Dichloromethane; CASRN 75-09-2

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 Dichloromethane

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	Yes	11/18/2011
Inhalation RfC (I.B.)	Yes	11/18/2011
Carcinogenicity Assessment (II.)	Yes	11/18/2011

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Dichloromethane
CASRN — 75-09-2
Section I.A. Last Revised — 11/18/2011

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is

essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

In the previous IRIS assessment (posted on the website in 1987), the RfD for dichloromethane was 6×10^{-2} mg/kg-day based on liver toxicity in a 2-year rat drinking water bioassay sponsored by the National Coffee Association and conducted by Hazleton Laboratories in 1982 (published subsequently in Serota et al., 1986a).

I.A.1. Chronic Oral RfD Summary

Critical Effect	Point of Departure*	UF	Chronic RfD
Hepatic effects (hepatic vacuolation, liver foci) **2-Year rat drinking water bioassay** **Serota et al., 1986a**	1st percentile human equivalent dose: 0.19 mg/kg-day	30	6×10^{-3} mg/kg-day

*Conversion Factors and Assumptions – see Method of Analysis below.

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

Serota et al. (1986a) exposed F344 rats (85/sex/dose, 135 controls) to dichloromethane in drinking water. Mean doses were 0, 6, 52, 125, and 235 mg/kg-day in males and 0, 6, 58, 136, and 263 mg/kg-day in females. Treatment with dichloromethane did not induce adverse clinical signs or affect survival in the rats. Body weights of rats in the 125 and 250 mg/kg-day groups were generally lower than in controls throughout the study. Water consumption was lower throughout the study in both sexes of rats in the 125 and 250 mg/kg-day groups relative to controls; food consumption was also lower in these groups during the first 13 weeks of treatment. Mean hematocrit, hemoglobin, and red blood cell count were increased in both sexes at dichloromethane levels of 50, 125, and 250 mg/kg-day for 52 and 78 weeks. Clinical chemistry results showed decreases in alkaline phosphatase, creatinine, blood urea nitrogen, total protein, and cholesterol in both sexes at 250 mg/kg-day, and most of these changes were statistically significant at one or both of the intervals evaluated. No significant deviations in

urinary parameters were observed. Organ weights were not significantly affected by treatment with dichloromethane.

No treatment-related histopathological effects were noted in the tissues examined except for the liver. Examination of liver sections showed a dose-related positive trend in the incidences of foci/areas of cellular alteration in treated F344 rats. Comparisons of incidences with control incidences indicated statistically significant elevations at all dose levels except 5 mg/kg-day. These liver changes were first noted after treatment for 78 weeks and progressed until week 104. The authors indicate that 5 mg/kg-day was a no-observed-adverse-effect level (NOAEL) and 50 mg/kg-day was a lowest-observed-adverse-effect level (LOAEL) for liver changes (foci/areas of cellular alteration) in male and female F344 rats exposed to dichloromethane in drinking water for 2 years.

Method of Analysis. A physiologically based pharmacokinetic (PBPK) model for the rat (Andersen et al., 1991, modified by EPA) was used to estimate rat internal doses from the Serota et al. (1986a) study. The dose metric used to conduct the modeling was mg dichloromethane metabolized via the CYP pathway/liter of liver tissue/day. Liver incidence data (foci/areas of cellular alteration) for the male rat (Serota et al., 1986a) were fit to the available dichotomous models in BMDS version 2.0 (using internal dose as the dose measure) to obtain the rat internal $BMDL_{10}$. Because the dose metric is a rate of metabolism and the clearance of these metabolites may be slower per volume tissue in the human compared with the rat, this rodent internal dose metric was adjusted by dividing by a pharmacokinetic allometric scaling factor of body weight $(BW)^{0.75}$ (operationalized as $[BW_{human}/BW_{rat}]^{0.25} \approx 4.09$) to obtain a human equivalent internal $BMDL_{10}$. The human equivalent internal $BMDL_{10}$ was then converted to the human equivalent dose (HED) using a human PBPK model (adapted from David et al., 2006) that provided a distribution of HEDs. The 1^{st} percentile of the distribution of HEDs, 0.19 mg/kg-day, was used as the point of departure for the RfD. See Section 5.1.4 of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

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

UF = 30

Uncertainty factors, selected based on EPA's *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5), address five areas of uncertainty:

Uncertainty in extrapolating from laboratory animals to humans (UF_A): The use of PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty in extrapolating from the rat liver lesion data but does not account for the possibility that humans

may be more sensitive than rats to dichloromethane due to toxicodynamic differences. An UF of 3 ($10^{0.5}$) to account for this toxicodynamic uncertainty was applied.

Uncertainty about variation from average humans to sensitive humans (UF_H): The probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of dichloromethane in humans but does not account for humans who may be sensitive due to toxicodynamic factors. Thus, an UF of 3 ($10^{0.5}$) was applied to account for possible toxicodynamic differences in sensitive humans.

Uncertainty in extrapolating from LOAELs to NOAELs (UF_L): An UF for extrapolation from a LOAEL to a NOAEL was not applied because BMD modeling was used to determine the point of departure (POD), and this factor was addressed as one of the considerations in selecting the benchmark response (BMR). The BMR was selected based on the assumption that it represents a minimum biologically significant change.

Uncertainty in extrapolating from subchronic to chronic durations (UF_S): The derived RfD is based on results from a chronic-duration drinking water toxicity study such that no UF is necessary.

Uncertainty reflecting database deficiencies (UF_D): The oral database for dichloromethane includes well-conducted chronic drinking water studies in rats (Serota et al., 1986a) and mice (Serota et al., 1986b) and a supporting subchronic study in rats and mice (Kirschman et al., 1986). These studies provided dose-response data for the hepatic effects of dichloromethane. The database also includes one-generation oral reproductive toxicity (General Electric Company, 1976) and developmental toxicity (Narotsky and Kavlock, 1995) studies that found no reproductive or developmental effects at dose levels in the range of doses associated with liver lesions. A two-generation oral exposure study is not available; however, a two-generation inhalation exposure study by Nitschke et al. (1988b) reported no effect on fertility index, litter size, neonatal survival, growth rates, or histopathologic lesions at exposures of ≥100 ppm. This study is limited in its ability to fully evaluate reproductive and developmental toxicity, however, because exposure was not continued throughout the gestation and nursing periods.

No oral exposure studies that evaluated neurobehavioral effects in offspring were identified. This is a relevant endpoint given the neurotoxicity associated with dichloromethane exposure after oral and inhalation exposures, and the observed behavioral changes following inhalation developmental exposure to dichloromethane (Bornschein et al., 1980; Hardin and Manson, 1980). Dichloromethane is capable of crossing the placental barrier and entering fetal circulation (Withey and Karpinski, 1985; Anders and Sunram, 1982), and activity of CYP2E1 in the brain is relatively high compared to the liver of the developing human fetus (Hines, 2007; Johnsrud et al., 2003; Brzezinski et al., 1999). Dichloromethane, as well as the

metabolite carbon monoxide (CO), has been implicated in neurological effects; however, PBPK modeling predicts that CO levels from exposures around the RfD would not be high enough to result in neurodevelopmental toxicity. There are no oral exposure studies that include functional immune assays; however, there is a 4-week inhalation study of potential systemic immunotoxicity that found no effect of dichloromethane exposure at concentrations up to 5,000 ppm on the antibody response to sheep red blood cells (Warbrick et al., 2003). The Warbrick et al. (2003) data suggest that systemic immunosuppression does not result from dichloromethane exposure. Because of concerns regarding the lack of an oral two-generation reproductive study, limitations in the available inhalation two-generation reproductive study, and the adequacy of available data pertaining to possible neurodevelopmental toxicity, an UF_D of 3 was applied.

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

Human data for oral exposures to dichloromethane are limited to case reports involving intentional (i.e., suicidal) or accidental, acute ingestion exposures (Chang et al., 1999; Hughes and Tracey, 1993). No studies of human chronic oral exposures are available.

Hepatic effects (hepatic vacuolation, liver foci) are the primary dose-dependent noncancer effects associated with oral exposure to dichloromethane. The 90-day drinking water toxicity study in F344 rats (Kirschman et al., 1986) reported significant increases in hepatocyte vacuolation and necrosis in animals dosed between 166 and 1,200 mg/kg-day (males) or 200 and 1,469 mg/kg-day (females).

Moser et al. (1995) reported altered neurological functions in female F344 rats. In the 90-day (Kirschman et al., 1986) and 104-week (Serota et al., 1986a,b) drinking water studies, however, no obvious clinical signs of neurological impairment were observed in rats or mice at exposure levels that induced liver effects; these studies did not include standardized neurological testing batteries. Results from the available studies do not provide evidence for effects on reproductive or developmental endpoints. No effects on pup survival, resorptions, or pup weight were found following exposure of pregnant F344 rats to doses as high as 450 mg/kg-day on gestation days (GDs 6–19), a dose that depressed maternal weight gain (Narotsky and Kavlock, 1995), and no effects on reproductive performance endpoints (fertility index, number of pups per litter, pup survival) were found in studies in male and female Charles River CD rats (General Electric Company, 1976) and in male Swiss-Webster mice (Raje et al., 1988). There are no oral exposure studies focusing on neurobehavioral effects or other developmental outcomes.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.A.5. Confidence in the Chronic Oral RfD

Study — High
Database — Medium to High
RfD — High

A confidence level of high, medium, or low is assigned to the study used to derive the RfD, the overall database, and the RfD itself, as described in Section 4.3.9.2 of EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). The overall confidence in the RfD for dichloromethane is high. Confidence in the principal study, Serota et al. (1986a), is high. The 2-year drinking water study in rats is a well-conducted, peer-reviewed study that used four dose groups plus a control. Confidence in the oral database is medium to high. The oral database includes a 2-year drinking water study in rats (Serota et al., 1986a) and mice (Serota et al., 1986b) as well as a supporting subchronic exposure study (Kirschman et al., 1986) that reports similar liver effects to those observed in the chronic oral exposure studies. The toxicity of orally-administered dichloromethane has also been investigated in an oral administration immunotoxicity study (Warbrick et al., 2003), a one-generation oral reproductive toxicity study (General Electric Company, 1976), and an orally dosed developmental toxicity study (Narotsky and Kavlock, 1995). Several studies have also evaluated neurotoxicity associated with oral exposure to dichloromethane. The oral database lacks a two-generation reproductive study and a developmental neurotoxicity study; neurodevelopmental outcomes are relevant endpoints given that dichloromethane is capable of crossing the placental barrier and entering fetal circulation (Withey and Karpinski, 1985; Anders and Sunram, 1982) and has neurotoxic effects.

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

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

Source Document — *Toxicological Review of Dichloromethane* (U.S. EPA, 2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date — 11/18/2011

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 (email address).

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

Substance Name — Dichloromethane
CASRN — 75-09-2
Section I.B. Last Revised — 11/18/2011

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

An RfC for dichloromethane was not previously provided on the IRIS database.

I.B.1. Chronic Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Chronic RfC
Hepatic effects (hepatic vacuolation) **2-Year rat inhalation bioassay** **Nitschke et al. (1988a)**	1st percentile human equivalent concentration: 17.2 mg/m^3	30	0.6 mg/m^3

*Conversion Factors and Assumptions – see Method of Analysis below.

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

Nitschke et al. (1988a) exposed groups of 90 male and 90 female Sprague-Dawley rats to 0, 50, 200, or 500 ppm dichloromethane (>99.5% pure) for 6 hours/day, 5 days/week for 2 years. Interim sacrifices were conducted at 6, 12, 15, and 18 months (five rats/sex/interval). Exposure to dichloromethane at any of the exposure levels did not significantly alter mortality rates, body weights, organ weights, clinical chemistry values, or plasma hormone levels. Blood carboxyhemoglobin (COHb) was elevated in a dose-related manner but not in an exposure duration-related fashion, suggesting lack of accumulation with repeated exposures. Statistically significantly increased incidences of nonneoplastic liver lesions (hepatic lipid vacuolation and multinucleated hepatocytes) occurred only in females in the 500 ppm group. Male rat incidence for hepatocyte vacuolation was elevated at 500 ppm but not to a statistically significant degree. In the group of female rats exposed for only 12 months to 500 ppm, significantly increased incidences of nonneoplastic lesions compared with controls were restricted to liver cytoplasmic vacuolization (16/25 = 64%) and multinucleated hepatocytes (9/25 = 36%) in rats exposed during the first 12 months of the study; rats exposed only during the last 12 months of the study showed no elevated incidences of the liver lesions. Data from a similar two-year bioassay in Sprague-Dawley rats by Burek et al. (1984) provide additional support for the Nitschke et al. (1988a) observations; an increased incidence of hepatic vacuolation, correlated with fatty changes, was seen at exposures between 500 and 3,000 ppm. Because Nitschke et al. (1988a) examined a lower range of exposures than was included in the Burek et al. (1984) study, the former study was selected as the principal study for derivation of a chronic inhalation RfC. Accumulation of lipids in the hepatocyte may lead to the more

serious liver effects observed following dichloromethane exposure, such as hepatic steatosis (fatty liver) reported in dogs (Haun et al., 1971), and rats (Serota et al., 1986a). Given the liver findings for dichloromethane in the database as a whole, the evidence is consistent with hepatic vacuolation as a precursor of toxicity. Accordingly, hepatic vacuolation is considered a toxicologically relevant effect.

Method of Analysis. A PBPK model for the rat (Andersen et al., 1991, modified by EPA) was used to estimate rat internal doses from the Nitschke et al. (1988a) study. The dose metric used to conduct the modeling was mg dichloromethane metabolized via the CYP pathway/liter of liver tissue/day. Incidence data for hepatic effects (hepatic vacuolation) in the rat from Nitschke et al. (1988a) were fit to the available dichotomous models in BMDS version 2.0 (using internal dose as the dose measure) to obtain the rat internal $BMDL_{10}$. Because the dose metric is a rate of metabolism and the clearance of these metabolites may be slower per volume tissue in the human compared with the rat, this rodent internal dose metric was adjusted by dividing by a pharmacokinetic allometric scaling factor of body weight $(BW)^{0.75}$ (operationalized as $[BW_{human}/BW_{rat}]^{0.25} \approx 4.09$) to obtain a human equivalent internal $BMDL_{10}$. The human equivalent internal $BMDL_{10}$ was then converted to the human equivalent concentration (HEC) using a human PBPK model (adapted from David et al., 2006) that provided a distribution of HECs. The 1st percentile of the distribution of HECs, 17.2 mg/m^3, was used as a point of departure for the RfC. See Section 5.2.3 of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

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

UF = 30

Uncertainty factors, selected based on EPA's *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002; Section 4.4.5), address five areas of uncertainty:

Uncertainty in extrapolating from laboratory animals to humans (UF_A): The use of PBPK models to extrapolate internal doses from rats to humans reduces toxicokinetic uncertainty in extrapolating from the rat liver lesion data but does not account for the possibility that humans may be more sensitive than rats to dichloromethane due to toxicodynamic differences. An UF of 3 ($10^{0.5}$) to account for this toxicodynamic uncertainty was applied.

Uncertainty about variation from average humans to sensitive humans (UF_H): The probabilistic human PBPK model used in this assessment incorporates the best available information about variability in toxicokinetic disposition of dichloromethane in humans but does not account for humans who may be sensitive due to toxicodynamic factors. Thus, an UF of 3 ($10^{0.5}$) was applied to account for possible toxicodynamic differences in sensitive humans.

Uncertainty in extrapolating from LOAELs to NOAELs (UF_L): An UF for extrapolation from a LOAEL to a NOAEL was not applied because BMD modeling was used to determine the POD, and this factor was addressed as one of the considerations in selecting the BMR. The BMR was selected based on the assumption that it represents a minimum biologically significant change.

Uncertainty in extrapolating from subchronic to chronic durations (UF_S): The derived RfC is based on results from a chronic-duration inhalation toxicity study such that no UF is necessary.

Uncertainty reflecting database deficiencies (UF_D): An UF of 3 was selected to address the deficiencies in the dichloromethane toxicity database. The inhalation database for dichloromethane includes several well-conducted chronic inhalation studies. In these chronic exposure studies, the liver was identified as the most sensitive noncancer target organ in rats (Nitschke et al., 1988a; NTP, 1986; Burek et al., 1984). The critical effect of hepatocyte vacuolation was corroborated in the principal study (Nitschke et al., 1988a) and in a supporting study (Burek et al., 1984), both of which identified 500 ppm as the lowest inhalation LOAEL for noncancer liver lesions. Gross signs of neurologic impairment were not seen in lifetime rodent inhalation bioassays for dichloromethane at exposure levels up to 4,000 ppm, and no exposure-related effects were observed 65 hours postexposure in an observational battery, a test of hind-limb grip strength, a battery of evoked potentials, or histologic examinations of nervous tissues in F344 rats exposed to dichloromethane concentrations as high as 2,000 ppm (Mattsson et al., 1990).

A two-generation reproductive study in F344 rats reported no effect on fertility index, litter size, neonatal survival, growth rates, or histopathologic lesions at exposures ≥100 ppm dichloromethane (Nitschke et al., 1988b). Since exposure was not continuous throughout the gestation and nursing periods, however, it may not be representative of a typical human exposure and would not completely characterize reproductive and developmental toxicity associated with dichloromethane. Fertility index (measured by number of unexposed females impregnated by exposed males per total number of unexposed females mated) was reduced following inhalation exposure of male mice to 150 and 200 ppm dichloromethane 2 hours/day for 6 weeks (Raje et al., 1988), but the statistical significance of this effect varied considerably depending on the statistical test used in this analysis.

The available developmental studies are all single-dose studies that use relatively high exposure concentrations (1,250 ppm in Schwetz et al. [1975]; 4,500 ppm in Hardin and Manson [1980]; and 4,500 ppm in Bornschein et al. [1980]). In one of the single-dose studies, decreased offspring weight at birth and changed behavioral habituation of the offspring to novel environments were seen following exposure of adult Long-Evans rats to 4,500 ppm for

14 days prior to mating and during gestation (or during gestation alone) (Bornschein et al., 1980; Hardin and Manson, 1980). The results from these single-dose developmental toxicity studies, the placental transfer of dichloromethane (Withey and Karpinski, 1985; Anders and Sunram, 1982), and the relatively high activity of CYP2E1 in the brain compared to the liver of the developing human fetus (Hines, 2007; Johnsrud et al., 2003; Brzezinski et al., 1999), raise concerns regarding possible neurodevelopmental toxicity from gestational exposure to inhaled dichloromethane. Dichloromethane, as well as the metabolite CO, has been implicated in neurological effects; however, at exposures around the RfC, PBPK models predicted that CO levels would not be high enough to result in neurodevelopmental toxicity.

In addition, Aranyi et al. (1986) demonstrated evidence of immunosuppression following a single 100 ppm dichloromethane exposure for 3 hours in CD-1 mice. This exposure is lower than the POD for the liver effects that serve as the critical effect for the RfC. This study used a functional immune assay that is directly relevant to humans (i.e., increased risk of Streptococcal pneumonia-related mortality and decreased clearance of Klebsiella bacteria). A recent study used a similar approach for the evaluation of immunosuppression from acute exposures to trichloroethylene and chloroform (Selgrade and Gilmour, 2010). Although dichloromethane was not included in this study, Selgrade and Gilmour (2010) provide support for the methodological approach used by Aranyi et al. (1986). Increases of some viral and bacterial diseases, particularly bronchitis-related mortality, is also suggested by some of the cohort studies of exposed workers (Radican et al., 2008; Gibbs et al., 1996; Lanes et al., 1993; Gibbs, 1992; Lanes et al., 1990). Systemic immunosuppression was not seen in a 4-week, 5,000-ppm inhalation exposure study measuring the antibody response to sheep red blood cells in Sprague-Dawley rats (Warbrick et al., 2003). These studies suggest a localized, portal-of-entry effect within the lung rather than a systemic immunosuppression. Because the Aranyi et al. (1986) study involved a single acute inhalation exposure, interpretation of the findings from this study in the context of chronic inhalation exposure is unclear.

In consideration of the entire database for dichloromethane, a database UF of 3 was selected. This UF accounts for limitations in the two-generation reproductive toxicity study (i.e., discontinuous exposure throughout the lifecycle) and limitations in the design of the available developmental studies (including a lack of neurodevelopmental endpoints). There is an additional potential concern for immunological effects as suggested by a single acute inhalation study, specifically immunosuppressive effects that may be relevant for infectious diseases spread through inhalation.

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

Several acute-duration controlled exposure studies and cross-sectional occupational studies in humans are available that show neurological effects from dichloromethane exposure. These

effects include an increase in prevalence of neurological symptoms among workers (Cherry et al., 1981) and possible detriments in attention and reaction time in complex tasks among retired workers whose past exposures were in the 100–200 ppm range (Lash et al., 1991). The values of the candidate RfCs based on the data from Cherry et al. (1981) (1.2 mg/m^3) and Lash et al. (1991) (1.8 mg/m^3) are similar to the derived RfC of 0.6 mg/m^3 based on liver lesions in rats. Ott et al. (1983) reported an increase in serum bilirubin among exposed workers, but there was no association seen with respect to the other hepatic enzymes examined (serum γ-glutamyl transferase, serum aspartate aminotransferase, serum alanine aminotransferase), and no evidence of hepatic effects was seen in a later study of the same cohort (Soden, 1993). These epidemiologic studies are quite limited, however, in their ability to detect subclinical changes in liver function.

The database of experimental animal dichloromethane inhalation studies includes numerous 90-day and 2-year studies, with data on hepatic, pulmonary, and neurological effects, and reproductive and developmental studies. Hepatic effects (hepatic vacuolation and necrosis, hemosiderosis, hepatocyte degeneration) were seen in mice (Mennear et al., 1988; NTP, 1986) and rats (Mennear et al., 1988; Nitschke et al., 1988a; NTP, 1986; Burek et al., 1984) but not in Syrian golden hamsters (Burek et al., 1984).

Reproductive performance (e.g., as assessed by number of litters, resorption rate, fetal survival, and growth) was not affected in two generations of F344 rats exposed to up to 1,500 ppm for 14 or 17 weeks before mating of the F0 and F1 generations, respectively (Nitschke et al., 1988a), or in a study of Swiss-Webster mice or Sprague-Dawley rats exposed to 1,250 ppm on GDs 6–15 (Schwetz et al., 1975). A decrease in fertility index was seen in the 150 and 200 ppm groups in a study of male Swiss-Webster mice exposed via inhalation for 6 weeks prior to mating (Raje et al., 1988), but the statistical significance of this effect varied considerably depending on the statistical test used in this analysis. Developmental effects (decreased offspring weight at birth and changed behavioral habituation of the offspring to novel environments) were seen in Long-Evans rats following exposure to 4,500 ppm for 14 days prior to mating and during gestation (or during gestation alone) (Bornschein et al., 1980; Hardin and Manson, 1980); this was the only dose used in these studies. Schwetz et al. (1975) observed increase in delayed ossification of the sternebrae in Swiss-Webster mice or Sprague-Dawley rats following exposure to 1,250 ppm on GD 6.

Neurological impairment was not seen in lifetime rodent bioassays involving exposure to airborne dichloromethane concentrations of ≤2,000 ppm in F344 rats (Mennear et al., 1988; NTP, 1986), ≤3,500 ppm in Sprague-Dawley rats (Nitschke et al., 1988a; Burek et al., 1984), or ≤4,000 ppm in $B6C3F_1$ mice (Mennear et al., 1988; NTP, 1986). The only subchronic neurotoxicity study found no effects in an observational battery, a test of hind-limb grip strength, a battery of evoked potentials, or brain, spinal cord, or peripheral nerve histology in

F344 rats exposed to concentrations up to 2,000 ppm for 13 weeks, with the tests performed beginning 65 hours after the last exposure (Mattsson et al., 1990).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

I.B.5. Confidence in the Chronic Inhalation RfC

Study — High
Database — Medium to high
RfD — Medium to high

A confidence level of high, medium, or low is assigned to the study used to derive the RfD, the overall database, and the RfD itself, as described in Section 4.3.9.2 of EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). The overall confidence in the RfC for dichloromethane is medium to high. Confidence in the principal study, Nitschke et al. (1988a), is high. The 2-year inhalation study in mice is a well-conducted, peer-reviewed study that used three concentration groups plus a control. Confidence in the inhalation database is medium to high. The inhalation database includes several well-conducted chronic inhalation studies that consistently identified the liver as the most sensitive noncancer target organ in rats (Nitschke et al., 1988a; NTP, 1986; Burek et al., 1984). A two-generation reproductive toxicity study (Nitschke et al., 1988b), developmental studies at relatively high exposures (≥1,250 ppm), several neurotoxicity studies, and an immunotoxicity study have been conducted in animals following inhalational exposures to dichloromethane. However, the two-generation study is limited in its ability to fully evaluate reproductive and developmental toxicity, since exposure was not continued through the gestation and nursing periods. The results from the single dose developmental toxicity study in rats (Bornschein et al., 1980; Hardin and Manson, 1980), the placental transfer of dichloromethane, and the relatively high activity of CYP2E1 in the brain compared to the liver of the developing human fetus (Hines, 2007; Johnsrud et al., 2003; Brzezinski et al., 1999), raise uncertainty regarding possible neurodevelopmental toxicity from gestational exposure to inhaled dichloromethane. An acute, 3-hour exposure to 100 ppm dichloromethane demonstrated evidence of immunosuppression in CD-1 mice (Aranyi et al., 1986). This study used a functional immune assay that is relevant to humans (i.e., increased risk of Streptococcal pneumonia-related mortality and decreased clearance of Klebsiella bacteria). Chronic and/or repeated exposure studies evaluating functional immunity are not available and represent a data gap. The inhalation database lacks adequate developmental neurotoxicity and immunotoxicity studies at chronic low exposures.

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 Chronic Inhalation RfC

Source Document — *Toxicological Review of Dichloromethane* (U.S. EPA, 2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

Agency Completion Date – 11/18/2011

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

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II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Dichloromethane
CASRN — 75-09-2
Section II. Last Revised — 11/18/2011

This section 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 and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*

(U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

In the previous IRIS assessment (posted on the website in 1990), dichloromethane was assigned a cancer descriptor of B2 (probable human carcinogen). The previous oral slope factor was 7.5×10^{-3} per mg/kg-day and the previous inhalation unit risk was 4.7×10^{-7} per $\mu g/m^3$.

II.A. Evidence for Human Carcinogenicity

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

Following U.S. EPA (2005a) *Guidelines for Carcinogen Risk Assessment*, dichloromethane is "likely to be carcinogenic in humans," based predominantly on evidence of carcinogenicity at two sites in 2-year bioassays in male and female $B6C3F_1$ mice (liver and lung tumors) with inhalation exposure (NTP, 1986) and at one site in male $B6C3F_1$ mice (liver tumors) with drinking water exposure (Serota et al., 1986b; Hazleton Laboratories, 1983). The incidence rates for liver tumors in female mice in the drinking water exposure study were not presented (Serota et al., 1986b; Hazleton Laboratories, 1983), but it was reported that exposed female mice did not show increased incidences of proliferative hepatocellular lesions. Additional evidence of the tumorigenic potential of dichloromethane in rats comes from the observation of an increase in benign mammary tumors following inhalation exposure in rats (Nitschke et al., 1988a; NTP, 1986; Burek et al., 1984). A gavage study in female Sprague-Dawley rats reported an increased incidence of malignant mammary tumors, mainly adenocarcinomas (8, 6, and 18% in the control, 100, and 500 mg/kg dose groups, respectively), but the increase was not statistically significant; data were not provided to allow an analysis that accounts for differing mortality rates (Maltoni et al., 1988). An inhalation study (exposures of 0, 50, 200, and 500 ppm) also reported the presence of another relatively rare tumor in rats, astrocytoma or glioma (mixed glial cell) tumors (Nitschke et al., 1988a). Taken together, the rat data provide supporting evidence of carcinogenicity. Studies in humans also observed evidence linking occupational exposure to dichloromethane and increased risk for some specific cancers, including brain cancer (Cocco et al., 1999; Hearne and Pifer, 1999; Heineman et al., 1994; Tomenson, In Press), liver and biliary tract cancer (Lanes et al., 1993; Lanes et al.,

1990), non-Hodgkin lymphoma (Barry et al., 2011; Wang et al., 2009; Seidler et al., 2007; Miligi et al., 2006), and multiple myeloma (Gold et al., 2010).

The proposed mode of action for dichloromethane-induced tumors is through a mutagenic mode of carcinogenic action. In brief, mode-of-action data indicate that dichloromethane-induced DNA damage in cancer target tissues of mice (i.e., liver and lung) involves DNA-reactive metabolites produced via a metabolic pathway initially catalyzed by glutathione S-transferase-theta1-1 (GST-T1). Evidence of mutagenicity includes in vitro bacterial assays in several strains (Demarini et al., 1997; Pegram et al., 1997; Oda et al., 1996; Thier et al., 1993; Dillon et al., 1992), and in vitro mutagenicity tests in mammalian systems, including the *hprt* gene mutation assay in Chinese hamster ovary (CHO) cells with added glutathione S-transferase (GST) activity (Graves et al., 1996) and the micronucleus test in human MCL-5 and h2E1 cell lines (Doherty et al., 1996). In in vivo studies using mouse red blood cells, the micronucleus test and assays for chromosome aberrations were also positive at inhalation doses consistent with the doses that induced mouse tumors (Allen et al., 1990). Additional in vivo evidence of genotoxicity as evidenced by sister chromatid exchanges and DNA damage (comet assay) has also been seen in mouse liver and lung cells (Sasaki et al., 1998; Graves et al., 1995; Graves et al., 1994a; Casanova et al., 1992; Allen et al., 1990), although a dichloromethane distinctive mutational spectrum in critical genes (Kras, Hras, p53) leading to tumor initiation and tumor promotion has not been established (Devereux et al., 1993; Hegi et al., 1993). The GST-T1 metabolic pathway has been found in human tissues, albeit at lower activities than in mouse tissues; therefore, the cancer results in animals are considered relevant to humans.

EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) indicate that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. An exception occurs when there is convincing toxicokinetic data that absorption does not occur by other routes. For dichloromethane, systemic tumors were observed in mice following inhalation and oral exposure. No animal cancer bioassay data following dermal exposure to dichloromethane are available. Based on the observance of systemic tumors following oral exposure and inhalation exposure, and in the absence of information to indicate otherwise, it is assumed that an internal dose will be achieved regardless of the route of exposure. Therefore, dichloromethane is "likely to be carcinogenic to humans" by all routes of exposure.

For more detail on Dose-Response Assessments, exit to the toxicological review, Section 5 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

II.A.2. Human Carcinogenicity Data

The available epidemiologic studies provide evidence of an association between dichloromethane and brain cancer, liver and biliary tract cancer, and some hematopoietic cancers (specifically non-Hodgkin lymphoma and multiple myeloma). Two small cohort studies with relatively good exposure metrics and relatively long follow-up periods (mean over 25 years) reported an increased risk of brain cancer, with SMRs of 1.83 (95% CI 0.79–3.60) in Tomenson et al. (In Press) and 2.2 (95% CI 0.79–4.69) in Cohort 1 of Hearne and Pifer (1999). Cohort 1 is an inception cohort, following workers from the beginning of employment, which is methodologically more robust than Cohort 2 of Hearne and Piffer (1999), which only included workers who were working between 1964 and 1970. In Hearne and Pifer (1999) and in Tomenson et al. (In Press), an increasing risk was seen with cumulative exposure in the middle exposure groups (e.g., 400 to 800 ppm-years), with a decrease in risk above 800 ppm-years; the small number of observations and resulting imprecision in relative risk estimates makes it difficult to interpret these patterns. These observations are supported by the data from a case-control study of brain cancer using lifetime job history data that reported relatively strong trends ($p < 0.05$) with increasing probability, duration, and intensity measures of exposure but not with a cumulative exposure measure (Heineman et al., 1994). This difference in results among different exposure measures could reflect a relatively more valid measure of relevant exposures in the brain from the intensity measure, as suggested by the study in rats reported by Savolainen et al. (1981) in which dichloromethane levels in the brain were much higher with a higher intensity exposure scenario compared with a constant exposure period with an equivalent TWA. The combination of high intensity of exposure and long (>20 years) duration of employment in exposed jobs was strongly associated with brain cancer risk (OR 6.1, 95% CI 1.5–28.3) in the Heineman et al. (1994) study; similar associations were seen with the measure combining high probability with long duration. In a case-control study of female brain cancer cases, Cocco et al. (1999), using more limited occupation data obtained from death certificates, observed a weak overall association with dichloromethane exposure, and no trends with probability or intensity.

With respect to epidemiologic studies of liver and biliary duct cancer, the highest exposure cohort, based in the Rock Hill, South Carolina, triacetate fiber production plant, suggested an increased risk of liver and biliary tract cancer with an SMR of 2.98 (95% CI 0.81–7.63) in the latest study update (Lanes et al., 1993). This observation was based on four cases (three of which were biliary tract cancers); an earlier analysis in this cohort reported an SMR of 5.75 (95% CI 1.82–13.8), based on the same four cases but with a shorter follow-up period (and thus a lower number of expected cases) (Lanes et al., 1990). The authors estimated a total of

0.15 expected cases of biliary tract cancer in the first of the follow-up studies (Lanes et al., 1990). This subset of cancers may represent a particularly relevant form of cancer with respect to dichloromethane exposure based on the localization of GST-T1 in the nuclei of bile duct epithelial cells seen in human samples (Sherratt et al., 2002). No other cohort study has reported an increased risk of liver cancer mortality, although it should be noted that there is no other inception cohort study of a population with exposure levels similar to those of the Rock Hill plant, and no data from a case-control study of liver cancer are available pertaining to dichloromethane exposure.

The primary limitation of all of the available dichloromethane cohort studies is the limited statistical power for the estimation of effects relating to relatively rare cancers (such as brain cancer, liver cancer, and leukemia). Limitations with respect to studies of other cancers can also be noted. With respect to breast cancer, the only cohort that included a significant percentage of women had limited exposure information (analysis was based on a dichotomous exposure variable) and had exposure to other solvents that also exhibited associations of similar magnitude to that seen with dichloromethane (Radican et al., 2008). Thus, in this situation, potential confounding by these other exposures should be considered. The only breast cancer case-control study available used death certificate data to classify disease and occupational exposure (Cantor et al., 1995), which is likely to result in significant misclassification; exposure misclassification in particular would be expected to result in an attenuated measure of association (Rothman and Greenland, 1998). The available epidemiologic studies do not provide a definitive evaluation of non-Hodgkin lymphoma, but the consistent observations of associations seen in three large case-control studies in Germany (Seidler et al., 2007), Italy (Miligi et al., 2006), and the United States (Barry et al., 2011; Wang et al., 2009) provide evidence of an increased risk of specific types of hematopoietic cancers in humans. These studies are limited by relatively small number of exposed cases, resulting in imprecise effect estimates.

II.A.3. Animal Carcinogenicity Data

Several dichloromethane cancer bioassays in animals are available. In the only oral exposure cancer bioassay involving lifetime exposure, increases in incidence of liver adenomas and carcinomas were observed in male but not female B6C3F$_1$ mice exposed for 2 years (Serota et al., 1986b; Hazleton Laboratories, 1983). Based on the Hazleton Laboratories (1983) statistical analysis, EPA concluded that dichloromethane induced a carcinogenic response in male B6C3F$_1$ mice as evidenced by a marginally increased trend test ($p = 0.058$) for combined hepatocellular adenomas and carcinomas, and by small but statistically significant ($p < 0.05$) increases in hepatocellular adenomas and carcinomas at dose levels of 125 ($p = 0.021$), 185 ($p = 0.019$), and 250 mg/kg-day ($p = 0.036$).

In a similar study in F344 rats (Serota et al., 1986a), no increased incidence of liver tumors was seen in male rats, and the pattern in female rats was characterized by a jagged stepped pattern of increasing incidence of hepatocellular carcinoma or neoplastic nodule. Information was not provided which would allow characterization of the nodules as benign or malignant. Statistically significant increases in incidences were observed in the 50 and 250 mg/kg-day groups (incidence rates of 0, 3, 10, 3, and 14%, respectively, for the 0, 5, 50, 125, and 250 mg/kg-day groups) and in the group exposed to 250 mg/kg-day for 78 weeks followed by a 26-week period of no exposure (incidence rate 10%). A similar pattern, but with more sparse data, was seen for hepatocellular carcinomas, with two incidences in the 50 mg/kg-day and two in the 250 mg/kg-day groups. The authors concluded that dichloromethane exposure did not result in an increased incidence of liver tumors because the increase was based on a low rate (0%) in the controls and because of a lack of monotonicity.

Gavage exposure studies in Sprague-Dawley rats and in Swiss mice provide limited data concerning cancer incidence because the study was terminated early (at 64 weeks) due to high treatment-related mortality (Maltoni et al., 1988). Exposure groups included controls (olive oil), 100, or 500 mg/kg-day 4–5 days/week. High-dose female rats showed an increased incidence of malignant mammary tumors, mainly adenocarcinomas (8, 6, and 18% in the control, 100, and 500 mg/kg dose groups, respectively), but the increase was not statistically significant. Data were not provided to allow an analysis accounting for differing mortality rates. A dose-related increase, although not statistically significant, in pulmonary adenomas was observed in male mice (5, 12, and 18% in control, 100, and 500 mg/kg-day groups, respectively).

Repeated inhalation exposure to concentrations of 2,000 or 4,000 ppm dichloromethane produced increased incidences of lung and liver tumors in $B6C3F_1$ mice (Mennear et al., 1988; NTP, 1986). Elevated incidences of lung and liver tumors in $B6C3F_1$ mice were observed with 52 weeks of exposure to 2,000 ppm, and lung tumors were also elevated by week 104 in mice exposed for only 26 weeks to 2,000 ppm, followed by 78 weeks without exposure (Maronpot et al., 1995; Kari et al., 1993).

A moderate trend of increasing incidence of neoplastic nodules or hepatocellular carcinoma was seen in female F344 rats (trend p-value = 0.08) but not males in the NTP (1986) study. Liver tumors are relatively rare in F344 rats. The nodules were not characterized as benign or malignant and there was no evidence of an increasing trend in incidence when hepatocellular carcinomas only were considered.

Female F344 rats exposed by inhalation to 2,000 or 4,000 ppm showed significantly increased incidences of benign mammary tumors (adenomas or fibroadenomas) (NTP, 1986); the number of benign mammary tumors per animal also increased with dichloromethane exposure

in studies in Sprague-Dawley rats at levels of 50–500 ppm (Nitschke et al., 1988a) and 500–3,500 ppm (Burek et al., 1984). Male rats in two of these studies (Nitschke et al., 1988a; NTP, 1986) also exhibited a low rate of sarcoma or fibrosarcoma in mammary gland or subcutaneous tissue around the mammary gland.

In Syrian golden hamsters exposed to 500, 1,500, or 3,500 ppm for 2 years, no statistically significantly increased incidences of tumors were found in any tissues (Burek et al., 1984).

II.A.4. Supporting Data for Carcinogenicity

Supporting evidence for the carcinogenicity of dichloromethane comes from the results of genotoxicity and mode of action studies. A mutagenic mode of carcinogenic action for dichloromethane involves metabolic activation by GST, as evidenced by several observations, including the observation in multiple studies of enhanced dichloromethane mutagenicity in bacterial and mammalian (i.e., CHO) in vitro assays with the introduction of GST metabolic capacity. In bacterial strains where GST activity was not present (e.g., TA1535, TA1538), mutagenic effects were not reported following dichloromethane exposure (Oda et al., 1996; Simula et al., 1993; Osterman-Golkar et al., 1983; Gocke et al., 1981); other studies demonstrated that the mutagenicity of dichloromethane is enhanced in the presence of GSH (Demarini et al., 1997; Graves et al., 1996; Graves and Green, 1996; Graves et al., 1995; Graves et al., 1994b; Thier et al., 1993). In an in vivo genotoxicity study examining liver and lung tissue in $B6C3F_1$ mice following acute inhalation exposure to 4,000 ppm dichloromethane, the formation of DNA SSBs was suppressed to the levels seen in controls when the mice were pretreated with a GSH depletor (Graves et al., 1995; Graves et al., 1994b), providing additional support for the involvement of GST metabolism.

Much of the experimental mode of action research has focused on the liver and lung, the sites of tumor formation in chronic bioassays in mice (Mennear et al., 1988; NTP, 1986; Serota et al., 1986b; Hazleton Laboratories, 1983). In vivo chromosomal aberration and micronucleus assays in the $B6C3F_1$ mouse lung were predominantly positive, with dose-response patterns seen in the two-week inhalation exposure studies examining a range of doses (Allen et al., 1990). These observations occurred in the absence of evidence of cytotoxicity, as measured by mitotic index. Similar results were seen in the in vivo studies using peripheral red blood cells (Allen et al., 1990), but not in the studies of the bone marrow, which were predominately negative (Allen et al., 1990; Westbrook-Collins et al., 1990; Gocke et al., 1981; Sheldon et al., 1987). This difference likely reflects the extent of GST-mediated metabolism and subsequent generation of reactive metabolites at these various tissue sites. (The liver is the other site of tumor response, but this tissue has not been examined in in vivo chromosomal instability assays in the mouse.) The in vitro tests of chromosomal instability in other types of cells also indicate the influence of GST-T1 metabolism; the only negative study in this set of studies

(Graves and Green, 1996; Graves et al., 1996; Thilagar and Kumaroo, 1983; Doherty et al. 1996, Jongen et al., 1981) was the study by Jongen et al. (1981) using Chinese hamster epithelial cells without any GST activation. Increases in *hprt* gene mutations and DNA damage (DNA SSBs) were seen in CHO cells when they are incubated with dichloromethane in the presence of mouse liver cytosol preparations rich in GST enzymatic activities (Graves and Green, 1996; Graves et al., 1996).

The chromosomal mutation results described above are further supported by the in vivo and in vitro data from indicator assays of DNA damage. In the in vivo studies, DNA damage is seen in all of the studies of liver cells with two exceptions: 1) one very low exposure (single dose, 5 mg/kg) study in which inconsistent results were seen in the duplicate assays conducted (Watanabe et al., 2007) and 2) the studies using DNA synthesis and unscheduled DNA synthesis (Lefevre and Ashby, 1989; Trueman and Ashby, 1987). It is generally recognized that unscheduled DNA synthesis is an insensitive assay for detecting genotoxic chemicals (Eastmond et al., 2009; Madle et al., 1994). In vivo studies of mouse lung cells reported positive results for the comet assay, DNA single strand breaks (SSBs) by alkaline elution and sister chromatid exchange (Allen et al. 1990; Sasaki et al. 1998; Graves 1995), but not for DNA-protein cross-links (Casanova et al., 1996; 1992). The type of tissue specificity that was seen with the chromosomal instability studies was also seen with the mouse in vivo indicator assays, with predominately negative results at sites other than lung or liver, and in the rodents other than mice.

Since there are limited data on mutagenic events following oral exposure, EPA conducted a pharmacokinetic analysis to evaluate how comparable the internal doses to the liver in the oral bioassay (Serota et al., 1986b; Hazleton Laboratories, 1983) were to the internal doses to the liver in the inhalation bioassay (Mennear et al., 1988; NTP, 1986). The PBPK model of Marino et al. (2006) predicted that the average daily amount of dichloromethane metabolized via GST/L liver was about 14-fold lower in mice exposed to the highest dose of 234 mg/kg-day in the drinking water bioassay than in mice exposed to the lowest inhalation exposure of 2,000 ppm inducing liver tumors. Thus, the lower incidence of liver tumors induced by oral doses of 234 mg/kg-day compared with the higher incidence induced by inhalation exposure to 2,000 ppm is consistent with the predicted lower liver dose of GST metabolites (and hence lower probability of DNA modification) with oral exposure. See Section 4.7.2 of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

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

II.B.1. Summary of Risk Estimates

II.B.1.1. Oral Slope Factor — 2×10^{-3} per mg/kg-day

EPA has concluded, by a weight of evidence evaluation, that dichloromethane is carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (Supplemental Guidance)* (U.S. EPA, 2005b) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for dichloromethane are not sufficient to develop separate risk estimates for childhood exposure. The oral slope factor of **2×10^{-3} per mg/kg-day**, calculated from data from adult exposure as described below, does not reflect presumed early-life susceptibility for this chemical and age dependent adjustment factors (ADAFs) should be applied to this slope factor when assessing cancer risks. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance.*

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). The 10 fold and 3 fold adjustments in oral slope factor are to be combined with age specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to dichloromethane. These ADAFs and their age groups were derived from the 2005 *Supplemental Guidance*, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for dichloromethane, age-specific values for cancer potency are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance*).

The oral slope factor, calculated from exposures beginning after early development (e.g., beginning at 7-9 weeks of age), was derived from mouse liver tumor incidence data (from Serota et al., 1986b; Hazleton Laboratories, 1983) using a modified mouse PBPK model (Marino et al., 2006) and the multistage dose-response model (BMDS 2.0) to approximate a mouse $BMDL_{10}$ (expressed in units of internal dose, or mg dichloromethane metabolized via the GST pathway/L liver tissue/day), with the $BMDL_{10}$ defined as the 95% lower bound on the exposure associated with a 10% extra cancer risk. A human (internal dose) $BMDL_{10}$ was derived by dividing the mouse (internal dose) $BMDL_{10}$ by an allometric scaling factor of 7 (based on body weight [BW] raised to the ¾ power). A probabilistic human PBPK model

(David et al., 2006) was used to determine a distribution of human internal doses from a unit of oral dose (1 mg/kg) and corresponding oral slope factor values expressed as external dose (mg/kg-day). The mean of the distribution of candidate values from the most sensitive (GST-$T1^{+/+}$) genotype (that is, the group that would be expected to be most sensitive to the carcinogenic effects of dichloromethane) was chosen as the oral slope factor. The oral slope factor represents an upper bound risk estimate for continuous lifetime exposure without consideration of increased early-life susceptibility due to dichloromethane's mutagenic mode of action.

The slope of the linear extrapolation from the lower 95% bound estimate $BMDL_{10}$ is 0.1/60 mg/kg-day = **1.7×10^{-3} per mg/kg-day, or 2×10^{-3} per mg/kg-day (rounded to one significant figure) [oral slope factor].**

$BMDL_{10}$, lower 95% bound on exposure at 10% extra risk: 60 mg/kg-day
BMD_{10}, central estimate of exposure at 10% extra risk: 111 mg/kg-day

The slope of the linear extrapolation from the central estimate (BMD_{10}) is 0.1/111 mg/kg-day = 9×10^{-4} per mg/kg-day. See Section II.B.3 for additional explanation.

The oral slope factor for dichloromethane should not be used with exposures exceeding the point of departure ($BMDL_{10}$ = 60 mg/kg-day), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of dichloromethane. Additionally, age dependent adjustment factors (ADAFs) should be applied to this slope factor when assessing cancer risks to individuals <16 years old as discussed above (U.S. EPA, 2005b).

II.B.1.2. Drinking Water Concentrations at Specified Risk Levels

Drinking water unit risk and concentrations at specified risk levels are not provided for dichloromethane. Since dichloromethane is carcinogenic by a mutagenic mode of action and increased susceptibility is assumed for early-life exposures (<16 years of age), the unit risk and concentrations at a specified risk levels will change based on the age of the individuals in the exposed group. Risk assessors should use the oral slope factor and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/

II.B.1.3. Extrapolation Method

Multistage model with linear extrapolation from the point of departure ($BMDL_{10}$).

II.B.2. Dose-Response Data

Tumor Type — Hepatocellular carcinomas or adenomas
Test species — Male $B6C3F_1$ mice
Route — Oral (drinking water)
Reference — Serota et al. (1986b)

Incidence data for liver tumors and internal liver doses, based on GST metabolism dose metrics in male $B6C3F_1$ mice exposed to dichloromethane in drinking water for 2 years

Sex	Nominal (actual) daily intake (mg/kg-day)	Mouse liver tumor incidence[a]	Mouse internal liver metabolism dose[b]	Mouse whole body metabolism dose[c]
Male	0 (0)	24/125 (19%)	0	0
	60 (61)	51/199 (26%)	17.5	0.73
	125 (124)	30/99 (30%)	63.3	2.65
	185 (177)	31/98 (32%)	112.0	4.68
	250 (234)	35/123 (28%)	169.5	7.1

[a]Hepatocellular carcinoma or adenoma, combined. Mice dying prior to 52 weeks, as estimated from the survival data shown in Figure 1 of Hazleton Laboratories (1983), were excluded from the denominators. Cochran-Armitage trend *p*-value = 0.058. *P*-values for comparisons with the control group were 0.071, 0.023, 0.019, and 0.036 in the 60, 125, 185, and 250 mg/kg-day groups, respectively, based on statistical analyses reported by Hazleton Laboratories (1983)
[b]mg dichloromethane metabolized via GST pathway/L liver/day. Internal doses were estimated from simulations of actual daily doses reported by the study authors.
[c]Based on the sum of dichloromethane metabolized via the GST pathway in the lung plus the

liver, normalized to total BW (i.e., [lung GST metabolism (mg/day) + liver GST metabolism (mg/day)]/kg BW). Units = mg dichloromethane metabolized via GST pathway in lung and liver/kg-day.

Sources: Serota et al. (1986b); Hazleton Laboratories (1983).

II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The oral slope factor was derived using a modified mouse PBPK model (from Marino et al. [2006]) which approximated the internal dichloromethane dose (mg dichloromethane metabolized via the GST pathway/liter of liver tissue/day) from the mouse cancer bioassay by Serota et al. (1986b). The multistage dose-response model (BMDS version 2.0) was used to fit the mouse liver tumor incidence and PBPK model-derived internal doses and to derive a mouse internal BMD_{10} and $BMDL_{10}$ (73.0 and 39.6 mg dichloromethane metabolized via GST pathway/liter tissue/day, respectively). The human (internal dose) $BMDL_{10}$ was derived by dividing the mouse (internal dose) $BMDL_{10}$ by a $BW^{0.75}$ allometric scaling factor (operationalized as $[BW_{human}/BW_{mouse}]^{0.25} \approx 7$) to account for the potential slower clearance per volume tissue in the human compared with the mouse, resulting in an allometric-scaled human $BMDL_{10}$ value of 5.66 mg dichloromethane metabolized via GST pathway/liter tissue/day. Linear extrapolation from the human (internal dose) $BMDL_{10}$ ($0.1/BMDL_{10}$) was used to derive a human oral risk factor for liver tumors (i.e., $0.1/5.66 = 1.77 \times 10^{-2}$ [extra risk per unit internal dose]).

The human PBPK model adapted from David et al. (2006), using Monte Carlo sampling techniques, was used to calculate a distribution of human internal dose metrics (expressed in units of mg dichloromethane metabolized via the liver-specific GST pathway/liter liver tissue/day) resulting from a long-term average drinking water dose of 1 mg/kg-day dichloromethane. The oral slope factor values were derived for a sensitive population; i.e., a population composed entirely of carriers of the GST-$T1^{+/+}$ homozygous genotype (that is, the group that would be expected to be most sensitive to the carcinogenic effects of dichloromethane). A distribution of oral slope factors was derived by multiplying the human oral liver tumor risk factor (1.77×10^{-2}, expressed in units of internal dose) by the distribution of human average daily internal doses resulting from chronic, unit oral exposures of 1 mg/kg-day dichloromethane (mean of the distribution: 0.094, expressed in units of internal dose). The mean oral slope factor ($[1.77 \times 10^{-2}] \times 0.094 = 1.7 \times 10^{-3}$) was selected as the recommended value. See Section 5.4.1, in particular Tables 5-12 and 5-13, of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

The BMD_{10} and $BMDL_{10}$ expressed in units of administered dose can be derived by:

$BMDL_{10}$ = (5.66 mg/L-day) ÷ 0.094 (mg/L-day)/(mg/kg-day) = 60.2 mg/kg-day
BMD_{10} = (10.43 mg/L-day) ÷ 0.094 (mg/L-day)/(mg/kg-day) = 111 mg/kg-day

The central estimate of the oral slope factor can be derived as above, but substituting the mouse BMD_{10} of 73 (expressed as an internal dose in units of mg dichloromethane metabolized via the GST pathway/L liver tissue/day) for the mouse $BMDL_{10}$ of 39.6 (see Table 5-12 of the *Toxicological Review of Dichloromethane* [U.S. EPA, 2011]). The resulting central estimate of the oral slope factor is 9×10^{-4} per mg/kg-day.

For comparison, two alternative oral slope factors were derived based on 1) whole body metabolism using a dose metric based on the total metabolites formed in liver and lungs via GST metabolism per BW, and 2) route-to-route extrapolation from the data for liver tumors in male and female $B6C3F_1$ mice exposed by inhalation for 2 years (Mennear et al., 1988; NTP, 1986). The comparison oral slope factor based on the whole body metabolism analysis is 9×10^{-4} per mg/kg-day, and the comparison oral slope factor based on route-to-route extrapolation is 1×10^{-4} per mg/kg-day. Another comparison, based on administered dose, resulted in an alternative oral slope factor of 1×10^{-2} per mg/kg-day. See Sections 5.4.1.4, 5.4.1.6, and 5.4.1.7 (in particular Tables 5-13, 5-14, and 5-15) of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

The database of animal bioassays identifies the liver as the most sensitive target organ for dichloromethane-induced tumor development from oral exposure. The dose-response data for liver cancer in mice from Serota et al. (1986b) represent the best available data for derivation of human cancer risks. There is uncertainty as to whether the reactivity of the toxic dichloromethane metabolites is sufficiently high enough to preclude systemic distribution. The mechanistic data support the hypothesis that reactive metabolites produced in the target tissues do not distribute significantly beyond those tissues and cause deleterious effects in the metabolizing tissues soon after generation. Thus, there is less uncertainty in the cancer oral slope factor values derived by using a tissue-specific GST metabolism dose metric compared with those derived using a whole-body GST metabolism dose metric.

Uncertainty in the ability of the PBPK models to estimate animal and human internal doses from lifetime bioassay low-level environmental exposures may affect the confidence in the cancer risk extrapolated from animal data. Uncertainties in the mouse and human model parameter values were integrated quantitatively into parameter estimation by utilizing hierarchical Bayesian methods to calibrate the models at the population level (David et al., 2006; Marino et al., 2006). However, with the subsequent deterministic application of the mouse model (using only the mean value for each parameter distribution), the information

contained in the mouse parameter uncertainties reported by Marino et al. (2006) is not integrated into the final risk estimates described here.

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

II.C.1. Summary of Risk Estimates

II.C.1.1. Inhalation Unit Risk — 1×10^{-8} per µg/m^3

EPA has concluded, by a weight of evidence evaluation, that dichloromethane is carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (Supplemental Guidance)* (U.S. EPA, 2005b) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for dichloromethane are not sufficient to develop separate risk estimates for childhood exposure. The inhalation unit risk of **1×10^{-8} per µg/m^3**, calculated from data from adult exposure as described below, does not reflect presumed early-life susceptibility for this chemical and age dependent adjustment factors (ADAFs) should be applied to this unit risk when assessing cancer risks. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance.*

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). The 10 fold and 3 fold adjustments in unit risk are to be combined with age specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to dichloromethane. These ADAFs and their age groups were derived from the Supplemental Guidance, and they may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for dichloromethane, age-specific values for cancer potency are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance*).

The inhalation unit risk, calculated from exposures beginning after early development (e.g., beginning at 7-9 weeks of age), was derived from mouse liver and lung tumor incidence data (from Mennear et al., 1988; NTP, 1986) using a modified mouse PBPK model (Marino et al., 2006) and the multistage dose-response model (BMDS 2.0) to approximate mouse $BMDL_{10}$ values (expressed in units of internal dose, or mg dichloromethane metabolized via the GST

pathway/liter of liver or lung tissue/day), with the $BMDL_{10}$ defined as the 95% lower bound on the exposure associated with a 10% extra cancer risk. Human (internal dose) $BMDL_{10}$ values for liver and lung tumors were derived by dividing the mouse (internal dose) $BMDL_{10}$s by an allometric scaling factor of 7 (based on BW raised to the ¾ power). A probabilistic human PBPK model (David et al., 2006) was used to determine a distribution of human internal doses from a unit of concentration (1 μg/m^3) and corresponding inhalation unit risk values expressed as external concentrations (μg/m^3). The mean of the distribution of candidate values from the most sensitive (GST-$T1^{+/+}$) genotype (that is, the group that would be expected to be most sensitive to the carcinogenic effects of dichloromethane) was chosen as the inhalation unit risk for liver and lung tumors. A procedure for combining risks for liver and lung tumors was used to derive the dichloromethane IUR. The IUR represents an upper bound estimate for continuous lifetime exposure without consideration of increased early-life susceptibility due to dichloromethane's mutagenic mode of action.

> The slope of the linear extrapolation from the lower 95% bound estimate $BMDL_{10}$ is 0.1/7,700 mg/m^3 = **1.3×10^{-8} per μg/m^3 or 1×10^{-8} per μg/m^3 (rounded to one significant figure) [inhalation unit risk].**
>
> The slope of the linear extrapolation from the BMD_{10}, the central estimate of exposure associated with 10% extra cancer risk, was also derived based on the male mouse liver and lung tumor incidence data as shown in Table 5-17 of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011). As indicated in Table 5-20 of the *Toxicological Review*, the slope of the linear extrapolation from the central estimate (BMD_{10}) is 5.1×10^{-9} per μg/m^3 and 4.4×10^{-9} per μg/m^3, respectively, for liver and lung tumors. The slope of the linear extrapolation from the central estimate (BMD_{10}), summing across tumors, is 9.5×10^{-9} per μg/m^3.

The inhalation unit risk for dichloromethane should not be used with exposures exceeding the point of departure ($BMDL_{10}$ = 7,700 mg/m^3), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of dichloromethane. Additionally, age dependent adjustment factors (ADAFs) should be applied to this inhalation unit risk when assessing cancer risks to individuals <16 years old as discussed above (U.S. EPA, 2005b).

Air Concentrations at Specified Risk Levels

Air concentrations at specified risk levels are not provided for dichloromethane. Since dichloromethane is carcinogenic by a mutagenic mode of action and increased susceptibility is assumed for early-life exposures (<16 years of age), the concentrations at specified risk levels will change based on the age of the individuals in the exposed group. Risk assessors should

use the unit risk and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.C.1.2. Extrapolation Method

Multistage model with linear extrapolation from the point of departure ($BMDL_{10}$).

II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Types — Hepatocellular carcinomas or adenomas, bronchoalveolar carcinomas or adenomas
Test species — Male $B6C3F_1$ mice
Route — Inhalation
Reference — Mennear et al. (1988); NTP (1986)

Incidence data for liver and lung tumors and internal doses based on GST metabolism dose metrics in male $B6C3F_1$ mice exposed to dichloromethane via inhalation for 2 years

Sex, tumor type	BW (g)	External dichloromethane concentration (ppm)	Mouse tumor incidence	Mouse internal tissue dose[a]	Mouse whole body metabolism dose[b]
Male, liver[c]	–	0	22/50 (44%)[d]	0	0
	34.0	2,000	24/47 (51%)	2,363.7	100.2
	32.0	4,000	33/47 (70%)	4,972.2	210.7
Male, lung[e]	–	0	5/50 (10%)[d]	0	0
	34.0	2,000	27/47	475.0	100.2

Sex, tumor type	BW (g)	External dichloromethane concentration (ppm)	Mouse tumor incidence	Mouse internal tissue dose[a]	Mouse whole body metabolism dose[b]
			(55%)		
	32.0	4,000	40/47 (85%)	992.2	210.7

[a]For liver tumors: mg dichloromethane metabolized via GST pathway/L liver tissue/day from 6 hours/day, 5 days/week exposure; for lung tumors: mg dichloromethane metabolized via GST pathway/L lung tissue/day from 6 hours/day, 5 days/week exposure.
[b]Based on the sum of dichloromethane metabolized via the GST pathway in the lung plus the liver, normalized to total BW (i.e., [lung GST metabolism (mg/day) + liver GST metabolism (mg/day)]/kg BW). Units = mg dichloromethane metabolized via GST pathway in lung and liver/kg-day.
[c]Hepatocellular carcinoma or adenoma. Mice dying prior to 52 weeks were excluded from the denominators.
[d]Statistically significant increasing trend (by incidental and life-table tests; $p \leq 0.01$).
[e]Bronchoalveolar carcinoma or adenoma. Mice dying prior to 52 weeks were excluded from the denominators.

Sources: Mennear et al. (1988); NTP (1986).

II.C.3. Additional Comments

The inhalation unit risk was derived using a modified mouse PBPK model (from Marino et al. [2006]) which approximated the internal dichloromethane dose (mg dichloromethane metabolized via the GST pathway/unit volume of liver or lung/day) from the mouse cancer bioassay by Mennear et al. (1988) and NTP (1986). The multistage dose-response model (BMDS version 2.0) was used to fit the mouse liver and lung tumor incidence and PBPK model-derived internal doses and to derive mouse internal BMD_{10} and $BMDL_{10}$ values. For male liver tumors, the BMD_{10} and $BMDL_{10}$ were 913.9 and 544.4 mg dichloromethane metabolized via GST pathway/liter tissue/day, respectively; for male lung tumors, the corresponding values were 61.7 and 48.6 mg dichloromethane metabolized via GST pathway/liter tissue/day). The human (internal dose) $BMDL_{10}$s were derived by dividing the mouse (internal dose) $BMDL_{10}$s by a $BW^{0.75}$ allometric scaling factor (operationalized as

$[BW_{human}/BW_{mouse}]^{0.25} \approx 7$) to account for the potential slower clearance per volume tissue in the human compared with the mouse, resulting in allometric-scaled human $BMDL_{10}$ values of 77.8 and 7.0 mg dichloromethane metabolized via GST pathway/liter tissue/day, respectively, for liver and lung tumors. Linear extrapolation from the human (internal dose) $BMDL_{10}$ ($0.1/BMDL_{10}$) was used to derive inhalation risk factors for liver and lung tumors (i.e., $0.1/77.8 = 1.29 \times 10^{-3}$ and $0.1/7.0 = 1.44 \times 10^{-2}$, respectively [extra risk per unit internal dose]).

The human PBPK model adapted from David et al. (2006) using Monte Carlo sampling techniques was used to calculate distributions of human internal dose metrics (expressed in units of mg dichloromethane metabolized via the tissue-specific GST pathway/liter tissue/day) resulting from chronic unit inhalation (1 μg/m^3) exposures. The inhalation unit risks for liver and lung tumors were derived for a sensitive population; i.e., a population composed entirely of carriers of the GST-$T1^{+/+}$ homozygous genotype (that is, the group that would be expected to be most sensitive to the carcinogenic effects of dichloromethane). A distribution of inhalation unit risks was derived by multiplying the human inhalation liver or lung tumor risk factors (1.29×10^{-3} and 1.44×10^{-2}, respectively, both expressed in units of internal dose) by the respective distributions of human average daily internal doses resulting from chronic, unit inhalation exposures of 1 μg/m^3 dichloromethane (mean of the distribution: liver—6.61×10^{-6}; lung—3.89×10^{-7}, both expressed in units of internal dose). The mean inhalation unit risk was selected as the recommended value. A procedure to combine risks for liver and lung tumors using different dose metrics for the different tumors (i.e., liver-specific and lung-specific metabolism for liver and lung tumors, respectively) was used to derive the dichloromethane IUR. See Section 5.4.2.4, in particular Tables 5-18 and 5-19, of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

The inhalation unit risk is based on data from male $B6C3F_1$ mice; risk estimates were similar to the values based on female mice in the NTP (1986) inhalation study. For comparison, an alternative inhalation unit risk was derived based on whole body metabolism using a dose metric based on the total metabolites formed in liver and lungs via GST metabolism per kg body weight. The comparison inhalation unit risk based on the whole body metabolism analysis is 2×10^{-8} per μg/m^3. Another comparison, based on administered dose, resulted in an alternative inhalation unit risk of 4×10^{-7} per μg/m^3 based on liver tumors and 8×10^{-7} per μg/m^3 based on lung tumors in male mice. See Sections 5.4.2.4 and 5.4.2.7 (in particular Tables 5-20 and 5-21) of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

Mammary gland tumor data from male and female F344 rats following an inhalation exposure to dichloromethane were considered in development of a comparative inhalation unit risk for dichloromethane (Mennear et al., 1988; NTP, 1986). In both male and female rats, there were

significant increases in the incidence of adenomas, fibroadenomas, or fibromas in or near the mammary gland. The alternative inhalation unit risk based on female rat data was 1×10^{-7} per $\mu g/m^3$. There are considerably more uncertainties regarding the interpretation of these data with respect to carcinogenic risk compared with the data pertaining to liver and lung tumors. The trends were driven in large part by benign tumors; adenocarcinomas and carcinomas were seen only in the females with incidences of 1, 2, 2, and 0 in the 0, 1,000, 2,000, and 4,000 ppm exposure groups, respectively. There are little data to guide the choice of relevant dose metric, and the genotoxicity and mechanistic studies have not included mammary tissue. See Appendix I of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011) for further details.

II.C.4. Discussion of Confidence

The database of animal bioassays identifies the liver and lung as the most sensitive target organs for dichloromethane-induced tumor development following inhalation exposure, and there is high confidence that the dose-response data for liver and lung cancer in mice represent the best available data for derivation of human cancer risks. A dose-response relationship was seen with respect to liver and lung cancer in mice exposed by inhalation. See Section II.B.4 for additional discussion of uncertainties related to PBPK modeling.

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

II.D.1. EPA Documentation

Source Document — *Toxicological Review of Dichloromethane* (U.S. EPA, 2011)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Dichloromethane* (U.S. EPA, 2011). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***

II.D.2. EPA Review

Agency Completion Date — 11/18/2011

II.D.3. EPA Contacts

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 (email address).

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

VI. Bibliography

Substance Name — Dichloromethane
CASRN — 75-09-2

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VII. Revision History

Substance Name — Dichloromethane
CASRN — 75-09-2
File First On-line — 01/31/1987

Date	Section	Description
01/31/1987	I.A, II.	RfD and cancer assessment added.
09/01/1990	II.	Carcinogen assessment revised.
11/18/2011	I.A, I.B, II	RfD and cancer assessment updated. RfC added.

VIII. Synonyms

Substance Name — Dichloromethane
CASRN — 75-09-2
Last Revised — 11/18/2011

- 75-09-2
- Aerothene MM
- Chlorure de methylene
- DCM
- Dichlormethan, uvasol
- 1,1-Dichloromethane
- Freon 30
- Methane dichloride
- Methane, dichloro-
- Methylene bichloride
- Methylene chloride
- Methylene dichloride
- Metylenu chlorek
- Narkotil
- NCI-C50102

- R 30
- Solaesthin
- Solmethine
- WLN: G1G