

**HSIA**

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Trichloroethylene (TCE):

Supporting Material for the Presentation of Dr. M. Dourson before the EPA Science Advisory Board TCE Panel During the Conference Call, June 24, 2010

Provided by Paul H. Dugard, PhD

On behalf of the Halogenated Solvents Industry Alliance, Inc. (HSIA)

Please find the following materials to be referred to by Dr. M. Dourson during his presentation to be given during the conference call of the SAB TCE Panel on June 24, 2010.

1. Five slides: Please note that comment are accessible via Adobe that are linked to the first and the third slide in the series.
2. IRIS opinions on the carcinogenicity of various solvents. This document provides contrasts to the treatment of TCE in the current draft IRIS assessment.

Thank you for your attention.

Paul Dugard, PhD



# Experimental Animal Tumors from TCE

- For rat kidney tumors...
  - of 74 doses, 4 expected to be statistically significant by chance alone--- only 1 or perhaps 2 found to be so; however, I judged 6 doses to be biologically significant suggesting that TCE might cause kidney tumors. But wait...
  - Of 24 high doses, 1 expected to be statistically significant by chance alone; and only 1 was found (see note 2 below); thus, kidney tumors are not dose related and appear to be due to chance. Unless...
  - Review of historical control incidences for **all** strains and years is conducted and shown to be helpful in a different judgment.
- EPA describes 4 primary tissues for cancer, but only liver and perhaps lung tumors in mice, are biologically significant.
- **Conclusion from the experimental animal data:**
  - “Suggestive evidence of carcinogenicity”

# Dose Response Assessment

EPA (2005) cancer guidelines (page 3-22) states that

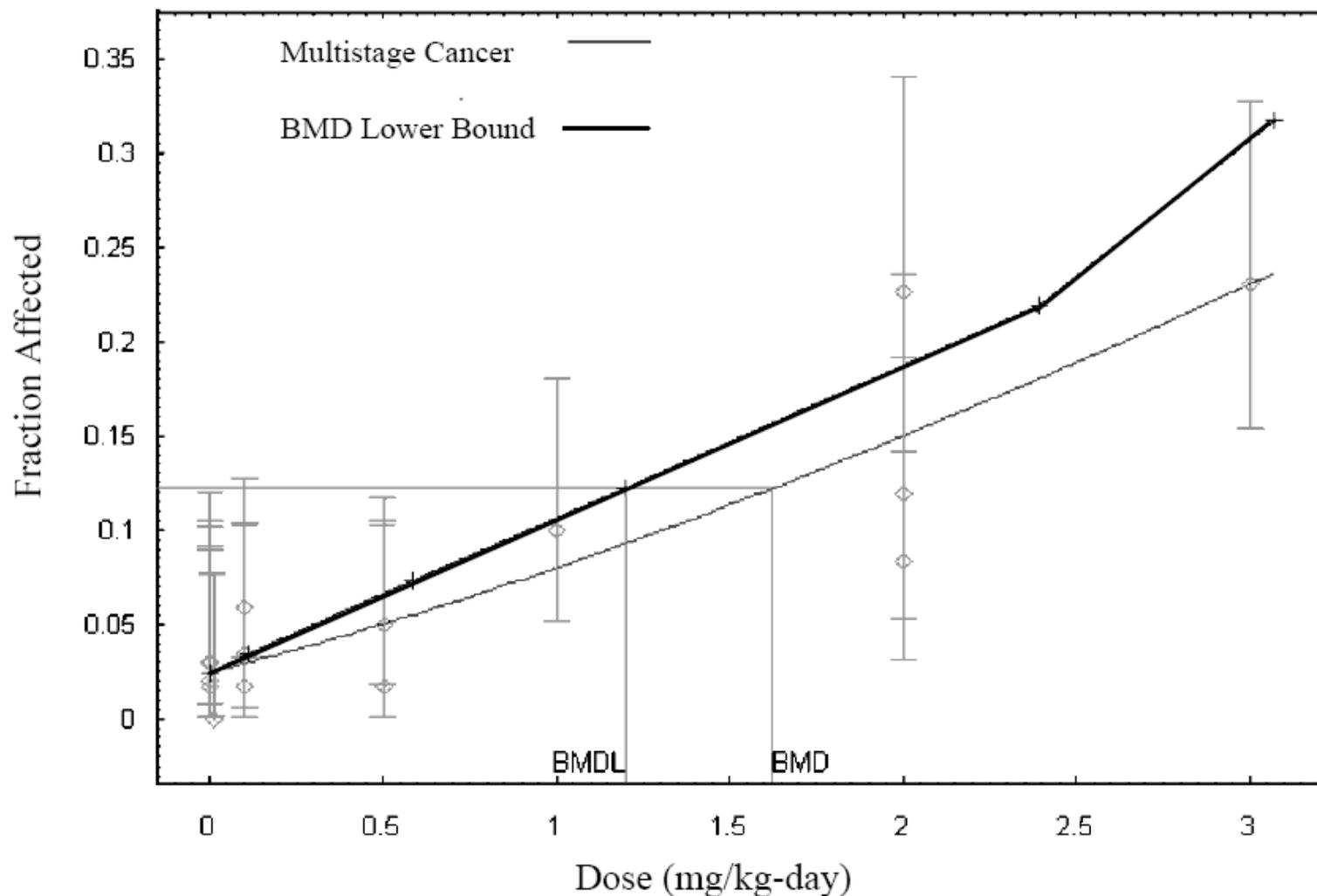
“If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur.”

The SAB Panel (page 23) agreed that:

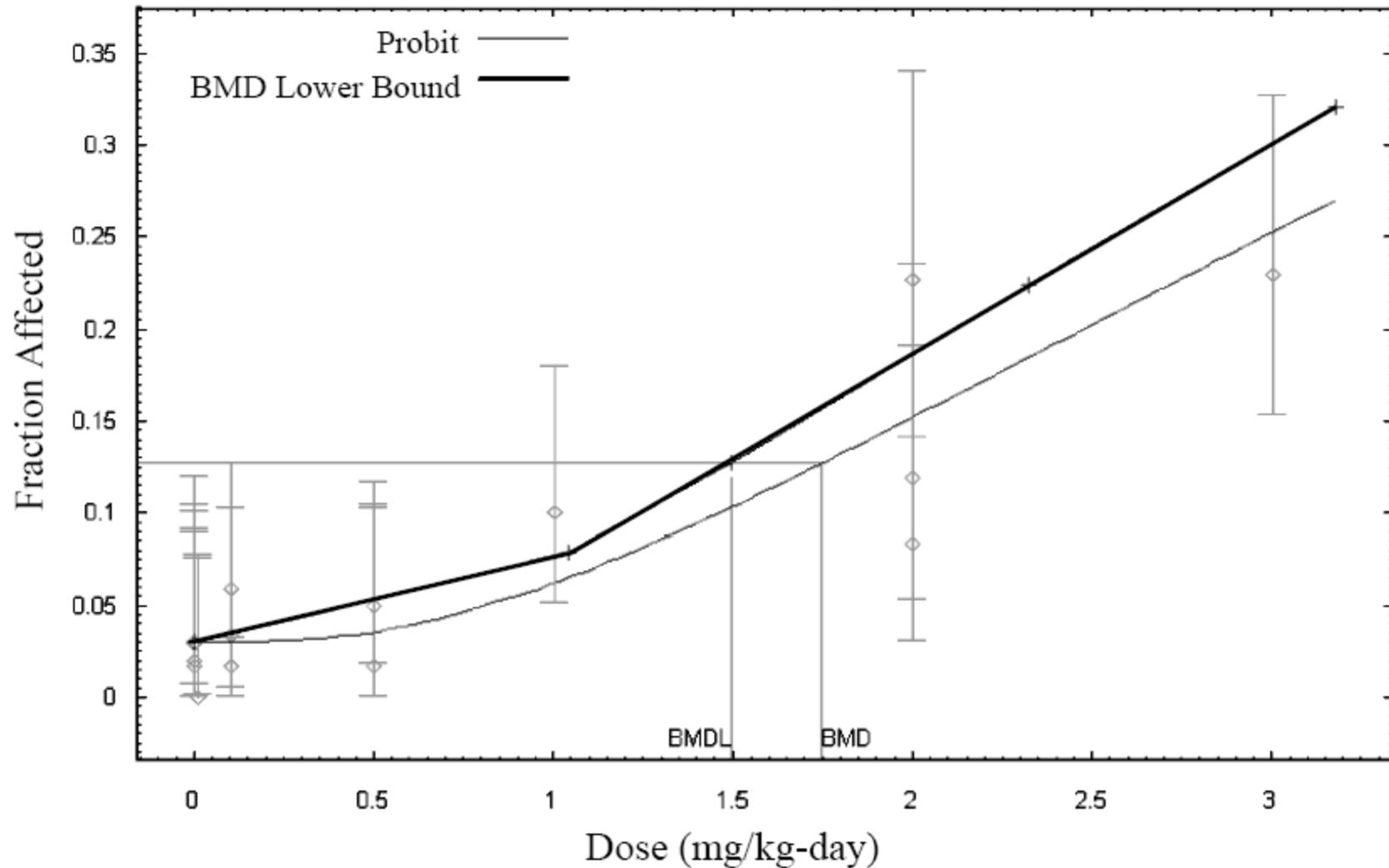
“Weight of evidence does not exclude the MOA for TCE-induced kidney tumors involving cytotoxicity and compensatory cell proliferation and including this MOA may more accurately reflect kidney tumor formation than a mutagenic mechanism alone. Furthermore, the combination of cytotoxicity, proliferation and DNA damage together may be a much stronger MOA than the individual components.”

**Conclusion: EPA should approach the dose response assessment as a dual mode of action.**

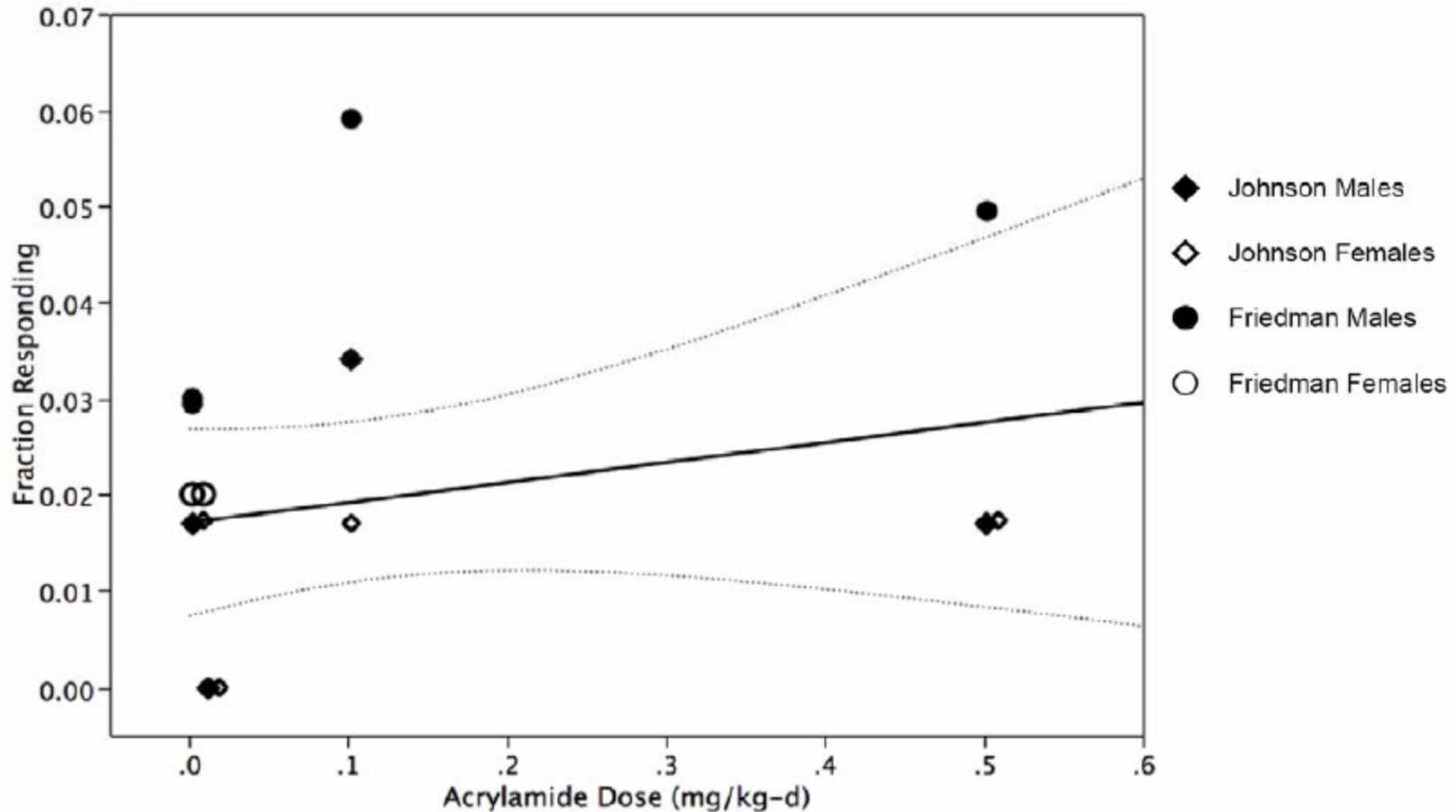
Single mode of action & multistage model of acrylamide induced pooled-all thyroid tumor data, showing little change in slope between the low & high doses.



Dual mode of action & probit model of acrylamide induced pooled-all thyroid tumor data, showing change in slope between the low & high doses.



Weighted linear regression on low-dose, pooled data with 95% confidence curves for the model. Data jittered to show all 14 data points. Single mode of action analysis does not fit these data points.



**Table 1. Cancer classifications and experimental animal & human information for several IRIS\* solvents.**

Chemical	Classification	Experimental animal information	Human information
1,1-Dichloroethylene (1,1-DCE)	<p>Group C, possible human carcinogen</p> <p>1,1-DCE exhibits suggestive evidence of carcinogenicity</p>	<p>Male mice developed kidney tumors at one exposure in a lifetime bioassay, a finding tempered by the absence of similar results in female mice or male or female rats and by the enzymatic differences (i.e., CYP2E1) between male mice and female mice, male and female rats, and human kidney cells. Limited evidence of genotoxicity has been reported in bacterial systems with metabolic activation. The data for 1,1-DCE are <i>inadequate</i> for an assessment of human carcinogenic potential by the oral route, based on the absence of statistically or biologically significant tumors in limited bioassays in rats and mice balanced against the suggestive evidence in male mice in a single bioassay by inhalation and the limited evidence of genotoxicity. The human epidemiological results on the carcinogenicity of 1,1-DCE are too limited to draw useful conclusions. EPA concludes that the results of kidney tumors in one sex and one exposure in a single species of rodents are too limited to support an exposure-response assessment.</p> <p>Bioassays for cancer by the oral route of exposure have been conducted in rats (Maltoni et al., 1985; NTP, 1982; Ponomarev and Tomatis, 1980; Quast et al., 1983) mice (NTP, 1982), and trout (Hendricks et al., 1995). Some of these bioassays were conducted at an exposure below the maximum tolerated dose. The bioassay conducted by Maltoni et al. (1985) exposed the animals for only 1 year. The bioassay conducted in rats by Quast et al. (1983) and the bioassay conducted in mice by NTP (1982) were well conducted and both showed some toxicity in the liver at the highest exposure. Neither of these bioassays provides any significant evidence that 1,1-DCE is a carcinogen by the oral route of exposure. The genotoxicity studies are incomplete, but most studies in mammalian cells indicate a lack of genotoxicity.</p> <p>Bioassays for cancer by the inhalation route of exposure have been</p>	<p>Ott et al. (1976) investigated the health records of 138 employees occupationally exposed to 1,1-DCE in processes not involving vinyl chloride. The individuals included in the study had worked in experimental or pilot plant polymerization operations, in a monomer production process as tankcar loaders, or in a production plant that manufactured a monofilament fiber. Time-weighted-average concentrations (8 hours) of 1,1-DCE in the workplace were estimated from job descriptions and the results of industrial hygiene sampling. The subjects were grouped into three exposure categories: less than 10 ppm, 10–;24 ppm, and greater than 25 ppm. The researchers estimated career exposure by taking into account average duration of employment. Results of the most recent health inventory for individuals in the cohort were compared with findings of matched controls. Analysis of mortalities among the cohort indicated no statistically significant findings. Overall, there were no significant differences between the exposed cohort and the controls in hematology and clinical chemistry parameters.</p>

Chemical	Classification	Experimental animal information	Human information
		<p>conducted in rats (Lee et al., 1977, 1978; Viola and Caputo, 1977; Hong et al., 1981; Maltoni et al., 1985; Quast et al., 1986; Cotti et al., 1988), mice (Lee et al., 1977, 1978; Hong et al., 1981; Maltoni et al., 1985), and hamsters (Maltoni et al., 1985). None of these bioassays was conducted by a protocol that meets current standards. The major defects in most of these bioassays include exposure of the animals for 1 year and exposure at less than the maximum tolerated dose. The only bioassay that showed some evidence of carcinogenicity was the study in Swiss-Webster mice (Maltoni et al., 1985). This study was conducted at or near the maximum tolerated dose, as animals exposed at 50 ppm died after a few exposures. Although the animals were exposed for only 1 year and then observed until natural death, this study showed an increased incidence of kidney adenocarcinomas in male mice at 25 ppm but not at 10 ppm. The incidence of mammary carcinomas in female mice and pulmonary adenomas in male and female mice did not increase with increased exposure. The responses were actually lower at 25 ppm than at 10 ppm, but survival and other toxicities were comparable.</p> <p><i>Oral</i></p> <p><b>Rats.</b> Ponomarkov and Tomatis (1980) treated 24 female BD IV rats by gavage with 1,1-DCE dissolved in olive oil (150 mg/kg body weight) on the 17th day of gestation. Their offspring (81 males and 80 females) were treated weekly with 1,1-DCE at 50 mg/kg body weight by gavage from the time of weaning for 120 weeks or until the animal was moribund. A control group of offspring (49 males and 47 females) received only olive oil. Liver and meningeal tumors were more frequently observed in treated than in untreated animals, but the difference was not statistically significant. The total number of tumor-bearing animals was not statistically different between treated and untreated animals.</p>	<p>Based on power considerations, this study is inadequate for assessing cancer risk in humans.</p>

Chemical	Classification	Experimental animal information	Human information
		<p>NTP (1982) conducted chronic toxicity and carcinogenicity studies of 1,1-DCE for 104 weeks in male and female F344 rats (200 of each sex, 9 weeks old) by gavage in corn oil at 0, 1, or 5 mg/kg-day. No significant differences were observed in survival, clinical signs, or body weight as compared with controls for any group, suggesting that the maximum tolerated dose was not achieved. All of the increased tumor incidences that were statistically significant by the Fisher exact test or by the Cochran-Armitage linear trend test (adrenal pheochromocytoma, pancreatic islet cell adenoma or carcinoma, and subcutaneous fibroma in males and pituitary adenoma in females) were not significant when life-table analyses were used. This difference occurs because life table analyses adjust for intercurrent mortality, and thus minimize the impact of animals dying before the onset of late-appearing tumor. This adjustment was particularly critical for the analyses of tumor incidences in male rats, because 12 controls and 10 low-dose animals were accidentally killed during week 82 of the study. Accordingly, NTP concluded that no increased incidence of tumors was found at any site in these bioassays. Under the conditions of this bioassay, 1,1-DCE administered by gavage was not carcinogenic for F344 rats.</p> <p>Quast et al. (1983) conducted a 2-year chronic toxicity and carcinogenicity study of 1,1-DCE in Sprague-Dawley rats (6–7 weeks old). There were 80 of each sex rats in the control group and 48 rats of each sex in each exposed group. The 1,1-DCE was incorporated in the drinking water of the rats at nominal concentrations of 0, 50, 100, or 200 ppm. The time-weighted-average exposure over the 2-year period was 7, 10, or 20 mg/kg-day for males and 9, 14, or 30 mg/kg-day for females. No significant differences were found among the groups in appearance and demeanor, mortality, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry determinations, organ weights, or organ-to-body-weight ratios. The only treatment-related effect observed in rats was a minimal amount of midzonal fatty change and hepatocellular swelling. No</p>	

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		<p>exposure-related neoplastic changes occurred at any exposure.</p> <p>Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Sprague-Dawley rats. Animals (9 or 10 weeks old) were exposed by gavage in olive oil to 0, 0.5, 5, 10, or 20 mg/kg, 4–5 days/wk for 52 weeks. There were two control groups, one with 150 animals (75 of each sex) and the other with 200 animals (100 of each sex). The exposed groups had 100 animals (50 of each sex). Following the 52-week exposure, animals were observed until spontaneous death (total duration 147 weeks). Body weight was measured every 2 weeks during the 52 week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed. No biologically significant changes were observed in mortality or body weight. There were no biologically significant noncancer or cancer effects in any organ.</p> <p><b>Mice.</b> NTP (1982) conducted 104 weeks of chronic toxicity and carcinogenicity studies on 1,1-DCE in male and female B6C3F<sub>1</sub> mice (200 of each sex, 9 weeks old) by gavage in corn oil at 0, 2, or 10 mg/kg. No significant differences in survival, clinical signs, or body weight were in any group, suggesting that the maximum tolerated dose was not achieved. The only observed significant increase (<math>p &lt; 0.05</math>) in tumor incidence occurred in low-dose females for lymphoma (2/48, 9/49, 6/50) and for lymphoma or leukemia (7/48, 15/49, 7/50). These increases were not considered to be related to 1,1-DCE administration because similar effects were not found in the high-dose females or in males. Under the conditions of this bioassay, 1,1-DCE administered by gavage was not carcinogenic for B6C3F<sub>1</sub> mice.</p> <p><b>Trout.</b> Hendricks et al. (1995) conducted an 18-month carcinogenicity study of 1,1-DCE in rainbow trout (8 weeks old) at 4 mg/kg-day. Tissues examined for neoplasms included liver, kidney, spleen, gill, gonads, thymus, thyroid, heart, stomach,</p>	

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		<p>pyloric ceca, duodenum, rectum, pancreas, and swimbladder. 1,1-DCE produced no neoplasms and no increase in liver weight. There was no evidence of any other chronic toxic effects.</p> <p><b>Inhalation</b></p> <p><b>Rats.</b> Lee et al. (1977, 1978) exposed 2-month-old Charles River CD rats (36 males and 35 females) to 55 ppm 1,1-DCE for 6 hrs/day, 5 days/wk, for 12 months. No significant changes were observed in survival, body weight, hematology, clinical blood chemistry, pulmonary macrophage count, cytogenetic analysis of bone marrow, x-ray examination of extremities, collagen contents in liver and lung, serum aminolevulinic acid (ALA) synthetase, urinary ALA level, and serum alpha-fetoprotein. A mild to markedly severe focal, disseminated vacuolization was observed in livers of most of the rats. No hemangiosarcomas were found in the liver or lung. The incidence of hemangiosarcomas in mesenteric lymph node or subcutaneous tissue was 2/36 in males and 0/35 in females.</p> <p>Viola and Caputo (1977) exposed 2-month-old Sprague-Dawley rats (30 males and 30 females per group) to 0, 75 ppm, or 100 ppm 1,1-DCE for 22–24 months (hours of daily exposure not reported). The incidence of tumors observed at necropsy (males and females combined) was 15/60; 10/36 and 20/60 at 0, 75 ppm, and 100 ppm, respectively. The tumors observed were classified as subcutaneous fibromas or abdominal lymphomas. The histopathological results from this study have not been published. No other data are reported for this study.</p> <p>Viola and Caputo (1977) also exposed 2-month-old albino Wistar rats (37 males and 37 females) to 1,1-DCE for 4 hrs/day, 5 days/wk, for 12 months. The exposure was at 200 ppm for the first 6 months and at 100 ppm for the rest of the study. A control group</p>	

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		<p>of 60 animals received air only. The incidence of tumors (described as reticulum cell sarcomas of a nonsyncytial type, primarily in the abdominal cavity) was 15/60 and 17/74 in control and exposed groups, respectively. No other data are reported from this study.</p> <p>Hong et al. (1981) evaluated mortality and tumor incidence in rats exposed to 1,1-DCE. Groups of 2-month-old CD rats of both sexes were exposed to 0 or 55 ppm 1,1-DCE 6 hrs/day, 4 days/wk for 1 month (four of each sex), 3 months (four of each sex), 6 months (four of each sex), or 10 months (16 of each sex). Following exposure, all animals were observed for an additional 12 months. In rats exposed for 10 months, there was an increase in mortality following the 12-month observation period (67% in exposed, 41% in controls). There was no significant increase in tumors at any site for any exposure period.</p> <p>Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Sprague-Dawley rats. Animals (16 weeks old) were exposed by inhalation to 0, 10, 25, 50, 100, or 150 ppm for 4 hrs/day, 4–5 days/wk for 52 weeks. The control group had 200 animals (100 of each sex); the 10, 25, 50, and 100 ppm groups had 60 animals (30 of each sex), and the 150 ppm group had 120 animals (60 of each sex). Following the 52-week exposure, animals were observed until spontaneous death (total duration 137 weeks). Body weight was measured every 2 weeks during the 52-week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed. No biologically significant changes were seen in mortality or body weight. There were no biologically significant noncancer effects in any organ in either sex and no increase in tumors in males at any site. There was a statistically significant increase (<math>p &lt; 0.05</math>) in each treatment group as compared with controls in the number of females with mammary fibromas and fibroadenomas. The incidence was 44/56 (78.6%), 24/24 (100%), 20/20 (100%), 21/22 (95.4%), 21/23 (91.3%), and</p>	

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		<p>38/43 (88.4%) in the control, 10, 25, 50, 100, and 150 ppm groups, respectively. The latency time and the number of tumors per tumor-bearing animal were similar among all groups. The incidence of mammary carcinoma in exposed groups was consistently less than that of controls. The incidence was 16/56 (28.6%), 5/24 (20.8%), 4/20 (20%), 1/21 (4.5%), 3/21 (13.0%), and 9/38 (20.9%) in the control, 10, 25, 50, 100, and 150 ppm groups, respectively.</p> <p>Quast et al. (1986) and Rampy et al. (1977) reported results from studies that exposed male and female Sprague-Dawley rats (Spartan substrain, 86 animals/group) to 1,1-DCE by inhalation 6 hrs/day, 5 days/wk, for up to 18 months. Interim sacrifices occurred at 1, 6, and 12 months. Rats were exposed to 1,1-DCE concentrations of 10 ppm and 40 ppm for the first 5 weeks of the study. Based on the absence of observable treatment-related effects among rats sacrificed after 1 month of exposure, the concentrations were increased to 25 and 75 ppm. Exposures were continued at these concentrations through the 18th month of the study. The surviving animals were then held without exposure to 1,1-DCE until 24 months. Cytogenetic evaluations were performed on a separate group of animals (four per sex) exposed to 0, 25, or 75 ppm for 6 months. There were no exposure-related changes in mortality, appearance and demeanor, body weight, clinical chemistry determinations, hematologic evaluations, urinalysis, or cytogenetic evaluation of bone marrow preparations. Although the incidences of several tumors and/or tumor types were found to be statistically increased or decreased as compared with controls, none of these differences were judged to be attributable to 1,1-DCE. The tumor incidence data for both control and treated rats in this study were comparable to historical control data for the Sprague-Dawley rats (Spartan substrain) used by this laboratory for several studies of similar design and duration.</p> <p>Cotti et al. (1988) exposed Sprague-Dawley rats to 1,1-DCE at 0 or</p>	

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		<p>100 ppm for 4–7 hrs/day, 5 days/wk. The exposures were to 13-week-old females for 104 weeks (60 control animals and 54 exposed animals) and to 12-day embryos for 15 or 104 weeks (158 males and 149 females as controls, 60 males and 60 females exposed for 15 weeks, and 62 males and 61 females exposed for 104 weeks). Animals were observed until spontaneous death. In males and females exposed for 104 weeks and in male offspring exposed for 15 weeks, a slight decrease in body weight (data not reported) was observed. An increased percentage of rats bearing malignant tumors (30.9% vs. 17.3 % in controls) and an increased number of malignant tumors per 100 animals (34.1% vs. 17.9% in controls) were observed in male and female offspring exposed for 104 weeks (statistical analysis not presented). An increase in leukemia in offspring, which appeared to be related to length of exposure (4.2% for controls, and 8.3% and 11.4% for exposure of 15 and 104 weeks, respectively), was also observed. Tumors at other sites (total benign and malignant tumors, total benign and malignant mammary tumors, malignant mammary tumors, and pheochromocytomas) showed no change or a decreased incidence. Data from this study are also reported in Maltoni et al. (1985).</p> <p><b>Mice.</b> Lee et al. (1977, 1978) exposed 2-month-old CD-1 mice (18 males and 18 females) to 0 or 55 ppm 1,1-DCE for 6 hrs/day, 5 days/wk, for up to 12 months. No deaths occurred in the control or exposed groups. Weight gain was comparable between groups. There was no change in hematology, clinical blood chemistry, cytogenetic analysis of bone marrow, x-ray examination of extremities, or serum alpha-fetoprotein. The livers showed no increase in mitotic figures using <sup>14</sup>C-thymidine incorporation. The incidence of bronchioalveolar adenoma (males and females combined) for 1–3 months exposure, 4–6 months exposure, 7–9 months exposure, and 10–12 months exposure was 0/24, 1/8, 2/10, and 3/28, respectively. The incidence of hemangiosarcomas in liver (males and females combined) for 6 months exposure, 7–9 months exposure, and 10–12 months exposure was 0/16, 1/10, and 2/28,</p>	

Chemical	Classification	Experimental animal information	Human information
		<p>respectively. No hemangiosarcomas were found in other tissues.</p> <p>Hong et al. (1981) evaluated mortality and tumor incidence rates in mice exposed to 1,1-DCE. Groups of 2-month-old albino CD-1 mice of both sexes were exposed to 0 or 55 ppm for 6 hrs/day, 4 days/wk, for 1 month (8 of each sex), 3 months (8 of each sex), or 6 months (12 of each sex). Following exposure, all animals were observed for an additional 12 months. In mice exposed for 6 months, there was a slight increase in mortality following the 12-month observation period (46% in exposed, 39% in controls). There was no significant increase in tumors at any site for any exposure period.</p> <p>Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Swiss mice. Animals (9 or 16 weeks old) were exposed by inhalation to 0, 10, or 25 ppm. Animals were exposed for 4 hrs/day, 4–5 days/wk, for 52 weeks. There were two control groups, one with 180 animals (90 of each sex) and the other with 200 animals (100 of each sex). The 10-ppm group had 60 animals (30 of each sex). Two groups were exposed to 25 ppm: one with 60 animals (30 of each sex) and the other with 240 animals (120 of each sex). Following the 52-week exposure, animals were observed until spontaneous death (total duration 126 weeks). Body weight was measured every 2 weeks during the 52-week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed.</p> <p>No biologically significant changes occurred in body weight. The exposed animals had a somewhat higher survival than controls. There was a statistically significant increase (<math>p &lt; 0.01</math>) as compared with controls in kidney adenocarcinomas in male mice at 25 ppm but not in male mice at 10 ppm or in female mice at either exposure. The incidence was 0/126 (0%), 0/25 (0%), and 28/119 (23.5%) in male mice in the combined controls, 10 ppm, and</p>	

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		<p>combined 25 ppm groups, respectively.</p> <p>There was a statistically significant increase (<math>p &lt; 0.01</math>) as compared with controls in mammary carcinomas in female mice at both exposures, but there was no clear exposure-response relationship. The incidence was 3/185 (1.6%), 6/30 (20%), and 16/148 (11%) in females in the combined controls, 10 ppm, and combined 25 ppm groups, respectively. There was also a statistically significant increase (<math>p &lt; 0.01</math>) compared with control in pulmonary adenomas in both exposed groups, but there was no clear exposure-response relationship. The incidence was 12/331 (3.6%), 14/58 (24.1%), and 41/288 (14.2%) in male and female mice combined in the combined controls, 10 ppm, and combined 25 ppm groups, respectively. There were no pulmonary carcinomas in any mice. The incidence data are reported as the number of tumor-bearing animals as compared with the number of animals alive when the first tumor was observed in that organ (kidney adenocarcinoma, 55 weeks; mammary tumor, 27 weeks; pulmonary adenoma, 36 weeks)</p> <p><b>Hamsters.</b> Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Chinese hamsters. Animals (28 weeks old) were exposed by inhalation to 0 or 25 ppm. Animals were exposed for 4 hrs/day, 4-5 days/wk, for 52 weeks. The control group had 35 animals (18 male and 17 female); the 25 ppm group had 60 animals (30 of each sex). Following the 52-week exposure, animals were observed until spontaneous death (total duration 157 weeks). Body weight was measured every 2 weeks during the 52-week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed. There were no biologically significant changes in mortality or body weight. No biologically significant noncancer or tumor effects were seen in any organ.</p>	

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		<p><b>Dermal.</b> Van Duuren et al. (1979) evaluated the carcinogenicity of 1,1-DCE in male and female noninbred Ha:ICR Swiss mice. Carcinogenicity was assessed in three types of tests: a dermal initiation-promotion assay, a repeated dermal application assay, and a subcutaneous injection assay. Vehicle, no-treatment, and positive control groups were included in the tests. In the initiation-promotion assay, 1,1-DCE was tested as a tumor-initiating agent with phorbol myristate acetate as the promoter. Thirty female mice were treated with 121 mg 1,1-DCE. A significant increase (<math>p &lt; 0.005</math>) was observed in skin papillomas (nine in eight mice). In the repeated dermal application assay, exposures of 40 and 121 mg/mouse were used. 1,1-DCE was applied to the back of the shaved animals (30 females/dose). No sarcomas were observed at the treatment site. Although 19 mice in the high-dose group and 12 in the low-dose group had lung tumors and 2 mice in the high-dose group had stomach tumors, the tumor incidence at both sites was not significantly different from that of controls (30 lung tumors and 5 stomach tumors). In the subcutaneous injection assay, the test animals were given weekly injections of 2 mg of 1,1-DCE. After 548 days on test, none of the injected animals developed sarcomas at the injection site. 1,1-DCE showed initiating activity in the two-stage carcinogenesis experiments but was inactive as a whole-mouse dermal carcinogen and after subcutaneous injection.</p>	
Carbon tetrachloride	Likely to be carcinogenic to humans	A general correspondence has been observed between hepatocellular cytotoxicity and regenerative hyperplasia and the induction of liver tumors. At lower exposure levels, this correspondence is less consistent. In particular, in the JBRC 2-year inhalation cancer bioassay in the mouse (Nagano et al., 2007b, JBRC, 1998), the lowest exposure concentration tested (5 ppm) was not hepatotoxic, whereas the incidence of liver adenomas in female	Studies in humans are inadequate to show an association between exposure to carbon tetrachloride and carcinogenicity. There is some evidence for certain types of cancer in occupational populations thought to have had some exposure to carbon

Chemical	Classification	Experimental animal information	Human information
		<p>mice at that concentration was statistically significantly increased compared to concurrent and historical controls.</p> <p>Carbon tetrachloride has been shown to induce hepatocellular carcinomas in rodents by oral, inhalation, and parenteral exposure. Researchers at the NCI conducted a series of oral gavage studies in mice of various strains and found large increases in the incidence of liver tumors in treated mice (Andervont, 1958; Edwards and Dalton, 1942; Edwards et al., 1942; Edwards, 1941). A similar result was obtained in hamsters (Della Porta et al., 1961). These animal studies were generally conducted using a single high dose of carbon tetrachloride, but one early study was conducted with multiple dose levels in order to investigate dose-response relationships for induction of liver tumors (Eschenbrenner and Miller, 1946). Eschenbrenner and Miller (1946) found liver tumors (hepatomas) in strain A male and female mice that received carbon tetrachloride by oral gavage (in olive oil) daily or every 4 days for 4 months.</p> <p>Oral bioassays of carbon tetrachloride using groups of 50 animals/sex were conducted in mice and rats by NCI (1977, 1976a, b) as a positive control for bioassays of chloroform, trichloroethylene, and 1,1,1-trichloroethane. The bioassay in mice employed very high doses (1,250 or 2,500 mg/kg, 5 days/week for 78 weeks) that produced close to 100% incidence of hepatocellular carcinoma. The incidence of adrenal adenoma and pheochromocytoma was also significantly increased in both dose groups in male and female mice. The bioassay in rats (47 or 94 mg/kg for males and 80 or 159 mg/kg for females, 5 days/week for 78 weeks) produced only a low incidence of liver tumors, but high early mortality, particularly in the high-dose group, may have affected the power of this study to detect a carcinogenic effect. Even so, the increase in carcinomas was statistically significant in</p>	<p>tetrachloride, including non-Hodgkin's lymphoma (NHL) (Blair et al., 1998; Spirtas et al., 1991), lymphosarcoma and lymphatic leukemia (Checkoway et al., 1984; Wilcosky et al., 1984), esophageal and cervical cancer (Blair et al., 1990, 1979), breast cancer (Cantor et al., 1995), astrocytic brain cancer (Heineman et al., 1994), and rectal cancer (Dumas et al., 2000). In these cases, exposure to carbon tetrachloride was poorly characterized and confounded by simultaneous exposures to other chemicals. Additionally, these studies were designed to evaluate tetrachloroethylene and trichloroethylene and had only limited ability to examine other chemical exposures such as carbon tetrachloride. None of the human epidemiology studies reported associations with cancer of the liver, which is the main site of carcinogenicity in animal studies, but this may be because of a lack of power to detect a relatively rare human tumor.</p>

Chemical	Classification	Experimental animal information	Human information
		<p>low-dose females (4/49) in relation to pooled controls (1/99).</p> <p>Carbon tetrachloride produced evidence of carcinogenicity in inhalation bioassays in rats and mice (Nagano et al., 2007b; JBRC, 1998). In rats, intermittent exposure (6 hours/day, 5 days/week) to 125 ppm for 2 years produced marked significant increases in the incidence of hepatocellular carcinomas and adenomas in both males and females. The incidence of tumors was not increased in rats exposed to 5 or 25 ppm by the same protocol although the incidence of liver carcinoma (3/50) in 25-ppm females exceeded the range of historical control incidence from JBRC 2-year bioassays. In mice, marked significant increases in hepatocellular carcinomas and (to a lesser extent) adenomas occurred at both 25 and 125 ppm in both sexes. Also, a statistically significant increase in the incidence of liver adenomas in female mice at 5 ppm was observed compared to the concurrent control and exceeded the historical control range for hepatocellular adenomas from JBRC 2-year bioassays. Significant increases were also observed in the incidence of benign adrenal pheochromocytomas in males at 25 or 125 ppm and females at 125 ppm. Only one pheochromocytoma in a high-exposure male mouse was classified as malignant.</p> <p>Subcutaneous injections of carbon tetrachloride at an average dose of 0.29 mg/kg-day for 33-47 weeks induced hepatocellular carcinomas in Osborne-Mendel, Japanese, and Wistar rats but not in Sprague-Dawley or black rats (Reuber and Glover, 1970, 1967a, b). Intraperitoneal injections at an average of 86 mg/kg-day induced hepatomas in C3H mice (Kiplinger and Kensler, 1963).</p>	
Chloroform	B2, probable human carcinogen	At high doses, chloroform has been reported to be carcinogenic in several chronic animal bioassays, with significant increases in the incidence of liver tumors in male and female mice and significant increases in the incidence of kidney tumors in male rats and mice	There are no epidemiological data attributing cancer to exposure to chloroform <i>per se</i> . Although there are some equivocal epidemiological data

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	likely to be carcinogenic to humans by all routes of exposure	<p>(U.S. EPA, 1994, 1998c). When examining the biology of the tumor production, the occurrence of tumors is demonstrably species-, strain-, and gender-specific, and has only been observed under dose conditions that caused cytotoxicity and regenerative cell proliferation in the target organ.</p> <p>In a gavage bioassay (NCI, 1976), Osborne-Mendel rats and B6C3F1 mice were treated with chloroform in corn oil 5 times/week for 78 weeks (50 animals per sex per dose group). Male rats received 90 or 125 mg/kg/day; females initially were treated with 125 or 250 mg/kg/day for 22 weeks and 90 or 180 mg/kg/day thereafter. A decrease in survival rate and weight gain was evident for all treated rats. A significant increase in kidney epithelial tumors was observed in male rats (0% in controls, 8% in the low dose and 24% in the high dose groups). Male mice received 100 or 200 mg/kg/day, raised to 150 or 300 mg/kg/day at 18 weeks; females were dosed with 200 or 400 mg/kg/day, raised to 250 or 500 mg/kg/day. Survival rates and weight gains were comparable for all groups except high dose female mice which had a decreased survival. In mice, highly significant increases in hepatocellular carcinomas were observed in both sexes (98% and 95% for males and females at the high dose; 36% and 80% for males and females at the low dose as compared with 6% of both matched and colony control males, 0% in matched control females and 1% in colony control females). Nodular hyperplasia of the liver was observed in many low dose male mice that had not developed hepatocellular carcinoma. Hepatomas have also developed in female strain A mice and NLC mice gavaged with chloroform (Eschenbrenner and Miller, 1945; Rudali, 1967).</p> <p>Jorgenson et al. (1985) administered chloroform (pesticide quality and distilled) in drinking water to male Osborne-Mendel rats and female B6C3F1 mice at concentrations of 200, 400, 900, and 1,800 mg/L for 104 weeks. These concentrations were reported by the</p>	<p>relating a weak association of drinking water exposures to bladder, rectal and colon cancer (Morris et al. 1992 ; McGeehin et al., 1993; Vena et al. 1993; Morris, 1995; King and Marrett, 1996; Doyle et al., 1997; Freedman et al., 1997; Cantor et al, 1998; Hildesheim et al., 1998), these studies can not attribute to chloroform among multiple other disinfection byproducts (DBPs) (SAB, 2000, ATSDR, 1997; IPCS, 2000). Morris et al. (1992) did a meta-analysis that pooled the relative risks from ten cancer epidemiology studies in which there was a presumed exposure to chlorinated water and its byproducts and estimated that approximately 10,000 cases of rectal and bladder cancer cases per year could be associated with exposure to DBPs in chlorinated water in the United States. Later, Poole (1997) reviewed the studies available to Morris et al. (1992) plus three additional studies (McGeehin et al., 1993; Vena et al., 1993; and King and Marrett, 1996). Poole (1997) observed that there was considerable heterogeneity among the data and that there was evidence of publication bias within the body of literature. In addition, Poole found that the aggregate estimates reported by Morris et al. were sensitive to small</p>

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		<p>author to correspond to 19, 38, 81, and 160 mg/kg/day for rats and 34, 65, 130, and 263 mg/kg/day for mice. The combined benign and malignant renal tumor incidence in male rats was 2%, 2%, 2%, 5%, 6% and 14% for the control, matched control, 19, 38, 81, and 160 mg/kg/day groups, respectively. A significant increase in renal tumors (14%) in rats was observed in the highest dose group (160 mg/kg/day). A reevaluation of the histopathology of the slides (Hard et al., 2000), found evidence of persistent cytotoxicity and regenerative hyperplasia in all rats of the highest dose group. Similar changes were also observed in rats at 81 mg/kg/day, but at a much lower incidence and grade. Thus, the histopathology reexamination provides evidence supporting chronic renal tubule injury as the mode of action underlying the renal tumor response. The liver tumor incidence in female mice was not significantly increased.</p> <p>Chloroform administered in toothpaste was not carcinogenic to male C57B1, CBA, CF-1, or female ICI mice or to beagle dogs. Male ICI mice administered 60 mg/kg/day were found to have an increased incidence of kidney epithelial tumors (Roe et al., 1979; Heywood et al., 1979). A pulmonary tumor bioassay in strain A/St mice was negative, as was one in which newborn C57X DBA2/F1 mice were treated s.c. on days 1 to 8 of life (Theiss et al., 1977; Roe et al., 1968).</p> <p>Matsushima (1994) exposed F344 rats (50/sex/group) and BDF1 mice (50/sex/group) to chloroform vapor 6 hours/day, 5 days/week for 104 weeks. Rats were exposed to concentrations of 0, 10, 30, or 90 ppm, and mice were exposed to 0, 5, 30, or 90 ppm. In order to avoid short- term lethality, mice in the two highest groups (30 and 90 ppm) were initially exposed to a lower levels for 2-6 weeks before the long-term exposure. The time-weighted average (TWA) for the 30 ppm group was 29.1 ppm and for the 90 ppm group was 85.7 ppm (U.S. EPA, 1998a). Statistically significant increases in</p>	<p>changes in the analysis (e.g., addition or deletion of a single study). Based on the observations, Poole recommended that the cancer epidemiology data considered in the Morris evaluation should not be combined into a single summary estimate and that the data had limited utility for risk assessment purposes. Based on the available cancer epidemiology database, bladder cancer studies provide the strongest evidence for an association between exposure to chlorinated water and cancer. Based on the studies of Cantor et al. (1985), McGeehin et al. (1993), King and Marrett (1996), Freedman et al. (1997), and Cantor et al. (1998), EPA calculated that the population attributable risk (the fraction of a disease that could be eliminated if the exposure of concern were eliminated) for bladder cancer ranged from 2% to 17% (U.S. EPA, 1998c). However, these calculations are based on a number of assumptions, including the assumption that there is a cause-effect relationship between exposure to chlorinated drinking water and increased risk of bladder cancer. This assumption is subject to considerable uncertainty, especially because findings are not consistent within or between studies. Evaluation of these</p>

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		<p>the incidence of overall renal cell adenoma and renal cell carcinoma were observed in male mice in the 30 (7/50) and 90 (12/48) ppm groups, when compared to controls (0/50). The overall incidence rates of renal cell carcinoma were statistically significantly increased in males in the 90-ppm group (11/48) when compared to controls (0/50). There were no statistically significant findings reported for female mice in any exposure groups.</p>	<p>studies by application of standard criteria for establishing causality from epidemiological observations (strength of association, consistency of findings, specificity of association, temporal sequence, dose-response relation, biological plausibility) has led EPA to conclude that the current data are insufficient to establish a causal relationship between exposure to chloroform and increased risk of cancer (U.S. EPA, 1998a). Moreover, if, in the future, the weight-of-evidence does reach a point where a causal link is established between exposure to chlorinated water and increased risk of bladder or other types of cancer, it could not be concluded from epidemiological studies of this type that chloroform per se is carcinogenic in humans, as chlorinated water contains numerous disinfection byproducts besides chloroform that are potentially carcinogenic (U.S. EPA, 1998a).</p>
Dichloromethane	B2; probable human carcinogen	<p>Dichloromethane administered in the drinking water induced a significant increase in combined hepatocellular carcinoma and neoplastic nodules in female F344 rats and a nonsignificant increase in combined hepatocellular carcinoma and neoplastic nodules in male B6C3F1 mice (NCA, 1982, 1983). Two inhalation studies with dichloromethane have shown an increased incidence of benign mammary tumors in both sexes of Sprague-Dawley (Burek</p>	<p>Neither of two studies of chemical factory workers exposed to dichloromethane showed an excess of cancers (Ott et al., 1983; Friedlander et al., 1978; Hearne and Friedlander, 1981). The Ott et al. (1983) study was designed to examine</p>

Chemical	Classification	Experimental animal information	Human information
		<p>et al., 1984) and F344 (NTP, 1986) rats. Male Sprague-Dawley rats had increased salivary gland sarcoma (Burek et al., 1984) and female F344 rats had increased leukemia incidence (NTP, 1986). Both sexes of B6C3F1 mice developed liver and lung tumors after dichloromethane treatment (NTP, 1986).</p> <p>In a 2-year study by the National Coffee Association (1982, 1983), groups of 85 F344 rats/sex/dose received 5, 50, 125, or 250 (mg/kg)/day of dichloromethane in the drinking water. Control groups consisted of 135 rats/sex. In female rats the incidence of combined hepatocellular carcinoma and neoplastic nodules was statistically significantly increased in the 50 and 250 mg/kg dose groups when compared with matched controls (0/134, 1/85, 4/83, 1/85, and 6/85 in the five dose groups 0, 5, 50, 125, and 250 (mg/kg)/day, respectively). The incidence of hepatocellular carcinoma alone was not significantly increased (0/134, 0/85, 2/83, 0/85, 2/85). The combined incidence of hepatocellular carcinoma and neoplastic nodules in controls and the 4 dose groups (472 rats: 4 with carcinoma and 8 with neoplastic nodules) was similar to that for historical controls (419 rats; 5 with carcinoma, 19 with neoplastic nodules). Male rats showed no increase in liver tumors.</p> <p>In the same National Coffee Association study (1982, 1983), B6C3F1 mice received 0, 60, 125, 185, or 250 (mg/kg)/day of dichloromethane in drinking water. Treatment groups consisted of 50 female mice and 200, 100, 100, and 125 male mice (low to high dose). One hundred females and 125 males served as controls. Male mice had an increased incidence of combined neoplastic nodules and hepatocellular carcinoma (24/125, 51/200, 30/100, 31/99, 35/125). The increase was not dose-related, but the pairwise comparisons for the two mid- dose groups were reported to be statistically significant (U.S. EPA, 1985a). The hepatocellular carcinoma incidence alone for male mice (which was about 55 to 65% of the total) was not significantly elevated. Female mice did</p>	<p>cardiovascular effects, and consequently the study period was too short to allow for latency of site-specific cancers. In the Friedlander et al. (1978) study, exposures were low, but the data provided some suggestion of an increased incidence of pancreatic tumors. This study was recently updated to include a larger cohort, followed through 1984, and an investigation of possible confounding factors (Hearne et al., 1986, 1987). A nonsignificant excess in pancreatic cancer deaths was observed, which was interpreted by EPA (1987a) as neither clear evidence of carcinogenicity in humans, nor evidence of noncarcinogenicity. An update of the Ott et al. (1983) study, based on longer follow-up, indicated possible elevation of liver and biliary tract cancers (TSCA section 8(e) submission no. 8eHQ-0198-0772 FLWP et seq., 1989).</p>

Chemical	Classification	Experimental animal information	Human information
		<p>not have increased liver tumor incidence. The EPA (1985b) regarded this study as suggestive but not conclusive evidence for carcinogenicity of dichloromethane.</p> <p>A gavage bioassay of dichloromethane conducted by NTP (1982) has not been published because of high mortality, much of which was attributed to gavage accidents.</p> <p>Inhalation exposure of 107 to 109 Syrian hamsters/sex/dose to 0, 500, 1500, or 3500 ppm of dichloromethane for 6 hours/day, 5 days/week for 2 years did not induce neoplasia (Burek et al., 1984). Sprague-Dawley rats (129/sex/ dose) were exposed under the same conditions. Female rats administered the highest dose experienced significantly reduced survival from 18-24 months. Female rats showed a dose-related increase in the average number of benign mammary tumors per rat (1.7, 2.3, 2.6, 3.0), although the numbers of rats with tumors were not significantly increased. A similar response was observed in male rats, but to a lesser degree. In the male rats there was a statistically significant positive trend in the incidence of sarcomas of the salivary gland (1/93, 0/94, 5/91, 11/88); the incidence was significantly elevated at the high dose. There is a question as to whether these doses reached the MTD, particularly in the hamsters and the male rats. In another study (Dow Chemical Co., 1982), 90 Sprague-Dawley rats/sex were exposed by inhalation to 0, 50, 200, or 500 ppm dichloromethane for 20 months (male) or 24 months (female). No salivary tumors were observed, but there was an exposure-related increase in the total number of benign mammary tumors in female rats, although the increase was not statistically significant in any individual exposure group.</p> <p>Groups of 50 each male and female F344/N rats and B6C3F1 mice were exposed to dichloromethane by inhalation, 6 hours/day, 5 days/week for 2 years (NTP, 1986). Exposure concentrations were</p>	

Chemical	Classification	Experimental animal information	Human information
		<p>0, 1000, 2000, or 4000 ppm for rats and 0, 2000, or 4000 ppm for mice. Survival of male rats was low; however, this apparently was not treatment-related. Survival was decreased in a treatment-related fashion for male and female mice and female rats. Mammary adenomas and fibroadenomas were significantly increased in male and female rats after survival adjustment, as were mononuclear cell leukemias in female rats. Among treated mice of both sexes there were significantly increased incidences of hepatocellular adenomas and carcinomas, and of alveolarbronchiolar adenomas and carcinomas, by life table tests. Adenomas and carcinomas were significantly increased alone as well as in combination. In addition, there were significant dose-related increases in the number of lung tumors per animal multiplicity in both sexes of mice.</p> <p>Two inhalation assays using dogs, rabbits, guinea pigs, and rats showed no tumors, but were not conducted for the lifetime of the animals (Heppel et al., 1944; MacEwen et al., 1972). Theiss et al., (1977) injected Strain A male mice intraperitoneally with 0, 160, 400, or 800 mg/kg of dichloromethane 16 to 17 times, over 5 to 6 weeks. Survival of the animals was poor. The animals remaining 24 weeks after the first treatment were killed and examined for lung tumors; pulmonary adenomas were found.</p>	
Bromodichloromethane	B2; probable human carcinogen	<p>In a 2-year carcinogenicity study (NTP, 1987), bromodichloromethane was administered in corn oil by gavage, 5 days/week for 102 weeks, to F344/N rats (50/sex/dose) at 0, 50 or 100 mg/kg/day. Similarly, groups of 50 male B6C3F1 mice were given oral doses of 0, 25 or 50 mg/kg/day and groups of 50 female B6C3F1 mice were administered doses of 0, 75 or 150 mg/kg/day. The study using the male rats was restarted 10.5 months into the original study because a temperature elevation killed 45/50 of the vehicle control male rats. Survival was reduced 52%, 26% and 30%</p>	<p>There are no epidemiologic studies of bromodichloromethane alone. Bromodichloromethane is one of several trihalomethanes (including chloroform, bromoform and dibromochloromethane) that are formed from the interaction of chlorine with organic materials found in water. A large number of other</p>

Chemical	Classification	Experimental animal information	Human information
		<p>in the control, low- dose and high-dose females, respectively, after week 84; the mortality was associated with ovarian abscesses.</p> <p>Bromodichloromethane caused compound-related statistically significant increases in tumors of the kidney in male mice, the liver in female mice, and the kidney and large intestine in male and female rats. In male mice, the incidence of tubular cell adenomas (vehicle control, 1/46; low dose, 2/49; high dose, 6/50) and the combined incidence of tubular cell adenomas and adenocarcinomas of the kidneys were significantly increased in the high-dose (50 mg/kg/day) group (1/46, 2/49 and 9/50 in the control, low-dose and high- dose groups, respectively). In female mice, significant increases of hepatocellular adenomas occurred at 75 mg/kg/day and 150 mg/kg/day while hepatocellular carcinomas were significantly increased at 150 mg/kg/day. The combined incidence of hepatocellular adenomas or carcinomas in vehicle control, low-dose and high-dose groups were 3/50, 18/48 and 29/50, respectively.</p> <p>In male and female rats, the incidences of tubular cellular adenomas, adenocarcinomas, and the combined incidence of adenomas and adenocarcinomas of the kidneys were statistically significantly increased only in the high-dose (100 mg/kg/day) groups. The combined incidence of tubular cell adenomas or adenocarcinomas in vehicle control, low-dose and high-dose groups were 0/50, 1/49 and 13/50 for males, and 0/50, 1/50 and 15/50 for females, respectively. Tumors of large intestines, namely adenocarcinomas (vehicle control, 0/50; low dose, 11/49; high dose, 38/50) and adenomatous polyps (0/50, 3/49 and 33/50 in the vehicle control, low-dose and high-dose groups, respectively) were significantly increased in male rats in a dose-dependent manner. These large intestinal tumors, however, were only observed in high-dose (100 mg/kg/day) female rats (adenocarcinomas 0/46, 0/50, 6/47; adenomatous polyps 0/46, 0/50, 7/47 in the vehicle control, low-dose and high-dose groups, respectively). The combined incidence of large intestine</p>	<p>byproducts are present in chlorinated water as well. Several ecologic studies (Cantor et al., 1978; Aldrich and Peoples, 1982; Isacson et al., 1983) and case-control studies (Young and Kanarek, 1983; Cantor et al., 1987) suggest a positive correlation between drinking chlorinated water and the incidence of several human cancers, particularly bladder, rectal and colon cancer. These studies have design limitations such as lack of individual exposure information, misclassification of exposure, and lack of data to control for diet, smoking or alcohol consumption. The agreement of findings in several independent studies strengthens the association between drinking chlorinated water and cancer (Cantor, 1983; Crump, 1983). However, in all studies exposure to chlorinated water resulted in intake of a mixture of compounds, including chloroform, which is considered to be a probable human carcinogen. Thus, these data are inadequate for assessing the carcinogenic potential of bromodichloromethane in humans.</p>

Chemical	Classification	Experimental animal information	Human information
		<p>adenocarcinomas and/or adenomatous polyps in vehicle control, low-dose and high-dose groups were 0/50, 13/49 and 45/50 for males and 0/46, 0/50 and 12/47 for females. The combined tumor incidence of large intestine and kidney in male and female rats at control, low dose and high dose were 0/50, 13/49, 46/50 and 0/46, 1/50, 24/48, respectively. Under the conditions of this bioassay, NTP concluded there was clear evidence of carcinogenicity of bromodichloromethane in male and female F344/N rats and B6C3F1 mice.</p> <p>Hepatic tumor data reported in female mice should be interpreted with caution, however, because of the possible role of the corn oil vehicle in induction of these tumors. Chloroform, a closely related structural analogue, induced hepatocellular carcinoma in mice (NCI, 1979) when administered in corn oil (NCI, 1976; Roe et al., 1976), but not in drinking water (Jorgenson et al., 1985). Based primarily on the fact that the drinking water study did not replicate hepatic tumors in female mice and on the potential role of corn oil in enhancing toxicity, the NAS Subcommittee on the Health Effects of Disinfectants and Disinfection By-Products recommended that kidney tumor data obtained from Jorgenson's study be used for estimating carcinogenic risk of chloroform (NAS, 1987; U.S. EPA, 1992a,b,c, 1993).</p> <p>On October 25-26, 1990, the Science Advisory Board's Drinking Water Committee held a meeting in Washington, DC to review the Office of Water's draft Drinking Water Criteria Document for Trihalomethanes (including bromodichloromethane) (1990 version). Based on the concern of the corn oil vehicle effect cited for chloroform, the Committee concluded that hepatic tumor induction by a trihalomethane administered in an oil vehicle should be utilized only in making the weight-of-evidence judgement for carcinogenicity, and these hepatic tumor data should be disregarded in making a quantitative estimation of the carcinogenic risk of a trihalomethane. Commenting on bromodichloromethane</p>	

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		<p>specifically, the Committee considered the use of renal or intestinal tumor incidence for carcinogenic risk calculation to be appropriate. The Committee regarded the resulting kidney tumors to be independent from the vehicle effects (U.S. EPA, 1992d). The Committee also commented that large intestinal tumors are not commonly seen in the rat, the tumor incidence was high in males, and was observed in both sexes (U.S. EPA, 1992d).</p> <p>Theiss et al. (1977) tested bromodichloromethane in a short-term lung adenoma test in strain A/St male mice. Twenty mice/group were injected intraperitoneally with 0, 20, 40 or 100 mg/kg of bromodichloromethane in tricaprylin, 3 times/week for a total of 18-24 injections (total doses were 0, 360, 960 or 2400 mg/kg, respectively). There was no effect of treatment on survival. Twenty-four weeks after the first injection, the mice were sacrificed and the lungs examined for surface adenomas. The number of pulmonary tumors per mouse appeared elevated in the high-dose animals, although the increase was not statistically significant (p=0.062).</p> <p>In a unpublished but documented 2-year study, SPF Wistar rats (40/sex/group) were fed a diet supplemented with 0.014, 0.055 or 0.22% microencapsulated bromodichloromethane (Tobe et al., 1982). Based on reported body weights (150-475 g) and food consumption (15-20 g/day), these levels correspond to doses of about 6, 24 or 130 mg/kg/day for males and 11, 41 or 220 mg/kg/day for females. Controls (70/sex) received empty microcapsules. At 6, 12 and 18 months, 9-12/sex of the controls and 5-7/sex/group of the treated rats were sacrificed. The remainder of the animals were sacrificed at 24 months. Body weight was decreased in the high-dose animals by 25% relative to controls. Mortality was not correlated with dose in either males or females. Survival at 24 months was 77, 81, 75 and 77% in females and 58, 60, 62 and 79% in males for the control, low-, mid- and high-dose groups, respectively. No gross tumors were observed at 18 or 24</p>	

Chemical	Classification	Experimental animal information	Human information
		<p>months; histopathology was not reported.</p> <p>Tumasonis et al. (1985) administered 1.2 mL bromodichloromethane per liter of drinking (tap) water to male and female Wistar rats for 72 weeks, after which concentrations were halved for the remainder of the lifetime of the animals (140-180 weeks). Controls were untreated. Body weight decreased in treated animals relative to controls by approximately 35-40%. The authors estimated the treated animals consumed 150 mg/kg/day (females) or 200 mg/kg/day (males). Hepatic neoplastic nodules were significantly elevated in female rats (17/53) when compared with controls (0/18). Neoplastic nodules in males and lymphosarcomas and pituitary tumors in both sexes were reported, but did not have an significantly increased incidence relative to the controls. Of the treated animals, two males and one female were noted to have renal adenoma or adenocarcinoma, while none were reported in the control group.</p> <p>Voronin et al. (1987) examined the carcinogenicity of bromodichloromethane in CBA x C57Bl/6 mice. Groups of 50-55 mice/sex were treated with bromodichloromethane in drinking water at concentrations of 0.04, 4.0 or 400 mg/L (0.0076, 0.76 or 76 mg/kg/day) for 104 weeks. An untreated control group with 75 male and 50 female mice was also maintained. Total tumor incidences, based on the number of mice surviving until detection of the first tumor, were 4/63 (6%), 3/35 (8%), 1/16 (6%) and 1/18 (9%) for males, and 3/34 (9%), 1/45 (2%), 1/18 (6%) and 1/13 (8%) for females in the control, low-, mid- and high- dose groups, respectively. The authors concluded that the results were not statistically significant by chi square analysis, and that under the conditions of this bioassay, bromodichloromethane was not carcinogenic.</p>	

\*Information taken from U.S. EPA (U.S. Environmental Protection Agency). 2010. Integrated Risk Information System (IRIS). National Center for Environmental Assessment. Online at [www.epa.gov/iris](http://www.epa.gov/iris).