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Provisional Peer-Reviewed Toxicity Values for

Iodomethane (Methyl Iodide)
(CASRN 74-88-4)

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COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR IODOMETHANE (CASRN 74-88-4)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No RfD, RfC, or carcinogenicity assessments for iodomethane are available on IRIS (U.S. EPA, 1995), and IRIS does not currently list a weight-of-evidence classification for carcinogenicity. No information on iodomethane is available in the HEAST (U.S. EPA, 1997) or in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2006). A cancer evaluation document (U.S. EPA, 1988) was the only U.S. EPA review located. In that document, the U.S. EPA (1988) considered the existing data to be inadequate to calculate a slope factor. Using the criteria outlined in the 1986 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986), U.S. EPA (1988) assigned iodomethane to weight-of evidence Group C, "Possible human carcinogen," on the basis of no evidence in humans and limited evidence in animals (production of sarcomas in BD rats administered iodomethane subcutaneously and equivocal evidence for production of lung tumors in Strain A mice administered iodomethane by intraperitoneal injection). No other EPA documents relevant to human toxicity or cancer assessments for iodomethane have been identified in the CARA list (U.S. EPA 1991, 1994).

Other sources of information were consulted for dose-response data on iodomethane. IARC (1977, 1986, and 1999) has reviewed the toxicity and carcinogenicity of iodomethane several times. An early evaluation by the IARC (1977) classified iodomethane as carcinogenic in rats. Two subsequent evaluations (IARC, 1986, 1999) determined that there is limited evidence for the carcinogenicity of iodomethane in experimental animals and that the compound is not classifiable as to its carcinogenicity to humans (i.e., weight-of-evidence Group 3). ACGIH (2001) has also reviewed iodomethane carcinogenicity and classified iodomethane as category A2, *suspected human carcinogen*, from 1981 to 1995; however, the A2 classification was withdrawn in 1996 (ACGIH, 2001). Both the NTP Health and Safety (NTP, 2002a) and the Testing Information and Study Results (NTP, 2002b) databases for iodomethane were searched. Iodomethane was delisted as a carcinogen in the NTP 5th Annual Report on Carcinogens on the basis of the 1986 IARC reevaluation (NTP, 2001). NTP (2002a,b) has not tested iodomethane for carcinogenicity. The State of California determined under Proposition 65 that methyl iodide is a carcinogen (CalEPA, 2009), based on the 1977 IARC evaluation. Neither a Toxicological Profile (ATSDR, 2008) nor an Environmental Health Criteria Monograph (WHO, 2009) has been published for iodomethane.

Literature searches were conducted for the interval from January 1965 to November 2001 to identify relevant studies. The following databases were examined in the search: TOXLINE, MEDLINE, TSCATS, GENETOX, HSDB, CANCERLIT, CCRIS, EMIC/EMICBACK, DART/ETICBACK, CHEMID, BIOSIS, NTIS, and RTECS. A subsequent check of the published literature was conducted for the interval from June 2002 to July 2009.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No relevant studies on the toxicity or carcinogenicity of iodomethane in humans following oral or inhalation exposure have been identified.

Animal Studies

Oral Exposure

Subchronic Studies—No chronic oral toxicity or cancer bioassays are available for iodomethane. Buckell, (1950) determined an LD_{50} of 0.15 to 0.22 mg/kg, for male white mice dosed with iodomethane dissolved in arachis oil. In the only available longer-term oral exposure study, Buckell (1950) gave iodomethane (0; 100; 200; 300; and 500 mg/kg-dose; source and purity not stated) orally to male mice (six mice per dose) for a total of 43 doses over a 71 day period. The duration adjusted doses were 0; 61; 121; 182; and 303 mg/kg-day respectively. The body weight of mice dosed with 303 mg/kg-day was "considerably less than in the controls" but there was no quantification or significance testing reported. The NOAEL for this effect was 121 mg/kg-day. The test animals were sacrificed at the termination of the study without a comprehensive histological examination. No additional details of the study were provided in U.S. EPA (1988). This study does not support assessments of oral toxicity or carcinogenicity because of its short duration and absence of histopathological examination. No subchronic or chronic oral exposure studies of iodomethane in experimental animals, having the potential to support toxicity value derivation, were identified.

Chronic Studies—No oral studies of chronic exposure have been identified in the published literature.

Inhalation Exposure

Subchronic Studies—Short-term (approximately 1 month) inhalation exposure studies have been performed in mice (i.e., Buckell, 1950) and rats (i.e., Blank et al., 1983). In a whole-body inhalation study with male white mice, Buckell (1950) reported renal changes (degeneration of tubular epithelium and numerous eosinophilous casts) in mice receiving 1 g/m^3 of iodomethane (source and purity not stated) in 20 exposures over 30 days. The NOAEL for renal effects was 500 mg/m^3. The total exposure periods ranged from 11 to 43 hours. Incomplete reporting precludes quantification of the exposures. Blank et al. (1983) reported a significant ($p < 0.01$) reduction in body weight gain at the mid-dose and high-dose (421 and 810 mg/m^3 respectively purity = 86.4%). The low-dose (141 mg/m^3) was a NOAEL for all the observed effects. These studies were not designed to evaluate chronic inhalation toxicity, and no neoplastic alterations were observed. Subchronic data are available from a 14-week inhalation study conducted in Sprague-Dawley rats by the Monsanto Company. This study is described in a published abstract (i.e., Blank et al., 1984) and in an unpublished research report (i.e.,

Blank et al., 1985). The subchronic study did not produce any evidence of neoplastic lesions and was of much shorter duration than the 50 to 100 week cancer bioassays.

Chronic Studies—No inhalation studies of chronic exposure have been identified in the published literature.

Other Routes of Administration

Two studies have examined the tumorigenicity of iodomethane administered by nonstandard routes. Druckrey et al. (1970) gave BD rats (8−16/group; sex unspecified) subcutaneous injections of iodomethane in vegetable oil. Groups of test animals received weekly doses of 10 or 20 mg/kg for 1 year, or a single dose of 50 mg/kg, and were observed for life. A control group (number unspecified) received the vehicle alone. Local subcutaneous sarcomas occurred 500−700 days after the first injection in 8/16 (50%) rats injected with 10 mg/kg, in 6/8 (75%) rats injected with 20 mg/kg, and in 4/14 (29%) rats injected with the single 50 mg/kg dose, as reported in U.S. EPA (1988). No tumors were reported in the vehicle control group. The results of this study have been reported differently in other publications. IARC (1977) reported incidences of 9/16 and 6/8 for the 10- and 20-mg/kg-day groups, respectively. IARC (1986) reported incidences of 9/12 and 6/6 for the 10- and 20-mg/kg-day groups, respectively, after adjustment of the incidence data for premature death of some test animals from pneumonia. No quantitative assessment of iodomethane carcinogenicity is possible because the animals were dosed by subcutaneous injection—which is not comparable with either oral or inhalation dosing.

Poirier et al. (1975) administered iodomethane dissolved in tricaprylin to male and female Strain A mice (10/sex/dose) three times weekly by intraperitoneal injection. The dosing schedule resulted in total doses of 8.5, 21.3, or 44.0 mg/kg in three treated groups plus one untreated group and a vehicle control. Surviving mice were sacrificed 24 weeks after the first injection. The incidence of lung tumors (adenomas) in surviving animals of both sexes (combined) was 4/19 (21%), 6/20 (30%), and 5/11 (45%) in the three groups, respectively. The incidence of lung tumors was 34/154 (22%) in vehicle control animals and 6/29 (21%) in untreated animals. There was a marginally statistically significant ($p = 0.048$) trend for increased lung tumor incidence in treated mice compared with vehicle—but not untreated—controls. Pairwise comparisons showed no significant ($p < 0.05$) differences between treated and control mice. This outcome is considered equivocal evidence of carcinogenicity because the observed results did not meet all of the predetermined criteria for a positive response in Strain A mice, which include (1) a statistically significant increase in the mean number of lung tumors per animal, (2) a clear dose-response relationship, and (3) the anticipated number of spontaneous tumors in untreated control mice. Consequently, no quantitative assessment of iodomethane carcinogenicity is possible

Other Studies

The mutagenicity of iodomethane has been assessed in multiple test systems in both the presence and absence of exogenous metabolic activation (Bolt and Gansewendt, 1993; IARC, 1999). Results of these studies have been mixed. Positive or weakly positive results have been obtained in bacterial reverse mutation assays conducted without exogenous metabolic activation in *Salmonella typhimurium* test strains TA100 (McCann et al., 1975; Simmon et al., 1977) and TA1535 (Rosenkranz and Poirier, 1979); and in *Escherichia coli* strains WP2 *uvr* (Hemminki et al., 1980) and WP2 (Takahashi and Kawazoe, 1987). The *E. coli* spot test was also positive without activation (Rosenkranz and Poirier, 1979). Negative results

for reverse mutation assays were obtained with and without metabolic activation in *S. typhimurium* strains TA98, TA100, TA1535, TA1536, TA1537 (Simmon, 1979a), and TA1538 (Rosenkranz and Poirier, 1979; Simmon, 1979a). Among lower eukaryotes, positive results were obtained for mitotic conversion in *Saccharomyces cerevisiae* without metabolic activation (Simmon, 1979b), while negative results were found for mutation in *Aspergillus nidulans* (Moura Duarte, 1972). Iodomethane did not induce chromosomal aberrations in the plant *Vicia faba* (Rieger et al., 1988). In mammalian studies, positive or weakly positive results were obtained for mutagenic potential in Chinese hamster ovary cells at the *hprt* locus (Amacher and Zelljadt, 1984); in mouse lymphoma L5178Y cells at the *tk* locus (Clive et al., 1979; Moore and Clive, 1982; Moore et al., 1985) and the *hprt* locus (Moore and Clive, 1982); and in mouse lymphoma L5178Y cells for ouabain resistance (Amacher and Dunn, 1985). Negative results were obtained for gene mutation in mouse lymphoma L5178Y cells with exogenous activation (Clive et al.1979). Cell transformation assays were positive in Syrian hamster embryo cells (Pienta et al., 1977) but negative in C3H 10T1/2 mouse cells (Oshiro et al., 1981) without exogenous metabolic activation. Assays for covalent binding to DNA in F344 rats following oral or inhalation exposure in vivo were positive (Gansewendt et al., 1991).

Additional information, not summarized in this document, is available from the U.S. EPA, Office of Pesticide Programs (OPP). Because iodomethane is a currently registered pesticide, many potentially useful studies have been submitted to the OPP as confidential business information (CBI). This information is unpublished and is unavailable for use in this assessment. The OPP maintains its own program for developing health-based values (i.e. RfDs and RfCs) for pesticides. Consequently, no values will be developed here.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR IODOMETHANE

A provisional oral reference dose (p-RfD) are not derived for iodomethane because iodomethane is a currently registered pesticide. Additional information can be obtained by contacting the U.S. EPA, Office of Pesticide Programs.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfC VALUES FOR IODOMETHANE

A provisional inhalation reference concentration (p-RfC) are not derived for iodomethane because iodomethane is a currently registered pesticide. Additional information can be obtained by contacting the U.S. EPA, Office of Pesticide Programs.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR IODOMETHANE

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the lack of available evidence suggests that there is "inadequate information to assess the carcinogenic potential" of iodomethane.

Quantitative Estimates of Carcinogenic Risk

Oral Exposure

A provisional oral slope factor (p-OSF) are not derived for iodomethane because iodomethane is a currently registered pesticide. Further, existing tumor incidence data are not suitable for derivation of an oral slope factor because they were obtained from studies using parenteral routes (e.g. i.p injection) of administration. The parenteral route bypasses normal metabolism of the test agent by the liver and is not representative of oral exposure. Additional information can be obtained by contacting the U.S. EPA, Office of Pesticide Programs.

Inhalation Exposure

A provisional inhalation unit risk (p-IUR) are not be derived for iodomethane because iodomethane is a currently registered pesticide. Additional information can be obtained by contacting the U.S. EPA, Office of Pesticide Programs.

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