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Risk Evaluation for Methylene Chloride

Systematic Review Supplemental File:

Data Extraction Tables for Human Health Hazard Studies

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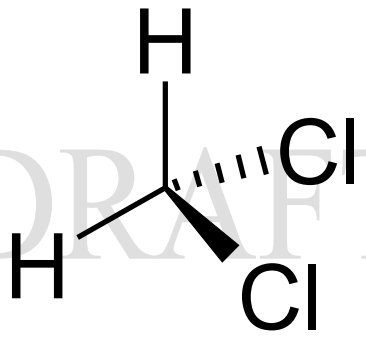

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NOTE: Within each table, rows that are shaded are the new studies identified in the updated literature search. Some of the studies from the updated literature search, although obtained recently, were submitted several years ago under TSCA (e.g., section 8e, 8d, etc) 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 DCM)	The risk of NHL was increased with exposure to DCM; 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 DCM; 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 DCM	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
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	DCM, exposure qualitatively stated as ever (job with likely exposure >1month) or never	Non-significant positive association between DCM and head/neck cancers in ever/never and continuous cumulative exposure analysis; non-significant negative association for those exposed exclusively to DCM (limited sample size)	Carton et al. (2017)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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.	DCM 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 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	DCM exposure based on employment questionnaire and expert rating,	A significant association between exposure to DCM and leukemia and chronic lymphatic leukemia was not observed at either exposure level	Costantini et al. (2008)	Medium
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 DCM 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 DCM exposure.	Garcia et al. (2015)	High

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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	DCM, 38.2 and 14.3 percent of men and women exposed at the high 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 DCM and liver or pancreatic cancer in both men and women.	Gibbs et al. (1996)	High
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 DCM 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 DCM; 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

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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
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 et al. (1996)	Medium
Cancer	Childhood acute lymphoblastic leukemia	790 mothers interviewed from both case and control groups in Quebec Canada between 1980 â€“ 2000; Children 0-14 yrs old. 848 cases, 916 controls	DCM exposure to mothers 2 years before pregnancy, and up to birth. Exposure ***level 0*** (baseline): No exposure (none or possible exposure); ***level 1***: Some exposure (concentration x frequency < 4); ***level 2:*** Greater exposure (concentration x frequency ≥ 4)	Maternal exposure to DCM before or during pregnancy resulted in increased, but non-significant risk of acute lymphoblastic leukemia in children	Infante-Rivard et al. (2005)	High

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	Cholangiocarcinoma	95 proof-printing workers, Osaka, Japan, 1987-2006	DCM, 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
Cancer	Cause-specific mortality	1271 textile workers, Rock Hill, South Carolina, 1954-1986	DCM, 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
Cancer	All causes, malignant neoplasms (total; buccal cavity; biliary passages and liver; melanoma; bronchus, trachea and lung; breast; pancreas), cerebrovascular disease, ischemic heart disease, and nonmalignant respiratory disease	Cellulose fiber production workers (n=1271, Rock Hill, South Carolina)	DCM in 1977 median of 140, 280, and 475 ppm in three main areas	DCM 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 DCM based on jobs	DCM was not significantly associated with lung cancer in men.	Mattei et al. (2014)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cancer	All Non-Hodgkin lymphoma 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 1991-1993 among men and women age 20 to 74 years in 11 areas in Italy	DCM 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.	DCM 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
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 DCM assessed with job exposure matrix	A negative, non-significant association was observed between Mycosis Fungoides and subjects with exposure to DCM >= 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 DCM via self-reported occupational history and industrial hygienist assigned level of exposure	DCM 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 DCM.	No significant associations observed between exposure to DCM and kidney cancer.	Purdue et al. (2016)	High

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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 DCM (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 DCM compared to no exposure	Radican et al. (2008)	Medium
Cancer	Glioma	Non-farm workers from the Upper Midwest Health Study (798 cases and 1141 controls from Iowa, Michigan, Minnesota, and Wisconsin 1995-1997)	DCM use (self-reported occupational history through 1992, bibliographic database of published exposure)	DCM was associated with a significant decrease in gliomas only when including proxy-only interviews and unexposed participants or as an 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 DCM [ppm*years] based on intensity, the frequency, and duration of DCM exposure (0, >0 to <26.3, >26.3 to <=175, >175 ppm*years)	DCM 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 years old (4263 cases, 533 population controls; also hospital and cancer controls).	Any or substantial exposure	The ORs for any and substantial exposure to DCM exposure and rectal cancer were significantly elevated at the p=0.1 level (one-sided).	Siemiatycki (1991) [a]	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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 DCM exposure score based on department-exposure matrix	DCM was not significantly associated with mortality from brain or other nervous system cancers.	Silver et al. (2014)	Medium
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 DCM 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 DCM, 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

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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	DCM, cumulative exposure, median (1000 ppm-years) 36.0	DCM exposure was not significantly associated with all malignant neoplasms mortality (p-value = 0.60); Non-significant excess of brain cancer deaths in exposed workers (p-value=0.9); DCM exposure not significantly associated with ischemic heart disease mortality (p-value=0.24); DCM exposure not significantly associated with respiratory cancer mortality (p-value=0.90); DCM exposure was not statistically associated with all cancer mortality after 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	DCM 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 DCM 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	All malignant neoplasms mortality	Male employees, United States, n=1346 men (1034 exposed, 312 unexposed) exposed from 1960 - 1988	Methylene chloride, cumulative exposure (1000 ppm-years)	Exposure not significantly associated with all malignant neoplasms. (p-value=0.6). No Cox regression coefficients were statistically evaluated.	Tomenson (2011)	Medium
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 DCM	Non-Hodgkin Lymphoma was associated with low probability of exposure to DCM, but not with medium-high probability of exposure to DCM	Wang et al. (2009)	Medium
Cancer	Mortality due to prostate cancer	2187 men working in Amcelle plant in Cumberland, Maryland, 1970-1981	DCM: none (0 ppm); low (50-100 ppm); high (350-700 ppm)	Deaths from prostate cancer were elevated in the high and low groups, and were statistically significant in high exposed workers with 20 years since initial exposure were included (SMR = 208.4, p<0.05)	Gibbs et al. (1996)	High
Cancer	All malignant neoplasms mortality	Male employees, United States, n=1346 men (1034 exposed, 312 unexposed) exposed from 1960 - 1988	Methylene chloride, cumulative exposure (1000 ppm-years)	Exposure not significantly associated with all malignant neoplasms. (p-value=0.6). No Cox regression coefficients were statistically evaluated.	Tomenson (2011)	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 DCM emissions	A weak negative association was observed between exposure to DCM and septal heart defects	Brender et al. (2014)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Cardiovascular	Cause-specific mortality	1271 textile workers, Rock Hill, South Carolina, 1954-1986	DCM, 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	All causes, malignant neoplasms (total; buccal cavity; biliary passages and liver; melanoma; bronchus, trachea and lung; breast; pancreas), cerebrovascular disease, ischemic heart disease, and nonmalignant respiratory disease	Cellulose fiber production workers (n=1271, Rock Hill, South Carolina)	DCM in 1977 median of 140, 280, and 475 ppm in three main areas	DCM 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
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)	DCM, 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	DCM, cumulative exposure, median (1000 ppm-years) 36.0	DCM exposure was not significantly associated with all malignant neoplasms mortality (p-value = 0.60); Non-significant excess of brain cancer deaths in exposed workers (p-value=0.9); DCM exposure not significantly associated with ischemic heart disease mortality (p-value=0.24); DCM exposure not significantly associated with respiratory cancer mortality (p-value=0.90); DCM exposure was not statistically associated with all cancer mortality after excluding respiratory cancers (p-value=0.62); 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 DCM 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 DCM emissions	No significant association was observed between exposure to DCM and oral clefts	Brender et al. (2014)	Medium

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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)	DCM 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
Hematological and Immune	Primary Sjogren syndrome	Cases (n= 175) from three University Hospitals and matched controls (n=350) (2010-2013)	Occupational DCM 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's syndrome with occupational DCM 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

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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)	DCM, 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
Hematological and Immune	Mortality due to infectious and parasitic diseases	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 significantly associated with a decrease in mortality from infectious and parasitic diseases	Hearne and Pifer (1999)	High
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	DCM; 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
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

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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 DCM exposure score based on department-exposure matrix	DCM 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)	DCM, 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	Meningioma mortality	Women in United States, (n= 649000, 12980 cases, 51920 controls) exposed from 1984-1992	Methylene chloride	Occupational hazard was not significantly associated with mortality from meningioma.	Cocco et al. (1999)	Medium
Mortality	Cause-specific mortality	1271 textile workers, Rock Hill, South Carolina, 1954-1986	DCM, 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
Mortality	All causes, malignant neoplasms (total; buccal cavity; biliary passages and liver; melanoma; bronchus, trachea and lung; breast; pancreas), cerebrovascular disease, ischemic heart disease, and 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	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

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Mortality	Mortality	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 for mortality through 2000	Exposure was assessed from a JEM using data from worker compensation files, histories and telephone books, organizational charts, technical orders, position descriptions, walk-through surveys, interviews, and limited measurement data.. For some analyses, exposure was categorized by cumulative exposure (using inputs of continuous or intermittent exposure, and low or peak exposure, and estimates of frequency and intensity).	A significantly elevated hazard ratio was observed for methylene chloride exposure and nonmalignant respiratory diseases in men.	Radican et al. (2008)	Medium
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 DCM emissions	No significant association was observed between exposure to DCM and neural tube defects	Brender et al. (2014)	Medium
Neurological/ Behavior	Dizziness/vertigo	854 workers in a plastic polymer facility in Indiana, USA. 1985	DCM; 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 DCM 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 DCM in ambient air, geometric mean concentration: 539.8 (NC) and 202..3 (WV) ng/m^3	A positive, non-significant association between ambient DCM (80th vs. 20th percentile) and autism spectrum disorder	Kalkbrenner et al. (2010) [a]	High

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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 DCM (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
Neurological/ Behavior	Autism Spectrum Disorder	Nurses' Health Study II children (US; 325 cases/22101 controls).	DCM air concentrations at mother's location at birth; Mean: 0.4 ug/m3	DCM 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 DCM exposure score based on department-exposure matrix	DCM 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)	DCM, 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	DCM exposure (239-273 ng/m3) during gestation estimated with National Air Toxics Assessment 2005 model from addresses at birth	DCM 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 DCM exposure during entire pregnancy	A positive, non-significant association was observed between autistic disorder by age 6 years and maternal ambient DCM 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 DCM 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 DCM 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	DCM exposure based on a questionnaire sent to factory physicians or their nurses	Borderline significant positive association between occupational DCM exposure and spontaneous abortion	Taskinen et al. (1986)	Low

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Respiratory	Cause-specific mortality	1271 textile workers, Rock Hill, South Carolina, 1954-1986	DCM, 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
Respiratory	All causes, malignant neoplasms (total; buccal cavity; biliary passages and liver; melanoma; bronchus, trachea and lung; breast; pancreas), cerebrovascular disease, ischemic heart disease, and nonmalignant respiratory disease	Cellulose fiber production workers (n=1271, Rock Hill, South Carolina)	DCM in 1977 median of 140, 280, and 475 ppm in three main areas	DCM 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
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 DCM (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 DCM 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

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
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						

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 (plus hemorrhage in stomach) of animals that died	General Electric (1976b)	Medium (2.0)
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*; ↓ bactericidal 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 hrs/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 [measured in acute test]	Dow (1988)	High (1.5)
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	Moser et al. (1995)	High (1.3)

								and sensorimotor parameters significantly different from controls		
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 parameters (including autonomic, neuro-muscular and sensorimotor and excitability measures) from day 4	Moser et al. (1995)	High (1.3)
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,	0, 2010, 3710 ppm (1 day);	1 or 10 days; 6 hrs/day	Not Reported	Not Determined	1 day: Selective vacuolation and	Shell Oil (1986)	High (1.5)

			vapor, whole body	0, 1990, 3960 ppm (10 day)				pyknosis of Clara cells in bronchiolar epithelium 10 days: No effects		
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 of organs – no clear dose-response by organ (lungs, liver, lymph nodes, gastrointestinal tracts, urethra) 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	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)

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=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)
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)
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)

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=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)
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)

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
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)
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)
Developmental Effects	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)
Developmental Effects	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)
Reproductive	Reproductive	Rat, Charles River, M/F (n=20/group)	Oral, gavage	0, 25, 75 or 225 mg/kg	90 days before mating (10 days between last exposure and mating period); 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
Reproductive	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)
Reproductive	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)
Reproductive	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)
Reproductive	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	-	-	-	
	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
Aiso et al. (2014)			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/Du Crj	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 rat	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	-	-	-	

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