3
Last Revised -- _/_/_

74-87-3
CHLOROMETHANE
MONOCHLOROMETHANE