United States
Environmental Protection Agency

Office of Chemical Safety and
Pollution Prevention

Final Risk Evaluation for Methylene Chloride

Systematic Review Supplemental File:

Data Extraction Tables for Human Health Hazard Studies

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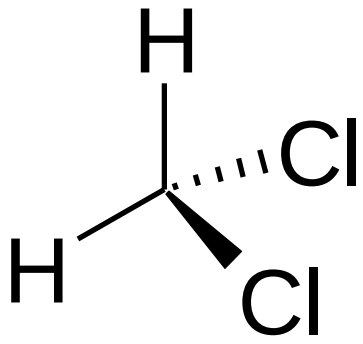

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NOTE: Within each table, rows that are shaded are the new studies identified in the updated literature search or newly identified. Some of these studies were submitted under TSCA (e.g., section 8e, 8d, etc) or published in journal articles several years ago and thus have older dates. Rows that are *not* shaded are the key and supporting studies from the IRIS Assessment (U.S. EPA, 2011). Studies that received unacceptable data quality ratings are not included in the tables below.

1 Data Extraction Table for Epidemiology Studies

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Non-Hodgkin lymphoma (NHL)	518 women diagnosed with NHL between 1996 and 2000 and 597 control women	Job exposure matrix (ever/never exposed to methylene chloride)	The risk of NHL was increased with exposure to methylene chloride; OR (95% CI) = 1.69 (1.06, 2.69). For the diffuse large B-cell lymphoma subtype, the risk was also significantly increased with exposure to methylene chloride; OR (95% CI) - 2.10 (1.15, 3.85).	Barry et al. (2011)	High
Cancer	Breast cancer mortality	132,352 white women and 18,591 black women across 24 US states, 14.2 percent and 24.7 percent of cases were under 50 for white and black women, respectively.	50 percent of black cases and 30 percent of white cases were considered exposed to methylene chloride.	Breast cancer mortality risk was significantly elevated for white and black women in the highest level of exposure. Risk of breast cancer mortality was significantly reduced in the first level of exposure for white women.	Cantor et al. (1995)	High

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Diagnosis of cancer in oral cavity, oropharynx, hypopharynx, oral cavity, and larynx (detailed list of codes in text)	Case-control, women only, 296 cases, 775 controls, diagnosed 2001-2007, general population, 18-85 years, subset of ICARE cohort	Methylene chloride exposure qualitatively stated as ever (job with likely exposure >1month) or never	Non-significant positive association between methylene chloride and head/neck cancers in ever/never and continuous cumulative exposure analysis; non-significant negative association for those exposed exclusively to methylene chloride (limited sample size)	Carton et al. (2017)	Medium
Cancer	Cancers of the bladder, prostate, colon, stomach, rectum, kidney, esophagus, liver, and pancreas, as well as melanoma and non-Hodgkin's lymphoma	3730 male, Canadian patients aged 35 to 70 years diagnosed 1979-1985 in 18 largest Montreal hospitals; 533 controls from electoral lists in Quebec. A second control group consisted of the population controls together with patients with cancers at sites distal to the primary cancer being assessed.	Methylene chloride exposure determined from self-reported job history categorized by chemists and industrial hygienists based on degree of confidence, frequency, and relative levels (not quantitative)	Non-significant OR for all cancer types	Christensen et al. (2013)	Medium
Cancer	Meningioma mortality	(1984-1992), United States, 649000 women (12980 cases, 51920 controls)	Methylene chloride exposure based on a job exposure matrix and occupation code	Methylene chloride was not significantly associated with risk of meningioma mortality.	Cocco et al. (1999)	Medium
Cancer	Leukemia and chronic lymphatic leukemia	355 cases of leukemia and 811 controls, and 103 cases of chronic lymphatic leukemia and 925 controls in Italy, ages 20 to 74	Methylene chloride exposure based on employment questionnaire and expert rating	A significant association between exposure to methylene chloride and leukemia and chronic lymphatic leukemia was not observed at either exposure level	Costantini et al. (2008)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Renal cell carcinoma	White newly diagnosed cases with age- and gender-stratified random sample white controls	JEM (developed by NCI)	No significant association between methylene chloride and RCC for the total population nor when separated by sex	Dosemeci et al. (1999)	Medium
Cancer	Breast cancer incidence	Participants in the California Teacher Study, 1995-2011, (n=112,378 women)	National-Scale Air Toxics Assessment modeled air concentrations	No significant association between breast cancer incidence and methylene chloride exposure	Garcia et al. (2015)	High
Cancer	Cause-specific mortality to liver cancer, prostate cancer, pancreatic cancer, and cervical cancer	2187 men and 1024 women working in Amcelle plant in Cumberland, Maryland, 1970-1981	38.2 and 14.3 percent of men and women exposed at the high methylene chloride exposure level (350 to 700 ppm), respectively	Prostate and cervical cancer mortality were elevated in both high and low exposure groups, but not significant. No significant association observed between exposure to methylene chloride and liver or pancreatic cancer in both men and women	Gibbs et al. (1996)	High

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Multiple myeloma	180 cases of multiple myeloma (diagnosed between January 1, 2000 and March 21, 2002; 35-74 years old) and 481 controls (35-74 years old)	Exposure to methylene chloride estimated with job exposure matrix. Individual cumulative exposure scores were calculated by multiplying the midpoint of the intensity (in ppm) by the midpoint of the frequency (in hours/week) by the number of years worked in each exposed job.	When individuals with reported exposure rated as "low confidence" were considered unexposed, a significantly increased risk of multiple myeloma was observed in individuals ever exposed to methylene chloride; OR (95% CI) = 2.0 (1.2 to 3.2). A significant exposure-related trend ($p < 0.05$) was also observed for duration of exposure. A near-significant exposure-related trend ($p=0.06$) was observed for cumulative exposure score with a 10-year lag.	Gold et al. (2010)	High
Cancer	Liver and biliary cancer	Male employees in photographic film support manufacturing (n=1,311), Eastman Kodak Company, Rochester, NY, 1946-1970	Methylene chloride, area and personal air samples	Occupational exposure to methylene chloride was not significantly associated with death from liver or biliary cancer.	Hearne and Pifer (1999)	High
Cancer	Astrocytic brain cancer risk	Men in southern Louisiana, United States, exposed from 1978 - 1980; in northern New Jersey and Philadelphia, Pennsylvania, United States, exposed from 1979 - 1981 (n=620, 300 cases, 320 controls)	Methylene chloride, medium exposure (2)	Chi trend for methylene chloride= 2.08; Exposure significantly associated with astrocytic brain cancer	Heineman et al. (1994)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Prostate cancer mortality	Employees of a cellulose acetate/triacetate fibers plant (n=3211; 2187 men, 1024 women), Cumberland, MD, 1970-1989	Methylene chloride, area and personal air samples taken at a similar plant owned by the same company	High occupational exposure to methylene chloride was significantly positively associated with death from prostate cancer in men with more than 20 years since first exposure. There was also evidence of a non-significant, positive dose-response relationship between methylene chloride exposure and prostate cancer mortality.	Gibbs (1992)	Medium
Cancer	Childhood acute lymphoblastic leukemia	790 mothers interviewed from both case and control groups in Quebec Canada between 1980 and 2000; Children 0-14 yrs old. 848 cases, 916 controls	Methylene chloride exposure to mothers 2 years before pregnancy, and up to birth; Exposure level 0 (baseline), no exposure (none or possible); level 1, some exposure (exposure resulting in concentration x frequency < 4), and level 2, greater exposure (concentration x frequency $\geq$ 4)	Maternal exposure to methylene chloride before or during pregnancy resulted in increased, but non-significant risk of acute lymphoblastic leukemia in children	Infante-Rivard et al. (2005)	High
Cancer	Cholangiocarcinoma	95 proof-printing workers, Osaka, Japan, 1987-2006	Methylene chloride, mean cumulative exposure (ppm-years), 591	Significant increase in cholangiocarcinoma incidence in this sample compared to the general population of Japan. Incidence rate ratios are not significant.	Kumagai et al. (2016)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Cause-specific mortality	1271 textile workers, Rock Hill, South Carolina, 1954-1986	Methylene chloride, 8-hour TWA (ppm) 1700	Significant excess mortality for cancer of the biliary passages & liver; all other cancer SMRs non-significant	Lanes et al. (1990)	Medium
Cancer	Mortality from malignant neoplasms (total; buccal cavity; biliary passages and liver; melanoma; bronchus, trachea and lung; breast; pancreas)	Cellulose fiber production workers (n=1271, Rock Hill, South Carolina)	Methylene chloride in 1977 median of 140, 280, and 475 ppm in three main areas	Methylene chloride was not significantly associated with any mortality; however, SMRs were elevated for biliary passages and liver malignant neoplasms and melanoma.	Lanes et al. (1993)	Medium
Cancer	Lung cancer	Investigation of occupational and environmental causes or respiratory cancers (ICARE) participants population-based case-control study in France 2001-2007 (2274 men cases and 2780 men controls)	Cumulative Exposure Index (CEI) based on self-reported job histories and probability, intensity, and frequency of exposure to methylene chloride based on jobs	Methylene chloride was not significantly associated with lung cancer in men.	Mattei et al. (2014)	Medium
Cancer	All Non-Hodgkin lympma and by Non-Hodgkin lymphoma subtype (i.e,. small lymphocytic, follicular, diffuse, other),	All newly diagnosed cases of Non-Hodgkin lymphomas, chronic lymphocytic leukemia (CLL) during 1991â€“1993 among men and women age 20 to 74 years in 11 areas in Italy	Methylene chloride exposure based on job-specific questionnaires and industrial hygiene experts for level of probability (i.e,. low, medium, high) and intensity of exposure (i.e., very low, low, medium, and high) with durations of less than 15 years and 15 or more years.	Methylene chloride was not significantly associated with non-Hodgkin lymphoma either based on intensity or duration of exposure; however, there was an increase in the risk for small lymphocytic non-Hodgkin lymphoma (borderline significance) with medium/high intensity.	Miligi et al. (2006)	High

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Mycosis fungoides (MF)	100 patients with Mycosis Fungoides and 2846 controls, 35-69 years of age, from Denmark, Sweden, France, Germany, Italy, and Spain, 1995-1997	Occupational exposure to methylene chloride assessed with job exposure matrix	A negative, non-significant association was observed between Mycosis Fungoides and subjects with exposure to methylene chloride >= median of control exposure vs. unexposed subjects	Morales-Suárez-Varela et al. (2013)	High
Cancer	Brain cancer: glioma and meningioma cases	489 glioma cases, 197 meningioma cases, and 799 controls from three USA hospitals in Arizona, Massachusetts and Pennsylvania	Occupational exposure to methylene chloride via self-reported occupational history and industrial hygienist assigned level of exposure	Methylene chloride was not associated with glioma or meningioma	Neta et al. (2012)	High
Cancer	Diagnosis of kidney cancer	General population case-control study of kidney cancer (1217 cases; 1235 controls). Detroit (2002 - 2007) and Chicago (2003).	Job exposure matrix was used to determine years exposed, average weekly exposure and cumulative hours exposed to methylene chloride.	No significant associations observed between exposure to methylene chloride and kidney cancer	Purdue et al. (2016)	High
Cancer	Mortality from breast cancer	Aircraft maintenance workers (n = 14,457; 10,730 men and 3725 women) at Hill Air Force Base (Utah, USA), for at least one year from 1952-1956, and followed up through 2000	Occupational exposure to methylene chloride (yes/no) based on job-exposure matrix; no quantitative assessment available	Positive, non-statistically significant association between breast cancer mortality in females and occupational exposure to methylene chloride compared to no exposure	Radican et al. (2008)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Glioma	Non-farm workers from the Upper Midwest Health Study (798 cases and 1141 controls from Iowa, Michigan, Minnesota, and Wisconsin 1995-1997)	Methylene chloride use (self-reported occupational history through 1992, bibliographic database of published exposure)	Methylene chloride was associated with a significant decrease in gliomas only when including proxy-only interviews and unexposed participants or as ever/never exposure.	Ruder et al. (2013)	High
Cancer	Total lymphoma, HL, B-NHL, T-NHL, B-NHL subentities (DLBCL, FL, CLL, multiple myeloma, marginal zone lymphoma)	710 participating cases (matched to 710 controls) with malignant lymphoma among men and women aged 18 to 80 years in 6 regions in Germany	Cumulative occupational exposure to methylene chloride [ppm*years] based on intensity, the frequency, and duration of methylene chloride exposure (0, >0 to <26.3, >26.3 to <=175, >175 ppm*years)	Methylene chloride was not significantly associated with malignant lymphoma; however, exposure to >175 ppm*yrs was associated with an increased (non-significant) risk of malignant lymphoma, B-cell non-Hodgkin's lymphoma and T-cell non-Hodgkin's lymphoma.	Seidler et al. (2007)	High
Cancer	Rectal cancer incidence	Greater Montreal metropolitan area. Case-control study of occupationally-exposed men aged 35 to 70 year old (4263 cases, 533 population controls; also hospital and cancer controls).	Any or substantial exposure	The ORs for any and substantial exposure to methylene chloride exposure and rectal cancer were significantly elevated at the p=0.1 level (one-sided).	Siemiatycki (1991) [a]	Medium
Cancer	Brain and other nervous system cancer mortality	National Institute for Occupational Safety and Health (NIOSH) Cohort, 34494 workers at NY microelectronics and business machine facility, 2009, 52-65yrs	Cumulative methylene chloride exposure score based on department-exposure matrix	Methylene chloride was not significantly associated with mortality from brain or other nervous system cancers.	Silver et al. (2014)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Acute myeloid lymphoma	Cases of acute myeloid leukemia (n=14,337) diagnosed between 1961 and 2005, and controls (n=71,027) matched by age, sex, and country identified from the Nordic Occupational Cancer Study cohort	Cumulative methylene chloride exposure estimated using job exposure matrix, Median (ppm-yr) 9.9	No significant increase in acute myeloid leukemia risk was observed with low, moderate, or high exposure to methylene chloride, compared to referent group, when hazard ratios were calculated using a 10-year lag (p-value = 0.43). Findings remained statistically nonsignificant when analysis was stratified by sex or age	Talibov et al. (2014)	High
Cancer	All malignant neoplasms mortality	Male employees from Brantham photographic film base, United Kingdom, n=1346 men (1034 exposed, 312 unexposed) exposed from 1960 - 1988	Methylene chloride, cumulative exposure, median (1000 ppm-years) 36.0	Methylene chloride exposure was not significantly associated with mortality from: all malignant neoplasms (p-value = 0.60); brain cancer (p-value=0.9); respiratory cancer (p-value=0.90); all cancers, excluding respiratory cancers (p-value=0.62); No Cox regression coefficients estimating relative risk were statistically evaluated	Tomenson (2011)	Medium
Cancer	Lung cancer	Lung cancer cases and randomly selected population-based controls frequency matched by sex and age in Montreal Canada	Methylene chloride exposure (any or substantial) was assessed by a team of industrial chemists and hygienists based on self-reported job histories.	No significant association observed between any or substantial exposure to Methylene chloride and lung cancer in the pooled analysis (or either study individually)	Vizcaya et al. (2013)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Non-Hodgkin Lymphoma	601 cases, 717 controls (all women) in Connecticut, 1996-2000, 21-84 years	Never, low, or medium-high probability of exposure to methylene chloride	Non-Hodgkin lymphoma was associated with low probability of exposure to methylene chloride, but not with medium-high probability of exposure to methylene chloride	Wang et al. (2009)	Medium
Cardiovascular	Birth defects	Offspring of 60,613 case-mothers and 244,927 control-mothers in United States (Texas)	Exposed or non-exposed; exposure risk estimates based on proximity of maternal residence to methylene chloride emissions	A weak negative association was observed between exposure to methylene chloride and septal heart defects	Brender et al. (2014)	Medium
Cardiovascular	Cause-specific mortality	1271 textile workers, Rock Hill, South Carolina, 1954-1986	Methylene chloride, 8-hour TWA (ppm) 1700	Significant excess mortality for accidents and cancer of the biliary passages & liver; all other SMRs non-significant	Lanes et al. (1990)	Medium
Cardiovascular	Mortality associated with cerebrovascular disease, ischemic heart disease	Cellulose fiber production workers (n=1271, Rock Hill, South Carolina)	Methylene chloride in 1977 median of 140, 280, and 475 ppm in three main areas	Methylene chloride was not significantly associated with cardiovascular-related mortality.	Lanes et al. (1993)	Medium
Cardiovascular	Chest discomfort with exercise	Adult employees of a triacetate fibers plant (n=150), 1984-1986, Rock Hill, SC, and matched non-exposed controls (n=260)	Methylene chloride, mean 475 ppm (8-hour time weighted average), for longer than 10 years	Occupational exposure to methylene chloride for more than 10 years did not result in significant differences in self-reported cardiovascular symptoms when comparing exposed to unexposed workers	Soden (1993)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cardiovascular	Ischemic heart disease mortality	Male employees from Brantham photographic film base, United Kingdom, n=1346 men (1034 exposed, 312 unexposed) exposed from 1960 - 1988	Methylene chloride, cumulative exposure, median (1000 ppm-years) 36.0	Methylene chloride exposure was not significantly associated with ischemic heart disease mortality (p-value=0.24); No Cox regression coefficients estimating relative risk were statistically evaluated	Tomenson (2011)	Medium
Growth (early life) and Development	Low birthweight	91,302 live births from 1976 to 1987 in Monroe County, New York among residents living near the Eastman Kodak Company	Kodak Air Management Program (KAMP) air dispersion modeling system: high (50 ug/m), moderate (25 ug/m), low (10 ug/m), and none	A significant association between exposure to methylene chloride at all three levels and low birthweight was not observed	Bell et al. (1991)	High
Growth (early life) and Development	Birth defects	Offspring of 60,613 case-mothers and 244,927 control-mothers in United States (Texas)	Exposed or non-exposed; exposure risk estimates based on proximity of maternal residence to methylene chloride emissions	No significant association was observed between exposure to methylene chloride and oral clefts	Brender et al. (2014)	Medium
Growth (early life) and Development	Spontaneous abortion	44 female pharmaceutical factory workers in Finland who had spontaneous abortions while employed (cases), 130 female pharmaceutical factory workers in Finland who had normal births while employed (controls)	Methylene chloride exposure based on a questionnaire sent to factory physicians or their nurses	A positive, borderline non-significant association was observed between occupational exposure to methylene chloride and spontaneous abortion	Taskinen et al. (1986)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Hematological and Immune	Primary Sjogren syndrome	Cases (n= 175) from three University Hospitals and matched controls (n=350) (2010-2013)	Occupational methylene chloride exposure based on self-reported occupational histories, expert judgement of industrial hygienists and occupational practitioners, as well as the French JEM (used more for the chlorinated solvents)	Significant increase in risk for Sjogren' syndrome with occupational methylene chloride exposure; OR was increased with high final cumulative exposure, but was not significant.	Chaigne et al. (2015)	Medium
Hematological and Immune	Total bilirubin, red cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, carboxyhemoglobin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and albumin.	266 exposed and 251 unexposed employees at two fiber production plants in North Carolina and Virginia	8 hour time-weighted average dichloromethane concentrations: unexposed, 60 and 140 ppm , 280 ppm, and 475 ppm	There was a statistical increase in aspartate aminotransferase with intensity of methylene chloride exposure among white women in the exposed group, but not among the white men, or nonwhites of either sex.	Ott et al. (1983)	Medium
Hematological and Immune	Hematocrit	Adult employees of a triacetate fibers plant (n=150), 1984-1986, Rock Hill, SC, and matched non-exposed controls (n=260)	Methylene chloride, mean 475 ppm (8-hour time weighted average), for longer than 10 years	Occupational exposure to methylene chloride for more than 10 years did not result in a significant difference in hematocrit when comparing exposed to unexposed workers	Soden (1993),	Medium
Hepatic	Serum gamma glutamyl transferase (GGT), serum total bilirubin, serum aspartate amino-transferase (AST), serum alanine aminotransferase (ALT)	854 workers in a plastic polymer facility in Indiana, USA. 1985	Methylene chloride; non-exposed group (>1.0 ppm), low-exposed group (3.3 ppm), med-exposed group (10.9 ppm), high-exposed group (49.0 ppm)	Serum gamma glutamyl transferase (GGT), serum total bilirubin, serum aspartate amino-transferase (AST), serum alanine aminotransferase (ALT)	General Electric Co (1990) [a]	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Hepatic	Total bilirubin, red cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, carboxyhemoglobin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and albumin.	266 exposed and 251 unexposed employees at two fiber production plants in North Carolina and Virginia	8 hour time-weighted average dichloromethane concentrations: unexposed, 60 and 140 ppm , 280 ppm, and 475 ppm	A consistent positively significant association between total bilirubin and methylene chloride exposure was found in white men and women, in non-white women, but not in non-white men.	Ott et al. (1983)	Medium
Hepatic	Mortality from cirrhosis and other chronic liver disease	National Institute for Occupational Safety and Health (NIOSH) Cohort, 34494 workers at NY microelectronics and business machine facility, 2009, 52-65yrs	Cumulative methylene chloride exposure score based on department-exposure matrix	Methylene chloride exposure was not significantly associated with mortality from diseases of the liver	Silver et al. (2014)	Medium
Hepatic	Total bilirubin	Adult employees of a triacetate fibers plant (n=150), 1984-1986, Rock Hill, SC, and matched non-exposed controls (n=260)	Methylene chloride, mean 475 ppm (8-hour time weighted average), for longer than 10 years	Occupational exposure to methylene chloride for more than 10 years did not result in significant differences in markers of hepatic injury when comparing exposed to unexposed workers	Soden (1993)	Medium
Mortality	Cause-specific, non-cancer mortality	1271 textile workers, Rock Hill, South Carolina, 1954-1986	Methylene chloride, 8-hour TWA (ppm) 1700	Significant excess mortality for accidents	Lanes et al. (1990)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Neurological/ Behavior	Birth defects	Offspring of 60,613 case-mothers and 244,927 control-mothers in United States (Texas)	Exposed or non-exposed; exposure risk estimates based on proximity of maternal residence to methylene chloride emissions	No significant association was observed between exposure to methylene chloride and neural tube defects	Brender et al. (2014)	Medium
Neurological/ Behavior	Dizziness/vertigo	854 workers in a plastic polymer facility in Indiana, USA. 1985	Methylene chloride; non-exposed group (>1.0 ppm), low-exposed group (3.3 ppm), med-exposed group (10.9 ppm), high-exposed group (49.0 ppm).	There was significant trend for increased dizziness/vertigo in the methylene chloride exposed groups.	General Electric Co (1990)	Medium
Neurological/ Behavior	Autism spectrum disorders	3,137 children in North Carolina (1,931 total, 201 cases) and West Virginia (1,246 total, 173 cases), 2000-2004, 8 years old	1996 modeled methylene chloride in ambient air, geometric mean concentration: 539.8 (NC) and 202..3 (WV) ng/m^3	A positive, non-significant association between ambient methylene chloride (80th vs. 20th percentile) and autism spectrum disorder	Kalkbrenner et al. (2010) [a]	High
Neurological/ Behavior	Grip strength, motor speed, reaction time, visual memory, verbal memory, attention, spatial ability	25 retired mechanics (mean age 67.5 yrs) who had worked between 1970 and 1984 for a single, unspecified airline; location not clearly specified but appears to be California	Mean time-weighted averages of methylene chloride (in air) ranged from 82 to 236 ppm	No statistically significant differences in composite scores between the exposed and unexposed groups	Lash et al. (1991)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Neurological/ Behavior	Autism Spectrum Disorder	Nurses' Health Study II children (US; 325 cases/22101 controls).	Methylene chloride air concentrations at mother's location at birth; Mean: 0.4 ug/m3	Methylene chloride exposure was not significantly associated with Autism Spectrum Disorder. Although it was close to significant (p=0.05 for Q1 compared to Q5, there was no trend over quintiles (p for trend =0.08). When separated by sex, there was a significant increase when comparing Q5 to Q1 (p=0.03) in boys, but not girls.	Roberts et al. (2013)	High
Neurological/ Behavior	Diseases of the nervous system mortality	National Institute for Occupational Safety and Health (NIOSH) Cohort, 34494 workers at NY microelectronics and business machine facility, 2009, 52-65yrs	Cumulative methylene chloride exposure score based on department-exposure matrix	Methylene chloride exposure was not significantly associated with mortality from diseases of the nervous system.	(Silver et al., 2014)	Medium
Neurological/ Behavior	Recurring severe headaches	Adult employees of a triacetate fibers plant (n=150), 1984-1986, Rock Hill, SC, and matched non-exposed controls (n=260)	Methylene chloride, mean 475 ppm (8-hour time weighted average), for longer than 10 years	Occupational exposure to methylene chloride for more than 10 years did not result in significant differences in self-reported neurological symptoms when comparing exposed to unexposed workers	Soden (1993)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Neurological/ Behavior	Autism spectrum disorder diagnosis with Social Communication Questionnaire score of 15+	217 cases, 224 interview controls, 4856 birth certificate controls, children born from 2005-2009 in 6 counties of Pennsylvania	Methylene chloride exposure (239-273 ng/m3) during gestation estimated with National Air Toxics Assessment 2005 model from addresses at birth	Methylene chloride positively associated with Autism Spectrum Disorder diagnosis relative to birth certificate controls, significant for fourth quartile compared to first quartile of exposure for singleton births, non-significant for all births combined.	Talbott et al. (2015)	Medium
Neurological/ Behavior	Autism diagnosis	Children (n=641 cases) born to mothers living within 5 km of air pollutant monitoring stations in Los Angeles County during pregnancy, 1995-2006, monitored until age 6	Maternal ambient Methylene chloride exposure during entire pregnancy	A positive, non-significant association was observed between autistic disorder by age 6 years and maternal ambient methylene chloride exposure	von Ehrenstein et al. (2014)	High
Neurological/ Behavior	Autism Spectrum Disorder	Children born 1994 followed for 9 years, 284 cases and 657 birth month- and sex-matched control births from the San Francisco area	1996 EPA estimated annual average concentrations of Methylene chloride on the census tract level, mean (SD) exposure for cases: 0.68 (0.48 ug/m3)	Positive association observed for 3rd (significant) and 4th (not significant) quartiles of methylene chloride exposure compared to those exposed to the median exposure level or less.	Windham et al. (2006) [a]	Medium
Reproductive	Spontaneous abortion	Female pharmaceutical factory workers in Finland. 44 cases, 130 controls, 1973-1981	Methylene chloride exposure based on a questionnaire sent to factory physicians or their nurses	Borderline significant positive association between occupational methylene chloride exposure and spontaneous abortion	Taskinen et al. (1986)	Low

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Mortality	Accidents	1271 textile workers, Rock Hill, South Carolina, 1954-1986	Methylene chloride, 8-hour TWA (ppm) 1700	Significant excess mortality from accidents	Lanes et al. (1990)	Medium
Respiratory	Mortality from nonmalignant respiratory disease	Cellulose fiber production workers (n=1271, Rock Hill, South Carolina)	Methylene chloride in 1977 median of 140, 280, and 475 ppm in three main areas	SMR not elevated for non-malignant respiratory disease	Lanes et al. (1993)	Medium
Respiratory	Mortality from bronchitis	Aircraft maintenance workers (n = 14,457; 10,730 men and 3725 women) at Hill Air Force Base (Utah, USA), for at least one year from 1952-1956, and followed up through 2000	Occupational exposure to methylene chloride (yes/no) based on job-exposure matrix; no quantitative assessment available	Positive, statistically significant, association between mortality from bronchitis in males and occupational exposure to methylene chloride compared to no exposure	Radican et al. (2008)	Medium
Respiratory	Mortality due to influenza and pneumonia	Employees of a cellulose acetate/triacetate fibers plant (n=3211; 2187 men, 1024 women), Cumberland, MD, 1970-1989	Methylene chloride, area and personal air samples taken at a similar plant owned by the same company	High occupational exposure to methylene chloride had a non-significant positive association with death from influenza and pneumonia men with more than 20 years since first exposure	Gibbs (1992)	Medium
Respiratory	Mortality due to respiratory illness	Male employees in photographic film support manufacturing (n=1,311), Eastman Kodak Company, Rochester, NY, 1946-1970	Methylene chloride, area and personal air samples	Occupational exposure to methylene chloride was not significantly associated with mortality from respiratory diseases	Hearne and Pifer (1999)	High

[a] Not identified in U.S. EPA (2011); Identified through backwards searching from other sources or from TSCA submissions.

[b] Other mortality-related results are listed under the specific target organ or under cancer.

2 Data Extraction Tables for Non-Cancer Endpoints From Animal Toxicity Studies

Noncancer endpoints/studies are divided into separate tables: (1) acute and short-term studies; (2) subchronic and chronic studies; and (3) reproductive and developmental studies (and related effects from repeat-dose studies). They are divided by endpoint. Within each endpoint, data from the inhalation exposure route is presented before the oral exposure route. Oral data are included because they are considered for the weight of the scientific evidence.

The LOAELs and NOAELs are presented for each endpoint and study that measured that endpoint to compare across toxicity studies. For studies cited in previous assessments, the NOAELs/LOAELs cited within that assessment are presented in the tables in this appendix. For newly-obtained studies, EPA reports any NOAELs and LOAELs chosen by the study authors (if available); if EPA disagreed with the NOAEL/LOAEL, a separate value is also presented below. The NOAELs/LOAELS are presented from lowest to highest for each endpoint and exposure route.

2.1 Acute and Short-term Animal Toxicity Studies [a]

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day)	Effect	Reference	Data Quality Evaluation
Body Weight	Short-term	Rat M/F (5/sex/group)	Oral	0, 100, 300, 600, 1200 mg/kg-bw/day	7 days/week for 14 days	Not Reported	LOAEL = 100 mg/kg-bw/day	↓ body weight (M)	General Electric (1976b)	Medium (2.0)
Gastrointestinal	Short-term	Rat Other Both (5)	Oral	0, 100, 300, 600, 1200 mg/kg-bw/day	7 days/week for 14 days	Not Reported	NOAEL = 300 mg/kg-bw/day	Blood/ congestion in intestines and stomach (hemorrhage) of dead animals	General Electric (1976b)	Medium (2.0)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day)	Effect	Reference	Data Quality Evaluation
Hepatic	Acute/ Short-term	Rat, Fischer 344	Inhalation, vapor, whole body	0, 1910, 3910 ppm (1 day); 0, 1950, 3870 ppm (10 day)	1 or 10 days; 6 hrs/day	Not Reported	LOAEL = 1950 ppm (10 days)	1 day: no effects 10 days: ↑ # eosinophils in centrilobular cells	Shell Oil (1986)	High (1.5)
Hepatic	Acute/ Short-term	Mouse, B6C3F1	Inhalation, vapor, whole body	0, 2010, 3710 ppm (1 day); 0, 1990, 3960 ppm (10 day)	1 or 10 days; 6 hrs/day	Not Reported	LOAEL = 1990 ppm (10 days)	1 day: ↓ liver wt at 3710 ppm 10 days: ↑ liver wt at both concentrations	Shell Oil (1986)	High (1.5)
Immune	Acute/ Short-term	Mouse, CD-1	Inhalation	Acute: 0, 52, 95 ppm Short-term: 0, 51 ppm	Acute = 3 hrs Short-term = 3 hrs/day for 5 days	Not Reported	NOAEL = 52 ppm	↑ mortality (12.2%; $p \leq 0.01$) from *S. zooepidemicus*; ↓ bacteriocidal activity (by 12%; $p \leq 0.001$)	Aranyi et al. (1986)	Medium (1.8)
Immune	Short-term	Rat, Sprague-Dawley	Inhalation	0, 5187 ppm	6 hrs/day, 5 days/wk for 28 days	Not Reported	NOAEL = 5187 ppm	No change in IgM response after injection with sheep red blood cells [↓ spleen wts]	Warbrick et al. (2003)	High (1.3)
Neurological	Short-term pre-test followed by acute test	Rat, F344, M, 16 (pretest) 8/group (during test)	Inhalation	Pre-test: 2000 ppm Test: 0, 2000 ppm	Pre-test: 6 hrds/day; 3 days; Test: 2.5-3.5 hrs	Not reported	LOAEL = 2000 ppm	Changes in somatosensory evoked potentials (cerebellum/ sensory cortex); reduced EEG power [acute]	Dow (1988)	High (1.5)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day)	Effect	Reference	Data Quality Evaluation
Neurological [clinical signs]	Acute/ Short-term	Rat, Fischer 344	Inhalation, vapor, whole body	0, 1910, 3910 ppm (1 day); 0, 1950, 3870 ppm (10 day)	1 or 10 days; 6 hrs/day	Not Reported	Not Determined	10 days: subdued; reduced response to noise stimulus	Shell Oil (1986)	High (1.5)
Neurological [clinical signs]	Acute/ Short-term	Mouse, B6C3F1	Inhalation, vapor, whole body	0, 2010, 3710 ppm (1 day); 0, 1990, 3960 ppm (10 day)	1 or 10 days; 6 hrs/day	Not Reported	Not Determined	10 days: subdued at 1990 ppm during last hr of exposure/day; Hyperactive first 3 hrs at 3960 ppm and then subdued later during exposure	Shell Oil (1986)	High (1.5)
Neurological	Acute	Rat, F344, F (n=8/group)	Oral, gavage	0, 101, 337, 1012 or 1889 mg/kg	Single dose (evaluated 4 and 24 hours after dosing)		NOAEL= 337 (F)	Functional observational battery (FOB) neuro-muscular and sensorimotor parameters significantly different from controls	Moser et al. (1995)	High (1.3)
Neurological	Short-term	Rat, F344, F (n=8/group)	Oral, gavage	0, 34, 101, 337, 1012 or 1889 mg/kg-day	14 days		NOAEL= 101 (F)	Alterations in FOB from day 4 (autonomic, neuro-muscular, sensorimotor, excitability)	Moser et al. (1995)	High (1.3)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day)	Effect	Reference	Data Quality Evaluation
Neurological	Short-term	Rat Other Both (5)	Oral	0, 100, 300, 600, 1200 mg/kg-bw/day	7 days/ week for 14 days	Not Reported	NOAEL = 100 mg/kg-bw/day	Decreased general activity	General Electric (1976b)	Medium (2.0)
Respiratory	Short-term	Rat Other Both (5)	Oral	0, 100, 300, 600, 1200 mg/kg-bw/day	7 days/ week for 14 days	Not Reported	NOAEL = 300 mg/kg-bw/day	Gross abnormalities in the lungs (pulmonary congestion) of animals that died during the study.	General Electric (1976b)	Medium (2.0)
Respiratory	Acute/ Short-term	Rat, Fischer 344	Inhalation, vapor, whole body	0, 1910, 3910 ppm (1 day); 0, 1950, 3870 ppm (10 day)	1 or 10 days; 6 hrs/day	Not Reported	NOAEL = 3870 ppm (10 days)	No effects on lung	Shell Oil (1986)	High (1.5)
Respiratory	Acute/ Short-term	Mouse, B6C3F1	Inhalation, vapor, whole body	0, 2010, 3710 ppm (1 day); 0, 1990, 3960 ppm (10 day)	1 or 10 days; 6 hrs/day	Not Reported	Not Determined	1 day: Selective vacuolation and pyknosis of Clara cells in bronchiolar epithelium 10 days: No effects	Shell Oil (1986)	High (1.5)
Multiple organs	Short-term	Dog M/F (1/sex/dose)	Oral (gavage)	0, 25, 75, 150, 300 mg/kg-bw/day	7 days/week for 14 days	Not reported	Not Determined	Congestion – no clear dose-response; Cyst in brain (at lowest dose)	General Electric (1976a)	Low (downgraded)

[a]Acute = ≤ 1 day; Short-term = > 1 day - ≤ 30 days

2.2 Subchronic and Chronic Animal Toxicity Studies [a]

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Mortality	Chronic	Rat, Sprague Dawley, M/F (n~190/dose)	Inhalation, vapor, whole body	0, 1755, 5264 or 12,283 mg/m^3 (0, 500, 1500 or 3500 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL = 5264 mg/m^3 (F)	↑mortality	Burek et al. (1984)	High (1.5)
Mortality	Subchronic	Rat, F344, M/F (n=20/group)	Inhalation, vapor, whole body	0, 1843, 3685, 7371, 14,742 or 29,483 mg/m^3 (0, 525, 1050, 2100, 4200 or 8400 ppm)	6 hours/day, 5 days/week for 13 weeks	NA	NOAEL= 14,742 mg/m^3	1/10 (M) and 1/10 (F) died	NTP (1986)	High (1.3)
Mortality	Subchronic	Mouse, B6C3F1, M/F (n=20/group)	Inhalation, vapor, whole body	0, 1843, 3685, 7371, 14,742 or 29,483 mg/m^3 (0, 525, 1050, 2100, 4200 or 8400 ppm)	6 hours/day, 5 days/week for 13 weeks	NA	NOAEL= 14,742 mg/m^3	4/10 (M) and 2/10 (F) died	NTP (1986)	High (1.3)
Mortality	Chronic	Rat, Sprague Dawley, M/F (n=100/dose)	Oral, gavage	0, 100 or 500 mg/kg-day	4-5 days/week, up to 64 weeks	NA	NOAEL = 100 mg/kg-bw/day (M)	↑ mortality (M/F) (M: stat. signif.) led to study termination at 64 weeks	Maltoni et al. (1988)	Medium (1.9)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Mortality	Chronic	Mouse, Swiss, M/F (n=100/treated group; 120/ control group)	Oral, gavage	0, 100 or 500 mg/kg-bw/day	4-5 days/ week, up to 64 weeks	NA	NOAEL = 100 (M/F)	↑ Mortality (M/F: stat. signif.) led to study termination at 64 weeks	Maltoni et al. (1988)	Medium (1.9)
Body weight	Subchronic	Rat, F344, M/F (n=20/group)	Inhalation, vapor, whole body	0, 1843, 3685, 7371, 14,742 or 29,483 mg/m^3 (0, 525, 1050, 2100, 4200 or 8400 ppm)	6 hours/day, 5 days/week for 13 weeks	NA	NOAEL= 14,742	↓Body weight (M: 23%) (F: 11%)	NTP (1986)	High (1.3)
Body Weight	Subchronic	Dog/Beagle (M/F) (4/sex/group)	Oral	0, 12.5, 50, 200 mg/kg-bw/day	90 days	Not Reported	NOAEL = 200 mg/kg-bw/day	No changes in body weight	General Electric (1976)	High (1.5)
Body weight	Develop-mental	Rat, F344, F (n=17-21/group)	Oral, gavage	0, 337.5 or 450 mg/kg-bw/day	Gestation days 6-19	NA	NOAEL= 337.5 (F)	↓Maternal weight gain	Narotsky and Kavlock (1995)	High (1.4)
Gastro-intestinal	Chronic	Mouse, B6C3F1, M/F (n=100/group)	Inhalation, vapor, whole body	0, 7019 or 14,038 mg/m^3 (0, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL=7019 (M/F)	Stomach dilation (M/F)	NTP (1986)	High (1.3)
Gastrointestinal	Subchronic	Dog/Beagle (M/F) (4/sex/group)	Oral	0, 12.5, 50, 200 mg/kg-bw/day	90 days	Not Reported	NOAEL = 200 mg/kg-bw/day	No effects	General Electric (1976)	High (1.5)
Immune	Chronic	Rat, F344, M/F (n=100/group)	Inhalation, vapor, whole body	0, 3510, 7019 or 14,038 mg/m^3 (0, 1000, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL= 3510 (M)	Splenic fibrosis	NTP (1986)	High (1.3)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Immune	Chronic	Mouse, B6C3F1, M/F (n=100/group)	Inhalation, vapor, whole body	0, 7019 or 14,038 mg/m^3 (0, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL= 7019 (M)	Splenic follicular atrophy	NTP (1986)	High (1.3)
Hepatic	Chronic	Rat, F344, M/F (n=100/group)	Inhalation, vapor, whole body	0, 3510, 7019 or 14,038 mg/m^3 (0, 1000, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	LOAEL= 3510 (M/F)	Hepatocyte vacuolation and necrosis, hemosiderosis in liver (M/F); hepatocyte-megaly (F)	NTP (1986)	High (1.3)
Hepatic	Chronic	Rat, Sprague-Dawley, M/F (n~190/group)	Inhalation, vapor, whole body	0, 1755, 5264 or 12,283 mg/m^3 (0, 500, 1500 or 3500 ppm)	6 hours/day, 5 days/week for 2 years	NA	LOAEL= 1755 (M/F)	Hepatocyte vacuolation (M/F); multinucleated hepatocytes (F)	Burek (1984)	High (1.5)
Hepatic	Chronic	Rat, Sprague Dawley, M/F (n=180/group)	Inhalation, vapor, whole body	0, 176, 702 or 1755 mg/m^3 (0, 50, 200 or 500 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL= 702 (F)	Hepatic lipid vacuolation and multinucleated hepatocytes	Nitschke (1988)	High (1.3)
Hepatic	Chronic	Rat, F344/DuCrj	Inhalation, vapor, whole body	0, 3510, 7019 or 14,038 mg/m^3 (0, 1000, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	LOAEL = 3510 mg/m3 (F)	Increased basophilic foci and increased abs/rel liver wt ($p < 0.01$)	Aiso et al. (2014)	High (1.1)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Hepatic	Chronic	Mouse, B6C3F1, M/F (n=100/group)	Inhalation, vapor, whole body	0, 7019 or 14,038 mg/m3 (0, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	LOAEL = 7019 (F)	Hepatocyte degeneration; (↑ hepatocellular adenoma or carcinoma)	NTP (1986)	High (1.3)
Hepatic	Chronic	Mouse, Crj: BDF1	Inhalation, vapor, whole body	0, 3510, 7019 or 14,038 mg/m^3 (0, 1000, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL = 7019 mg/m3 (F)	Increased abs/rel liver wt ($p < 0.01$, < 0.05); non-ss increase in basophilic foci (incidences of 1,1,3,5)	Aiso et al. (2014)	High (1.1)
Hepatic	Subchronic	Mouse, B6C3F1, M/F (n=20/group)	Inhalation, vapor, whole body	0, 1843, 3685, 7371, 14,742 or 29,483 mg/m^3 (0, 525, 1050, 2100, 4200 or 8400 ppm)	6 hours/day, 5 days/week for 13 weeks	NA	NOAEL= 7371 (F); NOAEL = 14,742 (M)	Hepatocyte centrilobular degeneration	NTP (1986)	High (1.3)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Hepatic	Chronic	Rat, F344, M/F (n=170/group + 270 controls)	Oral, drinking water	0, 6, 52, 125 or 235 mg/kg-day (M); 0, 6, 58, 136 or 263 mg/kg-day (F)	104 weeks	NA	NOAEL= 6 (M/F)	↑ Non-neoplastic Foci/areas of alteration (M/F); ↑ incidence of neoplastic nodules; fatty liver changes (incidence N/A)	Serota et al. (1986a)	High (1.3)
Hepatic	Subchronic	Rat, F344, M/F (n=30/group)	Oral, drinking water	0, 166, 420 or 1200 mg/kg-day (M); 0, 209, 607 or 1469 mg/kg-day (F)	90 days	NA	LOAEL= 166 (M); LOAEL = 209 (F)	Hepatic vacuolation (generalized, centrilobular, or periportal)	Kirschman et al. (1986)	Low (2.5)
Hepatic	Chronic	Mouse, B6C3F1, M/F (n=125, 200, 100, 100 and 125 [M]; n=100, 100, 50, 50 and 50 [F])	Oral, drinking water	0, 61, 124, 177 or 234 mg/kg-day (M); 0, 59, 118, 172 or 238 mg/kg-day (F)	104 weeks	NA	NOAEL= 185 (M/F)	Some evidence of fatty liver; marginal increase in the Oil Red-O-positive material in the liver	Hazleton Labs (1983)	Medium (1.7)
Hepatic	Subchronic	Mouse, B6C3F1, M/F (n=30/group)	Oral, drinking water	0, 226, 587 or 1911 mg/kg-day (M); 0, 231, 586 or 2030 mg/kg-day (F)	90 days	NA	NOAEL= 226 (M)	Hepatic vacuolation (increased severity of centrilobular fatty change)	Kirschman (1986)	Low (2.5)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Hepatic	Subchronic	Dog/Beagle (M/F) (4/sex/ group)	Oral	0, 12.5, 50, 200 mg/kg-bw/day	90 days	Not Reported	NOAEL = 200 mg/kg-bw/day	No changes in clinical chemistry, gross pathology, organ weight, or histopathological lesions	General Electric (1976)	High (1.5)
Neurological	Subchronic	Dog/Beagle (M/F) (4/sex/ group)	Oral	0, 12.5, 50, 200 mg/kg-bw/day	90 days	Not Reported	NOAEL = 200 mg/kg-bw/day	No changes in clinical chemistry, gross pathology, organ weight, or histopathological lesions	General Electric (1976)	High (1.5)
Renal	Chronic	Rat, F344, M/F (n=100/group)	Inhalation, vapor, whole body	0, 3510, 7019 or 14,038 mg/m3 (0, 1000, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL= 3510 (M); NOAEL = 7019 (F)	Renal tubular degeneration	NTP (1986) Mennear (1988)	High (1.3)
Renal	Chronic	Mouse, B6C3F1, M/F (n=100/group)	Inhalation, vapor, whole body	0, 7019 or 14,038 mg/m3 (0, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	LOAEL= 7019 (F); NOAEL = 7019 (M)	Renal tubule casts	NTP (1986)	High (1.3)
Respiratory	Chronic	Rat, F344, M/F (n=100/group)	Inhalation, vapor, whole body	0, 3510, 7019 or 14,038 mg/m3 (0, 1000, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NA	NOAEL= 7019 (F)	Nasal cavity squamous metaplasia	NTP (1986)	High (1.3)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL reported by study authors	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Respiratory	Subchronic	Rat, F344, M/F (n=20/group)	Inhalation, vapor, whole body	0, 1843, 3685, 7371, 14,742 or 29,483 mg/m3 (0, 525, 1050, 2100, 4200 or 8400 ppm)	6 hours/day, 5 days/week for 13 weeks	NA	NOAEL= 14,742 (M/F)	Foreign body pneumonia (focal accumulation of mononuclear and multinucleated inflammatory cells)	NTP (1986)	High (1.3)
Respiratory	Subchronic	Mouse, B6C3F1, M/F (n=20/group)	Inhalation, vapor, whole body	0, 1843, 3685, 7371, 14,742 or 29,483 mg/m3 (0, 525, 1050, 2100, 4200 or 8400 ppm)	6 hours/day, 5 days/week for 13 weeks	NA	NOAEL= 29,483 (M/F)	No nonneoplastic pulmonary lesions	NTP (1986)	High (1.3)

[a] Subchronic: > 30 - ≤ 90 days; Chronic = > 90 days

2.3 Reproductive and Developmental Outcomes from Animal Toxicity Studies

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Body weight	Developmental	Rat, F344, F (n=17-21/group)	Oral, gavage	0, 337.5 or 450 mg/kg-bw/day	Gestation days 6-19	NOAEL= 337.5 (F)	↓Maternal weight gain	Narotsky and Kavlock (1995)	High (1.4)
Develop-mental	Reproductive	Rat, Charles River, M/F (n=20/group)	Oral, gavage	0, 25, 75 or 225 mg/kg-bw/day	90 days before mating (10 days between last exposure and mating period)	NOAEL= 225	No effects on pup survival, F1 body weight, hematology, or clinical chemistry (up to 90 days of age), or histology of tissues from F1 offspring	General Electric (1976)	High (1.5)
Develop-mental	Developmental	Rat, F344, F (n=17-21/group)	Oral, gavage	0, 337.5 or 450 mg/kg-day	Gestation days 6-19	NOAEL= 450	No effect on pup survival, resorptions or pup weight	Narotsky and Kavlock (1995)	High (1.4)
Repro-ductive	Reproductive	Rat, Charles River, M/F (n=20/group)	Oral, gavage	0, 25, 75 or 225 mg/kg	90 days before mating; F1 offspring received same treatment as parents for 90 days	NOAEL= 225 (M/F)	No effects on fertility index or number of pups per litter	General Electric (1976)	High (1.5)

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	NOAEL/ LOAEL (mg/m3 or mg/kg-day) (Sex)	Effect	Reference	Data Quality Evaluation
Repro-ductive	Developmental	Rat, F344, F (n=17-21/group)	Oral, gavage	0, 337.5 or 450 mg/kg-day	Gestation days 6-19	NOAEL= 450 (M/F)	No effect on resorption rate, number of live litters, implants or live pups	Narotsky (1995)	High (1.4)
Repro-ductive	Reproductive	Mouse, Swiss Webster, M	Inhalation, vapor, whole body	0, 103, 144, 212 ppm	2 hrs/day, 5 days/week for 6 weeks; males then mated with unexposed females	NOAEL = 103 ppm	↓ fertility (80% vs. 95%) (stat. sig. by one test but not a second; see U.S. EPA (2011)	Raje et al. (1988)	Medium (2.0)
Repro-ductive	Chronic	Mouse, B6C3F1, M/F (n=100/group)	Inhalation, vapor, whole body	0, 7019 or 14,038 mg/m3 (0, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	NOAEL= 7019 (M)	Testicular atrophy	NTP (1986)	High (1.3)
Repro-ductive	Chronic	Mouse, B6C3F1, M/F (n=100/group)	Inhalation, vapor, whole body	0, 7019 or 14,038 mg/m3 (0, 2000 or 4000 ppm)	6 hours/day, 5 days/week for 2 years	LOAEL= 7019 (F)	Ovarian atrophy	NTP (1986)	High (1.3)

3 Data Extraction Tables for Animal Cancer Bioassays

The following tables focus on liver, lung and mammary tumors and other statistically significantly increased tumor types observed in animal cancer bioassays.

3.1 Liver Tumor Data from Cancer Bioassays

Reference	Strain and Species	Exposure route	Sex	Exposure levels	Tumor type	Significant dose-related trend	Significant pairwise comparison	Exposure level with significant increase	Data Quality Evaluation
NTP (1986)	B6C3F1 mouse	Inhalation	M	0, 2000, 4000 ppm	Hepatocellular adenoma or carcinoma	✓	✓	4000 ppm	High (1.3)
			F		Hepatocellular adenoma or carcinoma	✓	✓	≥ 2000 ppm	
Aiso et al. (2014)	BDF1 mouse	Inhalation	M	0, 1000, 2000, 4000 ppm	Hepatocellular adenoma or carcinoma	✓	✓	≥ 2000 ppm	High (1.1)
					Hepatic hemangioma	✓	✓	4000 ppm	
					Hepatic hemangioma or hemangiosarcoma	✓	-	-	
			F		Hepatocellular adenoma or carcinoma	✓	✓	≥ 1000 ppm	
					Hepatic hemangioma	✓	-	-	
					Hepatic hemangioma or hemangiosarcoma	✓	-	-	
NTP (1986)	F344 rat	Inhalation	M	0, 1000, 2000, 4000 ppm	Liver tumors	-	-	-	High (1.3)
			F		Liver tumors	-	-	-	
Aiso et al. (2014)	F344/DuCrj	Inhalation	M	0, 1000, 2000, 4000 ppm	Hepatocellular adenoma or carcinoma	✓	-	-	High (1.1)

Reference	Strain and Species	Exposure route	Sex	Exposure levels	Tumor type	Significant dose-related trend	Significant pairwise comparison	Exposure level with significant increase	Data Quality Evaluation
			F		Liver tumors	-	-	-	
Burek et al. (1984)	SD rat	Inhalation	M	0, 500, 1500, 3500 ppm	Liver tumors	-	-	-	High (1.5)
			F		Liver tumors	-	-	-	
Nitschke et al. (1988)	SD rat	Inhalation	M	0, 50, 200, 500 ppm	Liver tumors	-	-	-	High (1.3)
			F		Liver tumors	-	-	-	
Maltoni et al. (1988)	SD rat	Inhalation	F	0, 100 ppm	Liver tumors	-	-	-	Medium (2.0)
Burek et al. (1984)	Syrian golden hamster	Inhalation	M	0, 500, 1500, 3500 ppm	Liver tumors	-	-	-	High (1.5)
Hazleton Labs (1983) Serota et al. (1986b)	B6C3F1 mouse	Oral (DW)	M	0, 61, 124, 177, 234 mg/kg-day	Hepatocellular adenoma or carcinoma	± (p=0.058)	✓	≥ 124 mg/kg-day	Medium (1.7)
			F	0, 59, 118, 172, 238 mg/kg-day	Hepatocellular adenoma or carcinoma	-	-	-	
Serota et al. (1986a)	F344 rat	Oral (DW)	M	0, 6, 52, 125, 235 mg/kg-day	Hepatic neoplastic nodule or hepatocellular carcinoma	-	-	-	High (1.3)
			F	0, 6, 58, 136, 263 mg/kg-day	Hepatic neoplastic nodule or hepatocellular carcinoma	✓	✓	58 and 263 mg/kg-day	

3.2 Lung Tumor Data From Animal Cancer Bioassays

Reference	Strain and Species	Exposure route	Sex	Exposure levels	Tumor type	Significant dose-related trend	Significant pairwise comparison	Exposure level with significant increase	Data Quality Evaluation
NTP (1986)	B6C3F1 mouse	Inhalation	M	0, 2000, 4000 ppm	Bronchoalveolar adenoma or carcinoma	✓	✓	≥ 2000 ppm	High (1.3)
			F		Bronchoalveolar adenoma or carcinoma	✓	✓	≥ 2000 ppm	
Aiso et al. (2014)	BDF1 mouse	Inhalation	M	0, 1000, 2000, 4000 ppm	Bronchoalveolar adenoma or carcinoma	✓	✓	≥ 1000 ppm	TBD (1.1)
			F		Bronchoalveolar adenoma or carcinoma	✓	✓	≥ 2000 ppm	
NTP (1986)	F344 rat	Inhalation	M	0, 1000, 2000, 4000 ppm	Lung tumors	-	-	-	High (1.3)
			F		Lung tumors	-	-	-	
Aiso et al. (2014)	F344/DuCrj	Inhalation	M	0, 1000, 2000, 4000 ppm	Lung tumors	-	-	-	High (1.1)
			F		Lung tumors	-	-	-	
Burek et al. (1984)	SD rat	Inhalation	M	0, 500, 1500, 3500 ppm	Lung tumors	-	-	-	High (1.5)
			F		Lung tumors	-	-	-	
Nitschke et al. (1988)	SD rat	Inhalation	M	0, 50, 200, 500 ppm	Lung tumors	-	-	-	High (1.3)
			F		Lung tumors	-	-	-	
Maltoni et al. (1988)	SD rat	Inhalation	F	0, 100 ppm	Lung tumors	-	-	-	Medium (2.0)
Burek et al. (1984)	Syrian golden hamster	Inhalation	M	0, 500, 1500, 3500 ppm	Lung tumors	-	-	-	High (1.5)

3.3 Mammary Gland Tumors from Animal Cancer Bioassays

Reference	Strain and Species	Exposure route	Sex	Doses or Concentrations	Tumor type	Significant dose-related trend	Significant pairwise comparison	Dose or concentration with significant increase	Data Quality Evaluation
NTP (1986)	B6C3F1 mouse	Inhalation	M	0, 2000, 4000 ppm	Mammary tumors	-	-	-	High (1.3)
			F		Mammary tumors	-	-	-	
Aiso et al. (2014)	BDF1 mouse	Inhalation	M	0, 1000, 2000, 4000 ppm	Mammary tumors	-	-	-	High (1.1)
			F		Mammary tumors	-	-	-	
NTP (1986)	F344 rat	Inhalation	M	0, 1000, 2000, 4000 ppm	Mammary or subcutaneous tissue adenoma, fibroadenoma, or fibroma	✓	✓	4000 ppm	High (1.3)
			F		Mammary adenoma, fibroadenoma, or adenocarcinoma	✓	✓	≥ 2000 ppm	
Aiso et al. (2014)	F344/DuCrj	Inhalation	M	0, 1000, 2000, 4000 ppm	Mammary gland fibroadenoma	✓	✓	4000 ppm	High (1.1)
					Mammary gland fibroadenoma or adenoma	✓	✓	4000 ppm	
					Mammary gland fibroadenoma or adenoma or adenocarcinoma	✓	-		
			F		Mammary gland fibroadenoma	✓	-		
					Mammary gland fibroadenoma or adenoma	✓	-		
					Mammary gland fibroadenoma or adenoma or adenocarcinoma	✓	-		
Burek et al. (1984)	SD rat	Inhalation	M	0, 500, 1500, 3500 ppm	Mammary tumors	-	-	-	High (1.5)
			F		Mammary tumors	- (dose-related ↑ no. tumors/ tumor-bearing rat)	-	-	

Reference	Strain and Species	Exposure route	Sex	Doses or Concentrations	Tumor type	Significant dose-related trend	Significant pairwise comparison	Dose or concentration with significant increase	Data Quality Evaluation
Nitschke et al. (1988)	SD rat	Inhalation	M	0, 50, 200, 500 ppm	Mammary fibroma, fibrosarcoma, or undifferentiated sarcoma	-	-	-	High (1.3)
			F		Benign mammary tumors	- (dose-related ↑ no. tumors/ tumor-bearing rat)	-	-	
Maltoni et al. (1988)	SD rat	Inhalation	F	0, 100 ppm	Mammary tumors	-	-	-	Medium (2.0)
Burek et al. (1984)	Syrian golden hamster	Inhalation	M	0, 500, 1500, 3500 ppm	Mammary tumors	-	-	-	High (1.5)

3.1 Other Tumor Data From Animal Cancer Bioassays

Reference	Strain and Species	Exposure route	Sex	Doses or Concentrations	Tumor type	Significant dose-related trend	Significant pairwise comparison	Dose or concentration with significant increase	Data Quality Evaluation
NTP (1986)	B6C3F1 mouse	Inhalation	M	0, 2000, 4000 ppm	Hemangioma or hemangiosarcoma, any site	-	✓	4000 ppm	High (1.3)
			F		Hemangioma or hemangiosarcoma, any site	-	-	-	
Aiso et al. (2014)	BDF1 mouse	Inhalation	M	0, 1000, 2000, 4000 ppm	Adrenal gland pheochromocytoma	✓	-	-	High (1.1)
			F		Adrenal gland pheochromocytoma	-	-	-	
NTP (1986)	F344 rat	Inhalation	M	0, 1000, 2000, 4000 ppm	Subcutaneous fibroma or fibrosarcoma	✓	✓	4000 ppm	High (1.3)
					Mesothelioma (all sites)	✓	✓	2000 ppm	
			F		Subcutaneous fibroma or fibrosarcoma	-	-	-	
Aiso et al. (2014)	F344/ DuCrj	Inhalation	M	0, 1000, 2000, 4000 ppm	Subcutaneous fibroma	✓	✓	≥ 2000 ppm	High (1.1)
					Subcutaneous fibroma or fibrosarcoma	✓	✓	≥ 2000 ppm	
					Mesothelioma (peritoneal)	✓	-	-	
					Mononuclear cell leukemia	-	-	-	
			F		Subcutaneous fibroma	-	-	-	
					Subcutaneous fibroma or fibrosarcoma	-	-	-	
					Mesothelioma (peritoneal)	-	-	-	
					Mononuclear cell leukemia	✓	(only at 2000 ppm)	-	

Reference	Strain and Species	Exposure route	Sex	Doses or Concentrations	Tumor type	Significant dose-related trend	Significant pairwise comparison	Dose or concentration with significant increase	Data Quality Evaluation
					Endometrial stromal polyp	✓	-	-	
					Endometrial stromal sarcoma or leiomyosarcoma	✓	-	-	
Burek et al. (1984)	SD rat	Inhalation	M	0, 500, 1500, 3500 ppm	Salivary gland sarcomas	NR	✓	-	High (1.5)
			F		Salivary gland sarcomas	-	-	-	
Hazleton Labs (1983) Serota et al. (1986b)	B6C3F1 mouse	Oral (DW)	M	0, 61, 124, 177, 234 mg/kg-day	Mammary tumors	-	-	-	Medium (1.7)
			F	0, 59, 118, 172, 238 mg/kg-day	Mammary tumors	-	-	-	
Serota et al. (1986a)	F344 rat	Oral (DW)	M	0, 6, 52, 125, or 235 mg/kg-day	Mammary tumors	-	-	-	High (1.3)
			F	0, 6, 58, 136, or 263 mg/kg-day	Mammary tumors	-	-	-	

4 4 Data Extraction Tables for Genotoxicity Studies

4.1 Methylene Chloride Genotoxicity Studies not Cited in the 2011 IRIS Assessment

Species	Methylene Chloride Exposure		Outcome	Comments	Reference	Data Quality Evaluation
	Route	Dose/Duration				
Humans: workers in pharmaceutical industry	Inhalation/ dermal most likely	8 hrs/day for ≥ 8 months of irregular PPE use followed by 8 months of strict PPE use (same 16 worker volunteers for both phases)	*Irregular PPE:* Micronuclei, nuclear buds and nucleoplasmic bridges were higher in blood lymphocytes of workers exposed to multiple chemicals than controls. Tail length and percent DNA in tail of comet assay did not significantly differ from controls in blood leukocytes.	Workers were exposed to other possible carcinogens in addition to methylene chloride: phenylhydrazine, ethylene oxide, 1,2-dichlorethane; *Strict PPE*: some effects significantly decreased compared with irregular PPE after the strict use of PPE was implemented	Zeljezic et al. (2016)	NE
Mice: B6C3F1 males	Inhalation	0, 400, 800, 1600 ppm; 6 hrs/day, 5 days/week for 6 weeks	Total red blood cells – no increase in pig-A mutant frequencies Reticulocytes or normochromatic erythrocytes – no increase in micronuclei	Authors note that the results are indicative of lack of mutagenic potential in hematopoietic stem cells, and lack of clastogenicity/ aneugenicity in bone marrow of mice	Suzuki et al. (2014)	High
Mice: *gpt* Delta C57BL/6J males		0, 800 ppm; 6 hrs/day, 5 days/week for 4 weeks	Liver – no increase in DNA damage via comet assay or *gpt* mutations	DNA damage and *gpt* mutations were increased after co-exposure of methylene chloride and 1,2-dichloropropane, suggesting that the mutagenic potential of 1,2-dichloropropane may be enhanced by methylene chloride		

Species	Methylene Chloride Exposure		Outcome	Comments	Reference	Data Quality Evaluation
	Route	Dose/Duration				
Rats: F344 *gpt* delta	Gavage	0, 250 or 500 mg/kg-bw via gavage in corn oil every day for 4 weeks	No increase in *Gpt* and Spi- mutation frequencies; no changes in gene or protein expression of GST-T1 or CYP2E1	The *gpt* delta rats carry approximately 10 copies of the transgene lambda EG10 per haploid genome	Hirata et al. (2016)	High
Rats: Normal rat kidney (NRK) 52^{E} cell line	*In vitro* assay	50 to 5000 mg/L (comet assay); 10 to ~10,000 mg/L (cytotoxicity – MTT - viability); 10 to 1000 mg/L (apoptosis assay); 5000 mg/L (cell cycle analysis)	DNA damage at 5 x 10^{3} mg/L ($p < 0.05$) via comet (SCGE) assay; no increased cytotoxicity (MTT/cell viability or apoptotic cells); no changes in cell cycle	None	Yang et al. (2014)	High
S. typhimurium TA100	*In vitro* reverse mutation assay	Up to 3500 ppm vapor concentration	Increased revertants/plate and increased mutation rate	No metabolic activation used; method modified for evaluation of volatile compounds	Mimaki et al. (2016)	High
S. typhimurium TA98, TA100	*In vitro* reverse mutation assay	Not reported	Increased revertants in the presence of activation	Methods and procedures were cited to other publications	Khudoley et al. (1987)	Medium

4.2 Results from *in vitro* Genotoxicity Assays of Dichloromethane in Nonmammalian Systems

Endpoint	Test System	Dose/Concentration and Duration	Results[a]		Comments	Reference	Data Quality Evaluation
			–S9	+S9			
Reverse mutation	*Salmonella typhimurium* TA98, TA100	48-hr exposure to 0, 5,700, 11,400, 17,100, 22,800, and 57,000 ppm	+ (DR)	++[b] (DR)	Vapor phase exposure in enclosed 37°C system. Toxic at highest dose only.	Jongen et al. (1978)	High
Reverse mutation	*S. typhimurium* TA100	6-hr exposure to 0, 3,500, 7,000, and 14,000 ppm	+ (DR)	++[d] (DR)	Vapor phase exposure in enclosed 37°C system.	Jongen et al. (1982)	High
Reverse mutation	*S. typhimurium* TA100	3-day exposure, up to 84,000 ppm	+	+[e]	Vapor phase exposure in sealed jars. Peak response at 12 h. Exogenous GST or GSH had no effect.	Green (1983)	Medium
Reverse mutation	*S. typhimurium* TA100, TA98	24-hr exposure to 0, 0.01, 0.05, 0.1, 0.25, 0.5, and 1.0 mL/chamber	+ (DR)	++[f] (DR)	Vapor phase exposure in sealed desiccator jars required for positive result. Toxicity at highest dose only.	Zeiger (1990)	High
Reverse mutation	*S. typhimurium* TA100 *S. typhimurium* TA100, NG54 *E. coli* WP2 uvrA pKM101	2- and 6-hr exposures to 0, 2,500, 5,000, 7,500, 10,000 ppm; 6- and 48-hr exposures up to 50,000 ppm 6-hr exposure to 0, 2,500, 5,000, 7,500, 10,000, 20,000, 40,000 ppm 6- and 48-hr exposures to 6,300, 12,500, 25,000, and 50,000 ppm	+ (DR) + (DR) + (DR)	+[g] (DR) + (DR) + (DR)	Vapor phase exposure in sealed jars. NG54=TA100 with 4-fold lower GSH levels. Exogenous GSH slightly increased mutation frequency. Peak response at 6 h.	Dillon et al. (1992)	High
Reverse mutation	*S. typhimurium* TA1535 (+GST5-5) TA1535	0–2.0 mM/plate	+ (DR) –	ND ND	5 min preincubation. Transfected with rat GST5-5. Negative with exogenous S-(1-acetoxymethyl)GSH or HCHO. Parental strain negative with exogenous GSH or GST.	Thier et al. (1993)	Medium
Reverse mutation	*S. typhimurium* TA100 NG-11	3-day exposure, up to 100,000 ppm	++ (DR) + (DR)	ND ND	Vapor phase exposure in sealed jars. NG-11=TA100 without GSH; adding GSH increased mutagenicity of NG-11. Toxic at highest dose.	Graves et al. (1994a)	High

Endpoint	Test System	Dose/Concentration and Duration	Results[a]		Comments	Reference	Data Quality Evaluation
			–S9	+S9			
Reverse mutation	*S. typhimurium* TA1535 (+GST5-5) TA1535	0, 200, 400, 800, and 1600 ppm (0, 0.03, 0.06, 0.13, and 0.26 mM in medium)	+ (DR) – (T)	ND ND	Plate incorporation assay; 24 h exposure in sealed Tedlar bags. Transfected with rat GST5-5. Toxic at highest dose.	Pegram et al. (1997)	High
Forward mutation	*S. typhimurium* TA100, RSJ100 TA1535, TPT100	Up to 24,000 ppm	+ -(T)	ND ND	Plate incorporation assay; 24 h exposure in sealed Tedlar bags. RSJ100=TA1535+transfected rat GSTT1-1; TPT100= nonfunctional GSTT1-1 gene. Toxic at highest dose.	Demarini et al. (1997)	High
Forward mutation	*S. typhimurium* BA13	0, 8, 20, 40, and 85 µmol/plate	+++	+[c]	Preincubation assay for L-arabinose resistance (AraR test). Toxic ≥85 µmol.	Roldán-Arjona and Pueyo (1993)	High
Forward mutation	*E. coli* K12 (wild type) *E. coli* UvrA	2-hr exposures to 0, 30, 60, and 130 mM/plate (aqueous concentrations)	– –	+[h] –	Vapor phase exposure in sealed jars. "+" with mouse liver S9 only, not rat. No cell death in these strains and doses.	Graves et al. (1994a)	High
Fungi and yeasts							
Mitotic segregation	*Aspergillus nidulans* -diploid strain P1	0, 800, 2,000, 4,000, 6,000, and 8,000 ppm	+ (T)	ND	Positive only at 4,000 ppm.	Crebelli et al. (1988)	High
Gene conversion Mitotic recombination Reverse mutation	*Saccharomyces cerevisiae* -strain D7	0, 104, 157, and 209 mM	+ (T) + (T) + (T) (DR)	ND ND ND	Total cell death at 209 mM. Positive at 157 mM only with 58% cell death. Positive dose-response at 104 and 157 mM.	Callen et al. (1980)	High

[a] + = positive, – = negative, (T) = toxicity, ND = not determined, DR = dose-response observed.
[b] S9 liver fraction isolated from male Wistar rats induced with phenobarbital.
[c] S9 liver fraction isolated from rats induced with Aroclor 1254.
[d] S9 liver fraction isolated from male Wistar rats induced with Aroclor 1254 and phenobarbital and separated into microsomal and cytosolic fractions.
[e] S9 liver fraction isolated from male Sprague-Dawley rats induced with Aroclor 1254 and separated into microsomal and cytosolic fractions.
[f] S9 liver fraction isolated from male Sprague-Dawley rats induced with Aroclor 1254.
[g] S9 liver fraction isolated from male Fischer F344 rats induced with Aroclor and separated into microsomal and cytosolic fractions.
[h] S9 liver fractions isolated from male B6C3F1 mice or male Alpk:APfSD (AP) rats.

Source: U.S. EPA (2011), Table 4-20, pp. 104-106

4.3 Results from *in vitro* Genotoxicity Assays of Dichloromethane with Mammalian Systems by Test Type

Assay	Test System	Concentrations	Results	Reference	Data Quality Evaluation
Human					
Micronucleus test	Human AHH-1, MCL-5, h2E1 cell lines	Up to 10 mM	Positive in MCL-5, h2E1 cell lines, increasing with increasing concentrations from 2 to 10 mM	Doherty et al. (1996)	High
DNA damage by comet assay	Primary human lung epithelial cells	10, 100, 1,000 µM	Weak trend, independent of GST activity (GST enzymatic activity not present in the cultured cells)	Landi et al. (2003)	Medium
DNA SSBs by alkaline elution	Human hepatocytes	5–120 mM	Negative. Cytotoxicity >90 mM as measured by Trypan blue exclusion assay.	Graves et al. (1995)	High
Sister chromatid exchange	Primary human peripheral blood mononuclear cells	0, 15, 30, 60, 125, 250, 500 ppm	Sister chromatid exchanges significantly increased at exposures of 60 ppm and higher, most strongly in the high GST-T1 activity group; Mitotic indices decreased in a dose-dependent manner); changes in cell proliferation kinetics	Olvera-Bello et al. (2010)	High
DNA-protein cross-links	Human hepatocytes	0.5–5 mM	Negative	Casanova et al. (1997)	High
Mouse					
DNA breaks by alkaline elution	Mouse hepatocytes (B6C3F1)	0, 0.4, 3.0, 5.5 mM	Positive with dose-response. No toxicity at these doses as measured by trypan blue exclusion assay.	Graves et al. (1994b)	High
DNA SSBs by alkaline elution	Mouse Clara cells (B6C3F1)	0, 5, 10, 30, 60 mM	Positive with dose-response; DNA damage reduced by addition of GSH depletor. No toxicity at these doses as measured by trypan blue exclusion assay.	Graves et al. (1995)	High
DNA-protein cross-links	Mouse hepatocytes (B6C3F1)	0.5–5 mM	Positive	Casanova et al. (1997)	High
Rat					
DNA SSBs by alkaline elution	Rat hepatocytes (Alpk:APfSD [AP])	0, 30, 60, 90 mM	Positive with dose-response. Cytotoxicity at 90 mM as measured by trypan blue exclusion assay.	Graves et al. (1994b)	High
DNA-protein cross-links	Rat hepatocytes (Fischer-344)	0.5–5 mM	Negative	Casanova et al. (1997)	High

Assay	Test System	Concentrations	Results	Reference	Data Quality Evaluation
Hamster with GST activity from mouse					
hprt mutation analysis	CHO cells	3,000 and 5,000 ppm	Positive with mouse liver cytosol	Graves and Green (1996)	High
hprt mutation analysis	CHO cells	2,500 ppm[a]	Mutation spectrum supports role of glutathione conjugate	Graves et al. (1996)	High
DNA SSBs and DNA-protein cross-links	CHO cells	3,000 and 5,000 ppm	Positive at concentration of 0.5% (v/v) for SSBs in presence of mouse liver cytosol, but increase in DNA-protein cross-links marginal; formaldehyde (in absence of mouse liver cytosol) was positive at 0.5 mM for both DNA SSBs and DNA-protein cross-links; CHO cell cultures were suspended	Graves and Green (1996)	High
Comet assay	Chinese hamster V79 lung fibroblast cells transfected with mouse GST-T1	2.5, 5, 10 mM	A significant, dose-dependent increase in DNA damage resulting from DNA-protein cross-links in V79 cells transfected with mouse GST-T1 compared to parental cells	Hu et al. (2006)	High
DNA-protein cross-links	CHO cells (K1)	60 mM	Positive only with mouse liver S9 added; formaldehyde positive at lower concentrations (0.5–4 mM)	Graves et al. (1994b)	High
Hamster without GST activity from mouse					
Chromosomal aberrations	CHO cells	2 – 15 µl/ml	Positive, independent of rat liver S9	Thilagar and Kumaroo (1983)	High
Forward mutation (*hgprt* locus)	Chinese hamster epithelial cells	10,000, 20,000, 30,000, 40,000 ppm	Negative, without metabolic activation (Experiment was not run with metabolic activation)	Jongen et al. (1981)	Medium
DNA SSBs by alkaline elution	Syrian golden hamster hepatocytes	0.4–90 mM	Negative. Cytotoxicity at 90 mM as measured by Trypan blue exclusion assay.	Graves et al. (1995)	High
Sister chromatid exchange	Chinese hamster V79 cells	10,000, 20,000, 30,000, 40,000 ppm	Weak positive with or without rat-liver microsomal system	Jongen et al. (1981)	High
Sister chromatid exchange	CHO cells	2 – 15 µl/ml	Negative with or without rat liver S9	Thilagar and Kumaroo (1983)	High
DNA-protein cross-links	Syrian golden hamster hepatocytes	0.5–5 mM	Negative	Casanova et al. (1997)	High

Assay	Test System	Concentrations	Results	Reference	Data Quality Evaluation
Calf					
DNA adducts	Calf thymus DNA	50 mM	Positive in the presence of bacterial GST DM11 and dichloromethane dehalogenase; adducts primarily formed with the guanine residues	Kayser and Vuilleumier (2001)	High
DNA adducts	Calf thymus DNA	Up to 60 mM	Positive in the presence of bacterial GST DM11, rat GST5-5, and human GSTT11; adducts primarily formed with the guanine residues	Marsch et al. (2004)	High

CHO = Chinese hamster ovary; *hprt* = hypoxanthine-guanine phosphoribosyl transferase
[a]Methods section described concentration as 3,000 ppm (0.3%v/v) but Table I describes it as 2,500 ppm (0.25% v/v).

Source: U.S. EPA (2011), Table 4-21, pp. 108-110

4.4 Results from *in vivo* Genotoxicity Assays of Dichloromethane in Insects

Assay	Test System	Doses	Result	Reference	Data Quality Evaluation
Gene mutation (sex-linked recessive lethal)	Drosophila	125, 620 mM	Positive (feeding exposure)	Gocke et al. (1981)	High
Gene mutation (sex-linked recessive lethal, somatic mutation and recombination)	Drosophila	6 hrs—1,850, 5,500 ppm 1 wk—2,360, 4,660 ppm 2 wks—1,370, 2,360 ppm (all approximate)	Negative (inhalation exposure)	Kramers et al. (1991)	High
Somatic w/w+ assay	Drosophila	50, 100, 250, 500 mM	Positive (feeding exposure)	Rodriguez-Arnaiz (1998)	Medium

Source: U.S. EPA (2011), Table 4-22, p. 114

4.5 Results from *in vivo* Genotoxicity Assays of Dichloromethane in Mice

Assay	Test System	Route and Dose	Duration	Results	Reference	Data Quality Evaluation
Kras and Hras oncogenes	Mouse liver and lung tumors (B6C3F1)	0, 2,000 ppm	Up to 104 wks	No difference in mutation profile between control and dichloromethane-induced liver tumors; number of spontaneous lung tumors (n = 7) limits comparison at this site	Devereux et al. (1993)	High
p53 tumor suppressor gene	Mouse liver and lung tumors (B6C3F1)	0, 2,000 ppm	Up to 104 wks	Loss of heterozygosity infrequently seen in liver tumors from exposed or controls; number of spontaneous lung tumors (n = 7) limits comparison at this site	Hegi et al. (1993)	High
Micronucleus test	Mouse bone marrow (C57BL/6J/A1pk)	Gavage, 1,250, 2,500, and 4,000 mg/kg	Single dose	Negative at all doses	Sheldon et al. (1987)	High
Micronucleus test	Mouse peripheral red blood cells (B6C3F1)	Inhalation 6 hr/d, 5 d/wk, 0, 4,000, 8,000 ppm	2 wk	Positive at 4,000 and 8,000 ppm	Allen et al. (1990)	High
Micronucleus test	Mouse peripheral red blood cells (B6C3F1)	Inhalation, 6 hr/d, 5 d/wk, 0, 2,000 ppm	12 wks	Positive at 2,000 ppm	Allen et al. (1990)	High
Chromosome aberrations	Mouse bone marrow (C57BL/6J)	Intraperitoneal, 100, 1,000, 1,500, 2,000 mg/kg	Single dose	Negative	Westbrook-Collins et al. (1990)	High
Chromosome aberrations	Mouse bone marrow (B6C3F1)	Subcutaneous, 0, 2,500, 5,000 mg/kg	Single dose	Negative	Allen et al. (1990)	High
Chromosome aberrations	Mouse lung and bone marrow cells (B6C3F1)	Inhalation, 6 hr/d, 5 d/wk, 0, 4,000, 8,000 ppm	2 wks	Increase beginning at 4,000 ppm in lung cells; increase only at 8,000 ppm in bone marrow cells	Allen et al. (1990)	High
DNA SSBs by alkaline elution	Mouse hepatocytes (B6C3F1)	Inhalation, 2,000 and 4,000 ppm	3 or 6 hrs	Positive at 4,000 ppm at 3 and 6 hrs	Graves et al. (1994b)	Medium
DNA SSBs by alkaline elution	Mouse liver and lung homogenate (B6C3F1)	Liver: inhalation, 2,000, 4,000, 6,000, 8,000 ppm Lung: inhalation, 1,000, 2,000, 4,000, 6,000 ppm	3 hrs 3 hrs	Liver: positive at 4,000–8,000 ppm Lung: positive at 2,000–4,000 ppm	Graves et al. (1995)	High

Assay	Test System	Route and Dose	Duration	Results	Reference	Data Quality Evaluation
DNA damage by comet assay	Mouse stomach, urinary bladder, kidney, brain, bone marrow (CD-1)	Gavage, 1,720 mg/kg; organs harvested at 0 (control), 3, and 24 hrs	Single dose	Negative 3 or 24 hr after dosing	Sasaki et al. (1998)	High
DNA damage by comet assay	Mouse liver and lung cells (CD-1)	Gavage, 1,720 mg/kg; organs harvested at 0 (control), 3, and 24 hrs	Single dose	Positive only at 24 hrs after dosing	Sasaki et al. (1998)	High
DNA adducts	Mouse liver and kidney cells (B6C3F1)	Intraperitoneal, 5 mg/kg	Single dose	Negative	Watanabe et al. (2007)	Medium
DNA-protein cross-links	Mouse liver and lung cells (B6C3F1)	Inhalation, 6 hr/d, 3 d, 4,000 ppm	3 d	Positive in mouse liver cells at 4,000 ppm; negative in mouse lung cells	Casanova et al. (1992)	High
DNA-protein cross-links	Mouse liver and lung cells (B6C3F1)	Inhalation, 6 hr/d, 150, 500, 1,500, 3,000, 4,000 ppm	3 d	Positive in mouse liver cells at 500–4,000 ppm; negative in mouse lung cells	Casanova et al. (1996)	High
Sister chromatid exchange	Mouse bone marrow (C57BL/6J)	Intraperitoneal, 100, 1,000, 1,500, 2,000 mg/kg	Single dose	Negative	Westbrook-Collins et al. (1990)	High
Sister chromatid exchange	Mouse bone marrow (B6C3F1)	Subcutaneous, 0, 2,500, 5,000 mg/kg	Single dose	Negative at all doses	Allen et al. (1990)	High
Sister chromatid exchange	Mouse lung cells and peripheral lymphocytes (B6C3F1)	Inhalation 6 hr/d, 5 d/wk, 0, 4,000, 8,000 ppm	2 wks	Positive at 4,000 and 8,000 ppm - mouse lung cells; at 8,000 ppm – peripheral lymph.	Allen et al. (1990)	High
Sister chromatid exchange	Mouse lung cells (B6C3F1)	Inhalation 6 hr/d, 5 d/wk, 0, 2,000 ppm	12 wks	Positive at 2,000 ppm	Allen et al. (1990)	High
DNA synthesis	Mouse liver (B6C3F1)	Gavage, 1,000 mg/kg; inhalation, 4,000 ppm	Single dose; 2 hrs	Negative in both oral and inhalation studies	Lefevre and Ashby (1989)	High
Unscheduled DNA synthesis	Mouse hepatocytes (B6C3F1)	Inhalation, 2,000 and 4,000 ppm.	2 or 6 hrs	Negative	Trueman and Ashby (1987)	Medium

Source: U.S. EPA (2011), Table 4-23, pp. 115-116

4.6 Results from *in vivo* Genotoxicity Assays of Dichloromethane in Rats and Hamsters

Assay	Test System	Route and Dose	Duration	Results	Reference	Data Quality Evaluation
DNA SSBs by alkaline elution	Rat hepatocytes	Inhalation, 3 or 6 hrs, 2,000 and 4,000 ppm	3 or 6 hrs	Negative at all concentrations and time points	Graves et al. (1994b)	Medium
DNA SSBs by alkaline elution	Rat liver homogenate	Gavage, 2 doses, 425 mg/kg and 1,275 mg/kg, administered 4 and 21 hrs before liver harvesting	4 or 21 hrs (time between dosing and liver harvesting)	Positive at 1,275 mg/kg	Kitchin and Brown (1989)	High
DNA SSBs by alkaline elution	Rat liver and lung homogenate	Liver: inhalation, 4,000, 5,000 ppm Lung: inhalation, 4,000 ppm	3 hrs 3 hrs	Negative for both liver and lung at all concentrations	Graves et al. (1995)	High
DNA adducts	Rat liver and kidney cells	Intraperitoneal, 5 mg/kg	Single dose	Negative	Watanabe et al. (2007)	Medium
DNA-protein cross-links	Hamster liver and lung cells	Inhalation, 6 hr/d, 500, 1,500, 4,000 ppm	3 d	Negative at all concentrations	Casanova et al. (1996)	High
Unscheduled DNA synthesis	Rat hepatocytes	Gavage, 100, 500, 1,000 mg/kg	Liver harvested 4 and 12 hrs after dosing	Negative 4 or 12 hrs after dosing	Trueman and Ashby (1987)	Medium
Unscheduled DNA synthesis	Rat hepatocytes	Inhalation, 2 or 6 hrs, 2,000 and 4,000 ppm	2 or 6 hrs	Negative at both concentrations and exposure durations	Trueman and Ashby (1987)	Medium
Unscheduled DNA synthesis	Rat hepatocytes	Intraperitoneal, single dose, 400 mg/kg	Single dose	Negative 48 hrs after dosing	Mirsalis et al. (1989)	High

Source: U.S. EPA (2011), Table 4-24, p. 120

5 References

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