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Provisional Peer Reviewed Toxicity Values for

(mixed isomers)
1,4-Dichloro-2-butene (CASRN 764-41-0)
cis-1,4-Dichloro-2-butene (CASRN 1476-11-5)
trans-1,4-Dichloro-2-butene (CASRN 110-57-6

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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose

PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 1,4-DICHLORO-2-BUTENE (CASRN 764-41-0)

Background

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

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

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

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

Disclaimers

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

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

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

INTRODUCTION

1,4-Dichloro-2-butene and other dichlorobutene isomers belong to a family of compounds called haloalkenes. Several members of that family demonstrate carcinogenicity and mammalian toxicity regardless of the route of exposure (U.S. EPA, 1987). 1,4-Dichloro-2-butene is generally found as a mixture of the cis- and trans- isomers (trans- isomer shown in Figure 1). All the available toxicity tests were conducted with mixtures of the cis- and trans-isomers. In most cases the ratio of isomers is not reported.

1,4-Dichloro-2-butene is used as an intermediate in the production of chloroprene, as a starting material in the production of adiponitrile (the precursor to adipic acid and hexamethylenediamine, which are starting materials in the synthesis of nylon) and as a starting material in the production of butane-1,4-diol and tetrahydrofuran (Rossberg et al., 2006). For 1,4-dichloro-2-butene, the empirical formula for is $C_4H_6Cl_2$ (MW = 125.0) and it has a vapor pressure of 5 mm Hg (U.S. EPA, 1987).

Figure 1. 1,4-Dichloro-2-butene Structure

The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS; U.S. EPA, 2007) does not list a chronic oral reference dose (RfD), chronic inhalation reference concentration (RfC) or cancer assessment for 1,4-dichloro-2-butene. Neither the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997) nor the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) include subchronic or chronic RfDs or RfCs for 1,4-dichloro-2-butene; the HEAST cites inadequate data for noncancer quantitative risk assessment of dichlorobutenes. A cancer inhalation unit risk of 2.6×10^{-3} $(\mu g/m^3)^{-1}$ is listed in the HEAST (U.S. EPA, 1997), and a Health and Environmental Effects Document (HEED) for dichlorobutenes (U.S. EPA, 1987) is the cited source document. The inhalation unit risk for 1,4-dichloro-2-butene is based on nasal tumors in rats repeatedly exposed to 1,4-dichloro-2-butene vapors for 12-19 months and observed for up to 2 years (E.I. DuPont, 1985b, 1986). U.S. EPA (1987) did not derive subchronic or chronic RfC values for 1,4-dichloro-2-butene based on the appearance of benign and malignant nasal tumors in rats as early as 10-12 months following the initiation of inhalation exposures and the possibility that early nonneoplastic lesions were preneoplastic in nature. No RfD values were derived for 1,4-dichloro-2-butene based on the lack of oral data (U.S. EPA, 1987).

The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) includes the HEED for dichlorobutenes (U.S. EPA, 1987) and an earlier Health and Environmental Effects Profile (HEEP) for dichlorobutenes (U.S. EPA, 1983). The American Conference of Governmental Industrial Hygienists (ACGIH, 2006) has adopted a TWA of 0.005 ppm for 1,4-dichloro-2-butene based on upper respiratory tract and ocular irritation; the ACGIH (2006) includes a skin notation and A2 cancer classification (suspected human carcinogen). No standards for occupational exposure to 1,4-dichloro-2-butene have been established by the National Institute for Occupational Safety and Health (NIOSH, 2007), or the Occupational Safety and Health Administration (OSHA, 2007). Neither the Agency for Toxic Substances and Disease Registry (ATSDR, 2007) nor the World Health Organization (WHO, 2006) have published toxicological reviews on 1,4-dichloro-2-butene or dichlorobutenes. Toxicological review documents for *trans*-1,4-dichloro-2-butene include International Agency for Research on Cancer monographs (IARC, 1977, 1999) and a review of literature prepared for the National Institute of Environmental Health Sciences(NTP,1997), which were consulted for relevant information. A review of the toxicity of chloroprene, 1,3-dichloro-2-butene and 1,4-dichloro-2-butene (Clary, 1977) was examined for relevant information.

Literature searches for studies relevant to the derivation of provisional toxicity values for 1,4-dichloro-2-butene (CASRN 764-41-0) were conducted in PUBMED, TOXLINE special, and DART/ETIC (1960's-June 2007); BIOSIS (August 2000-June 2007); TSCATS/TSCATS2, RTECS, CCRIS, HSDB and GENETOX (not date limited); and Current Contents (January-June 2007). The NTP status report (NTP, 2007) was also consulted for relevant information. A final search of the published literature was conducted for the period from June 2007 through July 2008.

REVIEW OF PERTINENT DATA

Human Studies

In a retrospective cohort mortality study of male workers exposed to 1,4-dichloro-2-butene at a DuPont plant in Texas (E.I. DuPont, 1985a), cancer incidence and mortality from all causes and cancer among the workers were compared to those expected based on DuPont and U.S. rates and adjusted for age and calendar time period. The cohort consisted of current or former male employees (525 hourly and 73 salaried workers), from the year 1956 (for cancer incidence) or 1957 (for mortality rates) through December 31, 1980. Only those employees who were on the payroll at the time of first exposure to 1,4-dichloro-2-butene were included. Other vital information included birth date, occupation, and dates for each assignment to areas where 1,4-dichloro-2-butene was present. Person-years of risk were calculated for each member of the cohort, starting with the date of first exposure. Information regarding duration of exposures was not included in the study report. Information regarding cancer status among the cohort included only those persons who were actively employed at the time of diagnosis because not all cancer cases diagnosed after termination from the company could be identified. The study included analysis both without and with a 15-year latency adjustment to account for development of cancer at some time after initial exposure.

There were 23 deaths among the hourly workers versus 9.6 and 44.1 expected deaths based on DuPont and U.S. rates, respectively. Seven deaths due to malignant cancer (4 lung, 2 pancreas, 1 rectal) occurred among the cohort versus 6.6 and 8.4 expected based on DuPont and U.S. rates, respectively. No specific cause of death or type of cancer death was significantly in excess in either analysis. Separate analysis of the salaried workers revealed no significant excesses in death or type of cancer deaths. Among actively employed hourly workers (n=374), thirteen cases of cancer (2 lung, 3 pancreas, 2 malignant melanoma, 1 each large intestine, rectum, kidney, testis, leukemia, Hodgkin's disease) were recorded versus 12.7 and 15.0 expected based on DuPont and U.S. rates, respectively. The 3 cases of pancreatic cancer were higher than expected (0.3 and 0.4 expected based on DuPont and U.S. rates, respectively). Among 41 actively employed salaried workers, 2 cases of cancer (prostate and kidney) were observed. Analysis based on a 15-year latency period resulted in no statistically significant differences between observed and expected death or type of cancer death, although pancreatic cancer was still slightly higher than expected (2 cases observed versus 0.5 expected based on either DuPont or U.S rates. Overall, this study was equivocal with regard to compound-related increases in cancer mortality.

No other studies were located regarding health effects associated with 1,4-dichloro-2-butene exposure in humans.

Animal Studies

Oral Exposure

Oral studies of 1,4-dichloro-2-butene are limited to a series of poorly reported studies from the Russian literature. U.S. EPA (1987) summarized the results of a study (Petrosyan et al.,

1983) in which renal function was assessed in groups of white rats administered 1,4-dichloro-2-butene intragastrically at doses of 0, 0.001, 0.01 or 0.1 mg/kg (assumed daily doses) for 6 months. Renal function was monitored by measurement of daily diuresis, specific gravity of urine and blood serum, and urinary concentrations of creatinine and chlorides. Decreased diuresis, increased excretion of chlorides and decreased blood creatinine with increased urinary creatinine were observed at the two highest dose levels (0.01 and 0.1 mg/kg), although function appeared normal by the end of the test period. This study was limited to assessments of renal function.

The reproductive toxicity of 1,4-dichloro-2-butene was assessed in male rats administered the chemical orally at 0, 0.001, 0.01 or 0.1 mg/kg (presumed daily doses) for 2.5 months prior to mating with unexposed female rats (Bal'yan et al., 1983a). Pregnant dams were sacrificed on gestation day 21 for assessment of uterine contents. Parameters assessed included percentage of effective matings and morphological and functional characteristics of spermatozoa and numbers of *corpora lutea*. Pre- and post-implantation mortality indices were calculated as well. The study authors noted a treatment-related decrease in percentage of successful matings, although data regarding the magnitude or statistical significance were not included. Statistically significant treatment-related effects on testes were predominantly seen in mid- and high-dose males and included increased percentage of dead spermatozoa, decreased number of spermatozoa and increases in the numbers of seminiferous tubules with desquamated epithelium and tubules in 12^{th} stage of meiosis. Pathological examination of spermatozoa revealed frequent adhesion of the tail to the head. The study appears to identify a NOAEL of 0.001 mg/kg-day and a LOAEL of 0.01 mg/kg-day for sperm abnormalities and decreased fertility. However, poor reporting of study details precludes the usefulness of this study for RfD derivation.

Developmental toxicity was assessed in pregnant and nonpregnant rats exposed to 1,4-dichloro-2-butene by oral exposure for 21 days (Petrosyan et al., 1982). Intragastric doses were 0, 0.001, 0.01 and 0.1 mg/kg (additional exposure details were not included in the report). Reported exposure-related effects included increased post-implantation mortality, fetal hemorrhaging in liver and diaphragm, plethoric placentas, dilation of the capillaries and lacunae and decreased RNA content in hepatocytes, cerebral glia, alveolar cells and glomerular epithelium. Because more specific details of results were not included in the report, the results are not useful for quantitative risk characterization.

Inhalation Exposure

A subacute range-finding inhalation toxicity study (E.I. DuPont, 1992a) was conducted in rats to determine suitable exposure levels for a subsequent chronic cancer bioassay. Groups of young adult male and female Charles River-CD rats (15/sex/group) were exposed to 1,4-dichloro-2-butene (approximately 15:85 cis:trans ratio) at target concentrations of 0, 0.5, 2, 8, or 12 ppm (0, 2.56, 10.2, 40.9 or 61.3 mg/m^3) for 6 hours/day, 5 days/week for 4 weeks. Clinical signs and body weights were monitored. At termination of exposures, 10 rats/sex/group were sacrificed; the remaining 5 rats/sex/group were sacrificed following a 2-week post-exposure recovery period. Assessments at sacrifice included clinical chemistry, hematology, urinalysis, organ weights and gross and histopathologic examinations of major organs and tissues.

Occasional clinical signs of respiratory irritation (wheezing, rales, etc.) were observed in most test groups during the 4-week exposure period; however incidences were highest in 12 ppm males and females (approximately 40% affected) compared to 0 and 27% in control male and female rats, respectively (E.I. DuPont, 1992a). Rats of the 0.5 and 2 ppm exposure groups did not exhibit clinical signs that could be attributed to 1,4-dichloro-2-butene exposure. A single male rat exposed to 12 ppm died after the fourth exposure day, but the study authors did not consider the death to have been exposure related. At the end of the exposure period, mean body weights in male rats exposed to 8 and 12 ppm and female rats exposed to 12 ppm were approximately 9, 27 and 11% lower, respectively, than those of control rats (based on visual inspection of the graphed body weight results). The mean body weights of other exposure groups did not appear to differ significantly from those of controls. Significant exposure-related increases in several blood values (RBC count, hematocrit, MCV, MCH and WBC count) were observed after the final exposure period; however, by 14 days post-exposure, only hematocrit and WBC counts in 8 and 12 ppm exposure groups remained significantly elevated. Clinical chemistry and urinalysis results appeared normal in all exposure groups. Gross pathologic examinations revealed pale red and voluminous lungs in the 12 ppm exposure group. Histopathologic examinations revealed ocular and respiratory inflammation in rats exposed to 8 and 12 ppm. This study appears to have identified a NOAEL of 2 ppm and a LOAEL of 8 ppm for decreased mean body weight, ocular and respiratory inflammation and alterations in several hematological parameters of rats repeatedly exposed to 1,4-dichloro-2-butene for 4 weeks.

In a study designed to evaluate respiratory tract effects from the chronic exposure to 1,4-dichloro-2-butene (35:65 cis:trans ratio) vapor, groups of 140 male and 140 female Crl:CD® (SD)BR rats were exposed for 6 hours/day, 5 days/week at concentrations of 0 or 0.5 ppm (2.56 mg/m^3) for 2 years or 5/2.5 ppm (25.6/12.8 mg/m^3) for 12 months (5 ppm for 7 months, 2.5 ppm for 5 months and maintained for up to 1 year thereafter) (Mullin et al., 2002; E.I. DuPont, 1986). Body weights and clinical signs were monitored throughout the study and clinical laboratory and pathological evaluations were conducted at 3, 12, 18 and 24 months on selected rats from each exposure group.

There were no exposure-related clinical signs of toxicity (Mullin et al., 2002; E.I. DuPont, 1986). Rats exposed to 0.5 ppm exhibited body weight gains that were similar to those of controls. Male rats of the high-exposure group (5/2.5 ppm) exhibited 7-10% lower body weight gains than controls. Body weight gains of female rats exposed to 5/2.5 ppm were comparable to controls during the exposure phase and first 6 months of the post-exposure period, but became depressed during the last 6 months of the post-exposure period, resulting in final body weights that were approximately 18% lower than controls. Mortality during the 2-year study was 82 and 84% in male and female rats exposed to 5/2.5 ppm, respectively, compared to 39% in controls and 34% in the males and females exposed to 0.5 ppm. Clinical chemistry revealed no exposure-related effects. Tumors in the nasal tissues of all 1,4-dichloro-2-butene-exposed groups and in the trachea of the 5.0/2.5 ppm groups were observed upon histopathologic examination. Nasal tumor incidence data are presented in Table 1. Tumors in rats exposed to 0.5 ppm were predominantly adenomas; malignant tumors dominated in rats exposed to 5.0/2.5 ppm. Under the conditions of this study, 1,4-dichloro-2-butene was shown to be carcinogenic to both male and female rats.

Table 1. Number and Percent Incidence of Nasal Tumors in Rats Repeatedly Exposed to 1,4-Dichloro-2-Butene for 1 or 2 Years[a,b]

	Concentration (ppm)	Number of Examined Nasal Cavities	Benign Tumors[c]	Malignant Tumors[d]
Males	0	127	0 (0%)[e]	0 (0%
	0.5	130	33 (25.4%)[f]	11 (8.5%)[f]
	5.0/2.5	129	2 (1.65)[f]	114 (88.4%)[f]
Females	0	128	0 (0%)	0 (0%)
	0.5	128	23 (18%)[f]	2 (1.6%)
	5.0/2.5	128	5 (3.9%)[f]	113 (88.3%)[f]

[a]Mullin et al., 2002 and E.I. DuPont, 1986.
[b]Includes examination of nasal cavities of some rats found dead or sacrificed *in extremis*. Rats of the 0.5 ppm low exposure level were exposed for 2 years; rats of the high-exposure level were exposed to 5.0 ppm for 5 months, followed by 2.5 ppm for a subsequent 7 months and up to 1 year of observation following cessation of exposures.
[c]Benign tumors consist of adenomas and one hemangioma
[d]Malignant tumors consist of adenocarcinoma/carcinoma, squamous cell carcinoma, mixed cell carcinoma, carcinosarcoma and rhabdomyosarcoma.
[e]The number in parentheses is percent incidence
[f]Significantly different ($p < 0.05$) from controls by Fisher's Exact test.

In a chronic inhalation study designed to assess the time course and exposure-response relationships for 1,4-dichloro-2-butene-induced nasal tumors, groups of male Crl:CD® (SD)BR rats (128-160/group) were exposed to 1,4-dichloro-2-butene (35:65 cis:trans ratio) vapor at nominal concentrations of 0, 0.1, 0.3 or 1.0 ppm (0, 0.511, 1.53 or 5.11 mg/m^3) for 6 hours/day, 5 days/week for up to 19 months (Mullin et al., 2000; E.I. DuPont, 1985b). Scheduled interim sacrifices (n = 10 rats/group) were performed on control, 0.1, 0.3 and 1.0 ppm exposed rats at 12 and 15 months. Additional interim sacrifices were performed on control and 1.0 ppm rats at 3 months and on 1.0 ppm exposed rats at 6, 9, 10, 11 and 18 months. The treatment period was intended to span 24 months. However, due to a respiratory infection of *Corynebacterium kutscheri* observed in the control group after 6 months, these rats were isolated and exposures were suspended for 3 weeks. Because the infection was also noted in 0.1 ppm exposed rats during exposure month 7, all rats were treated with tetracycline-HCl/L in the drinking water for 2 weeks. Subsequent tetracycline treatments were performed when mortality increased during exposure months 9 and 17, and exposures were terminated after 19 months, at which time 10 rats each from the control, 0.1 and 0.3 ppm groups were sacrificed for toxicity assessment. Terminal sacrifice was performed on all surviving rats at 24 months. All rats were monitored for clinical signs, body weight and gross signs of abnormal masses. At death or sacrifice, each rat was subjected to comprehensive gross pathological examination and histopathological examination of the entire respiratory tract, cervical lymph nodes and brain (if not precluded by tissue autolysis). Brain, heart, lungs, liver, spleen, kidneys, testes, thymus, adrenals and pituitary weights were recorded for all rats that were terminated at scheduled sacrifice.

Group mean body weights of all rats exposed to 1,4-dichloro-2-butene were often significantly higher than those of controls (Mullin et al., 2000; E.I. DuPont, 1985b). Because the lack of weight gain in the controls coincided with the appearance of *C. kutscheri*, the higher

weight in the treated rats was not attributed to 1,4-dichloro-2-butene exposure. Clinical observations included grossly visible masses, skin sores, respiratory abnormalities (lung noise, irregular respiration) consistent with *C. kutscheri* infection; and colored ocular and nasal discharge consistent with both *C. kutscheri* infection and nasal lesions. The study authors indicated that observed clinical signs were not significantly increased in any particular group of rats. The *C. kutscheri* infection, first noted in control rats at month 6; was found in the 0.1 ppm group during month 8, the 0.3 ppm group during month 15 and the 1.0 ppm group during month 16. Cumulative incidences of *C. kutscheri* infection among the control, 0.1, 0.3 and 1.0 ppm groups were 62/160, 48/150, 64/150, and 10/128, respectively. When adjusted to eliminate scheduled sacrifices and rats with *C. kutscheri* infection, cumulative incidences of mortality by study end were 54/72 (75%), 62/85 (73%), 44/61 (72%) and 37/40 (92%) in the control, 0.1, 0.3 and 1.0 ppm groups, respectively, and mortality in the 1.0 ppm exposed rats was significantly greater than that of the controls. No exposure-related effects on organ weights were observed.

Nasal lesions were observed in rats exposed to 1.0 ppm as early as the first interim sacrifice at month 3 and consisted of focal mucosal atrophy and basal cell squamous hyperplasia of the mid-dorsal area of the nasal cavity (Mullin et al., 2000; E.I. DuPont, 1985b). By month 6, basal cell metaplasia and squamous metaplasia were detected. These lesions were more pronounced at month 9 and clusters of epithelial-like cells at the base of the olfactory epithelial lining were seen at month 10. At 12-month scheduled interim sacrifice, basal cell hyperplasia, mucosal atrophy of the dorso-anterior olfactory epithelium and clusters of cells in the basal epithelium were seen in all exposed groups, but not in controls (Table 2). Similar lesions were seen at 15-month scheduled sacrifice, in addition to clusters of epithelioid cells with atypical cells in 0.3 and 1.0 ppm exposed rats (Table 2). Nonneoplastic lesions observed at 15-month sacrifice were also present at 18- and 19-month sacrifices. The study authors noted that hyperplasia of the nasal olfactory region was observed in 1,4-dichloro-2-butene-exposed rats that survived the 5-month post-exposure period as well, and considered the effect to be exposure related because incidences of the lesion were higher in exposed rats than in controls. Observed pulmonary lesions (abscesses, pleural fibrinous or fibrous adhesions, broncho-bronchiolar luminal exudate, pleuritis and suppurative or necrotizing pneumonia) were considered to have been associated with the *C. kutscheri* infection and coincidental to increased incidences of respiratory abnormalities and mortality.

Table 2. Incidences of Selected Non-Neoplastic Nasal Lesions in Rats Exposed to 1,4-Dichloro-2-Butene for up to 19 Months and Observed for up to 24 Months[a]

Exposure concentration (ppm)	0	0.1	0.3	1.0
12-Month scheduled sacrifice[b]				
Basal cell flattening/hyperplasia	0/10	3/10	9/10[c]	10/10[c]
Mucosal atrophy	0/10	1/10	4/10[c]	3/10
Clusters of cells, basal epithelium	0/10	1/10	1/10	7/10[c]
15-Month scheduled sacrifice[d]				
Basal cell flattening/hyperplasia	0/10	6/10[c]	7/10[c]	9/10[c]
Mucosal atrophy/disorganization	0/10	5/10[c]	6/10[c]	9/10[c]
Clusters of cells, basal epithelium	0/10	2/10	6/10[c]	8/10[c]
Atypical cells, cellular cluster, basal epithelium	0/10	0/10	2/10	5/10[c]

[a]E.I. Dupont, 1985b (Appendix G).
[b]Fragmentation or disruption of nasal tissues at necropsy occurred in 3/10, 0/10, 6/10 and 6/10 of the controls, 0.1, 0.3 and 1.0 ppm rats, respectively, but some tissue evaluation was possible.
[c]Significantly different ($p < 0.05$) from controls by Fisher's Exact test, performed for this review.
[d]Fragmentation or disruption of nasal tissues at necropsy occurred in 0/10, 1/10, 1/10 and 0/10 of the controls, 0.1, 0.3 and 1.0 ppm rats, respectively, but some tissue evaluation was possible.

As shown in Table 3, benign and malignant nasal tumors were commonly found in rats exposed to 1,4-dichloro-2-butene; evidence of neoplastic nasal lesions in control rats was restricted to a solitary case of a nasal sarcoma in a rat that was sacrificed *in extremis* after 9 months (Mullin et al., 2000; E.I. DuPont, 1985b). Because *C. kutscheri* infection resulted in early mortality in control and 1,4-dichloro-2-butene-exposed rats, lifetime tumor incidence data were also adjusted for mortality. Exposure concentration-related increased incidences of benign, malignant and combined benign and malignant tumors were noted both with and without mortality adjustment. Nasal tumor detection began as early as month 10 in the 1.0 ppm group of rats and month 12 in the 0.3 ppm group. There were no incidences of nasal tumors in the 10 control rats sacrificed at 12 months. Between exposure months 12 and 19, incidences of nasal tumors exhibited concentration- and time-related characteristics. Although mostly benign nasal tumors were initially diagnosed during this time period, malignant tumor incidences appeared to increase with time. Thus, the severity and frequency of the nasal lesions appeared to be progressive in nature. According to the study authors, the increases in both benign and malignant tumors exhibited significant lifetime concentration-related trends when analyzed either independently or combined for total tumor incidence. Similar concentration-related increased incidences of benign and malignant tumors were observed even after elimination of all rats that exhibited signs of *C. kutscheri* infection at sacrifice (Table 4). Observed pulmonary lesions (abscesses, pleural fibrinous or fibrous adhesions, broncho-bronchiolar luminal exudate, pleuritis and suppurative or necrotizing pneumonia) were considered to have been associated with the *C. kutscheri* infection and coincidental to increased incidences of respiratory abnormalities and mortality.

In summary, chronic exposure of male Crl:CD® (SD)BR rats resulted in nonneoplastic and neoplastic lesions (Mullin et al., 2000; E.I. DuPont, 1985b). Nonneoplastic lesions in 1.0

Table 3. Nasal Tumor Incidences in Rats Exposed to 1,4-Dichloro-2-Butene for up to 19 Months and Observed for up to 24 Months[a]

Exposure concentration (ppm)	0	0.1	0.3	1.0
Number of nasal cavities examined	159	146	148	126
Number of benign tumors				
Adenoma	0	3	12	23
Incidence (%)	0	2.1	8.1	18.3
Adjusted incidence (%)[b]	0	7.6[c]	30.1[c]	82.2[c]
Number of malignant tumors				
Adenocarcinoma	0	0	2	11
Carcinosarcoma	0	0	0	3
Mixed carcinoma	0	0	0	3
Sarcoma, unclassified	1	0	0	0
Spindle cell sarcoma	0	1	0	0
Rhabdomyosarcoma	0	0	0	1
Incidence (%)	0.6	0.7	1.4	14.3
Adjusted incidence (%)[b]	0.8	1.2	6.0	88.8[c]
Total number of rats with nasal tumors				
Number of rats	1	4	14	35
Overall incidence (%)	0.6	2.8	9.5	25.7
Adjusted incidence (%)[a]	0.8	8.7	34.3[b]	100.0[b]

[a]Mullin et al., 2000 and DuPont, 1985b.
[b]Estimated lifetime tumor incidence after adjusting for mortality (Kaplan and Meier, 1958)
[c]Statistically significant increase at alpha = 0.05 (Peto et al., 1980)

Table 4. Nasal Tumor Incidence in Disease-Free Rats Exposed to 1,4-Dichloro-2-Butene for up to 19 Months and Observed for up to 24 Months[a]

Exposure concentration (ppm)	0	0.1	0.3	1.0
Number of nasal cavities examined	109	99	83	116
Number of benign tumors	0	3	10	2
Disease-free incidence (%)	0.0	3.0	12.0	18.1
Adjusted disease-free incidence (%)[b]	0.0	10.2	33.2	80.2[c]
Number of malignant tumors	0	1	2	17
Disease-free incidence (%)	0.0	1.0	2.4	14.7
Adjusted disease-free incidence (%)[b]	0.0	1.4	7.7	100.0[c]
Total number of rats with nasal tumors	0	4	12	32
Overall incidence (%)	0.0	4.0	14.5	27.5
Adjusted incidence (%)[b]	0.0	11.5	38.3	100.0[c]

[a]Mullin et al., 2000 and E.I. DuPont, 1985b.
[b]Estimated lifetime tumor incidence after adjusting for mortality (Kaplan and Meier, 1958)
[c]Statistically significant increase at alpha = 0.05 (Peto et al., 1980)

ppm exposed rats were observed as early as month 3 interim sacrifices. Significantly increased incidences of rats with benign nasal tumors (adenomas) were detected in all groups of 1,4-dichloro-2-butene-exposed rats; nasal adenomas appeared in rats exposed to 1.0 and 0.3 ppm as early as 10- and 12-month interim sacrifices, respectively. The group of 1.0 ppm rats also exhibited a significantly increased incidence of malignant nasal tumors (88.8% compared to 0.8% in controls, estimated lifetime tumor incidence after adjusting for mortality).

In a developmental toxicity study, groups of 26 pregnant ChR-CD rats in each group were exposed to 1,4-dichloro-2-butene vapors at concentrations of 0.5 or 5 ppm (2.56 or 25.6 mg/m^3) for 6 hours/day on gestation days 1 through 15 (Kennedy et al., 1982). The study included a group of 23 pregnant control (0 ppm) rats. Dams were assessed for clinical signs and body weight changes during the study. At sacrifice on gestation day 21, maternal ovaries from 23/26 and 21/26 in the control and 5ppm group, respectively, were examined for numbers of *corpora lutea*; assessments of uterine contents included numbers of implantation and resorption sites, numbers of live and dead fetuses and fetal size and body weight. Fetuses were subjected to gross external, visceral and skeletal examinations. The study authors noted significantly reduced maternal weight gain in 5 ppm dams (19% lower than controls). There were no indications of exposure-related effects on numbers of pregnant rats, implantation sites, resorption sites, or fetuses per dam, or on fetal size and weight. Gross external, visceral, and skeletal examinations revealed no exposure-related developmental effects, with the exception of an exposure-related increase in incidences of wavy ribs (0/120 fetuses [0/23 litters], 4/98 fetuses [2/21 litters] and 15/108 fetuses [7/21 litters] in controls, 0.5 and 5.0 ppm groups, respectively). The study authors considered the wavy rib effect to be a minor anomaly that did not affect survival; it was concluded that 1,4-dichloro-2-butene was neither embryotoxic nor teratogenic under the study conditions.

Other available studies come from the Russian literature; these studies are not reported in adequate detail to be useful for risk assessment. The U.S. EPA (1987) summarized the results of studies by Petrosyan and co-workers. Petrosyan et al. (1983) assessed renal function in groups of white rats exposed to 1,4-dichloro-2-butene vapor concentrations of 0, 1.77 or 8.7 mg/m^3 (0, 0.35 or 1.7 ppm, respectively) for 4 months (additional exposure details were not reported). Significant increases in urinary chlorides and creatinine at both exposure concentrations were considered indicative of some loss of renal filtration function. Petrosyan and Gizhlaryan (1982) exposed white rats to 1,4-dichloro-2-butene vapor concentrations of 0, 1.77, 8.7 or 21.2 mg/m^3 (0, 0.35, 1.7 or 4.15 ppm, respectively) for 4 hours/day for 30 days and assessed for exposure-related central nervous system responses. Exposed rats reportedly exhibited concentration-related effects including neuron dystrophy and necrosis and proliferation of lymphoid cellular proliferation around capillaries of the cortex and *pia mater*. More specific details of the study design and results were apparently not included in the original study report.

The reproductive toxicity of 1,4-dichloro-2-butene was assessed in male rats exposed to the chemical by inhalation of vapors at concentrations of 0, 1.8 or 8.3 mg/m^3 (0, 0.35 or 1.6 ppm, respectively) for 2.5 months prior to mating with unexposed female rats (Bal'yan et al., 1983a). The study report did not specify other temporal parameters of the exposure scenario. Pregnant dams were sacrificed on gestation day 21 for assessment of uterine contents. Parameters

assessed included percentage of effective matings and morphological and functional characteristics of spermatozoa and numbers of *corpora lutea*. Pre- and post-implantation mortality indices were calculated as well. Reported exposure-related effects included decreased percentage of successful matings and increased pre- and post-implantation mortality; however, the study report did not include data regarding the magnitude or statistical significance of these findings. Statistically significant exposure-related effects on testes were seen at both exposure levels and included decreased number of spermatogonia and increases in the numbers of seminiferous tubules in 12^{th} stage of meiosis. Pathological examination of the testes of 8.3 mg/m^3 rats revealed severe degeneration and necrosis in germinal epithelium. The study appears to identify a LOAEL of 1.8 mg/m^3 for decreased fertility and histopathologic abnormalities of the testes. However, poor reporting of study details limits the usefulness of this study for RfC derivation.

The U.S. EPA (1987) summarized the results of a Russian study (Bal'yan et al., 1983b) in which developmental toxicity was assessed in pregnant rats exposed to 1,4-dichloro-2-butene vapor concentrations of 0, 1.6, 9.2 or 33.9 mg/m^3 (0, 0.31, 1.8 or 6.6 ppm, respectively) for the first 20 days of pregnancy. Evaluation included numbers of *corpora lutea*, fetuses, resorptions, pre- and post-implantation losses and fetal mortality. Significantly increased post-implantation loss was noted in the 33.9 mg/m^3 exposure group, which also exhibited approximately 50% maternal death between gestation days 18 and 20. The 1,4-dichloro-2-butene-exposed groups exhibited reduced numbers of normal fetuses. Other reported exposure-related fetal effects included degenerative liver changes and hemorrhaging of the diaphragm. Exposure-related morphological placental changes were also reported. However, the paucity of study details precludes adequate assessment of concentration-response relationships.

Developmental toxicity was assessed in pregnant and nonpregnant rats exposed to 1,4-dichloro-2-butene by inhalation exposure for 21 days (Petrosyan et al., 1982). Inhalation exposure levels were 0, 1.8 and 8.3 mg/m^3 (0, 0.35 and 1.62 ppm, respectively). Reported exposure-related effects included increased post-implantation mortality, fetal hemorrhaging in liver and diaphragm, plethoric placentas, dilation of the capillaries and lacunae and decreased RNA content in hepatocytes, cerebral glia, alveolar cells and glomerular epithelium. Because more specific details of results were not included in the report, the results are not useful for quantitative risk characterization.

Other Studies

Acute Toxicity

1,4-Dichloro-2-butene (isomeric composition not specified) caused primary dermal and ocular irritation in rabbits (Smyth et al., 1951). Reported acute oral and dermal LD_{50} values for 1,4-dichloro-2-butene-exposed rats (isomeric composition not specified) are 89 mg/kg and 0.62 mL/kg, respectively (Smyth et al, 1951). A 4-hour exposure of rats to 1,4-dichloro-2-butene vapor (isomeric composition not specified) at a concentration of 62 ppm (317 mg/m^3) resulted in 2/6 deaths within 14 days post-exposure (Smyth et al., 1951).

The acute toxicity of 1,4-dichloro-2-butene (1.43% cis isomer and 97.17% trans isomer) was assessed in groups of male CD rats exposed for 30 minutes at vapor concentrations ranging from 240 to 3600 ppm (1227 to 18,405 mg/m^3) and observed for up to 14 days post-exposure (DuPont Chemical, 1992). The calculated 30-minute LC_{50} was 784 ppm (4008 mg/m^3). Exposure-related sublethal effects in 760 ppm rats included destruction of the air passage and kidney damage. Observed testicular atrophy and hypoplastic bone marrow were considered to have been related to stress and emaciation. Damage to the tracheobronchial epithelium was noted in 410 ppm (2096 mg/m^3) rats.

Genotoxicity Studies

Available test results consistently demonstrate the genotoxicity of 1,4-dichloro-2-butene. Mutagenicity assays *Salmonella typhimurium* strains TA1535, TA1537 and TA1538 resulted in positive results in strain TA1535 both with and without metabolic activation and strain TA1538 without (but not with) metabolic activation, but negative results for strain TA1537 (E.I. DuPont, 1992b). Bartsch et al. (1980) reported positive results for reverse mutations in *Salmonella typhimurium* strain TA100 exposed to 1,4-dichloro-2-butene; the effect was enhanced in the presence of liver microsomal fractions from mice or humans. In a published abstract, Mukai and Hawryluk (1973) reported 1,4-dichloro-2-butene to be mutagenic to *Escherichia coli* and *S. typhimurium*; additional details were not presented in the abstract. In genotoxicity tests of the individual 1,4-dichloro-2-butene isomers (cis and trans), both isomers were mutagenic to *S. typhimurium* strains TA98 and TA100 (Seifried et al., 2006). A mutagenic response was also elicited by each isomer in mouse lymphoma assays both with and without metabolic activation, although results of one test of trans-1,4-dichloro-2-butene using metabolic activation were considered inconclusive (Seifried et al., 2006). 1,4-Dichloro-2-butene elicited high frequencies of mitotic gene conversion at both yeast loci in *Saccharomyces cerevisiae* (E.I. DuPont, 1992b). A mutagenic response was elicited in 1,4-dichloro-2-butene exposed Chinese hamster ovary cells both with and without metabolic activation (E.I. DuPont, 1992c). Sex-linked recessive-lethal mutations were observed in male *Drosophila melanogaster* exposed to 1,4-dichloro-2-butene (22:78 cis:trans ratio) (Vogel, 1979). Nalbandyan and Gizhlaryan (1985) reported chromosomal damage in bone marrow cells of rats that had inhaled 1,4-dichloro-2-butene at concentrations of 1.7 or 7.9 mg/m^3 for 4 hours/day, 5 days/week for 30-120 days.

Other relevant carcinogenicity data

Van Duuren et al. (1975) performed several studies to assess the carcinogenicity of 1,4-dichloro-2-butene in female ICR/Ha Swiss mice. No tumors were detected following repeated dermal applications of 1,4-dichloro-2-butene (1 mg on shaved dorsal skin) for 77 weeks. The chemical did not initiate tumors when applied to the skin (1 mg dose), followed by repeated application of the tumor promoter, phorbol myristate acetate, for 77 weeks. Repeated intraperitoneal injections of a relatively low (0.05 mg) dose of 1,4-dichloro-2-butene for 77 weeks did not result in significantly increased incidences of tumors. A significant increase in the incidence of injection site sarcomas was observed following repeated subcutaneous injection of 0.05 mg of 1,4-dichloro-2-butene for 77 weeks.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR 1,4-DICHLORO-2-BUTENE

Studies evaluating subchronic or chronic oral exposure to 1,4-dichloro-2-butene in humans were not identified from the published literature. Oral studies of 1,4-dichloro-2-butene in animals are limited to a series of poorly reported studies from the Russian literature. These studies reported effects on renal function, reproduction (sperm abnormalities, fertility), and development (embryotoxicity) (Petrosyan et al., 1982, 1983; Bal'yan et al., 1983a), but provided inadequate details of study methods and results to permit independent evaluation of the findings. The lack of suitable data precludes derivation of subchronic or chronic p-RfDs for 1,4-dichloro-2-butene.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR 1,4-DICHLORO-2-BUTENE

There are no relevant human data. Animal studies identify nasal tissue as being particularly sensitive to inhaled 1,4-dichloro-2-butene. In rats exposed to 1,4-dichloro-2-butene vapor for up to 19 months, non-neoplastic nasal lesions were observed as early as month 3 and consisted of focal mucosal atrophy and basal cell squamous hyperplasia (Mullin et al., 2000; E.I. DuPont, 1985b). By month 6, basal cell metaplasia and squamous metaplasia were detected as well. These lesions were more pronounced at month 9, and clusters of epithelial-like cells at the base of the olfactory epithelial lining were seen at month 10. At 12-month interim sacrifice, basal cell hyperplasia, mucosal atrophy of the dorso-anterior olfactory epithelium and clusters of cells in the basal epithelium were seen in all exposed groups, but not in controls. When compared to controls, increased incidences of nonneoplastic nasal lesions reached the level of statistical significance ($p < 0.05$) as early as 12-month sacrifice at exposure levels of 0.3 and 1.0 ppm (1.53 and 5.11 mg/m^3) and by 15-month sacrifice at the 0.1 ppm (0.51 mg/m^3) exposure level (Table 2). Nasal tumors were first detected at exposure month 10 in the 1.0 ppm group of rats and month 12 in the 0.3 ppm group, exhibiting concentration- and time-related characteristics. Whereas the nasal tumors were predominantly benign (adenomas) at first, malignant tumors were detected with increasing frequency in 1.0 ppm rats between exposure month 15 and final sacrifice at month 24. The nonneoplastic and neoplastic lesions occurred in similar locations within the nasal cavity. The nonneoplastic lesions, consisting primarily of basal cell hyperplasia, basal cell and squamous metaplasia, cell clustering in basal epithelium and mucosal atrophy, appeared prior to the detection of neoplastic lesions and include types of lesions generally associated with progression to tumors (preneoplastic). Thus, the severity and frequency of the nasal lesions appeared to be progressive in nature, with the non-neoplastic lesions progressing eventually to tumors. Because the nonneoplastic lesions appear to be preneoplastic in nature, derivation of an RfC for 1,4-dichloro-2-butene from these data is precluded.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,4-DICHLORO-2-BUTENE

Weight-of-Evidence Descriptor

Available human toxicity information is limited to a single cohort mortality study in which equivocal compound-related increases in cancer mortality were observed among workers exposed to 1,4-dichloro-2-butene (E.I. DuPont, 1985a). Animal data are available from two cancer bioassays, a preliminary study that employed controls and two exposure levels using male and female rats (Mullin et al., 2002; E.I. DuPont, 1986) and a subsequent study that employed controls and three exposure levels using male rats (Mullin et al., 2000; E.I. DuPont, 1985b). In both bioassays, chronic exposure to 1,4-dichloro-2-butene resulted in exposure-related significantly increased incidences of benign and malignant tumors of the nasal cavity.

Several studies were designed to assess the carcinogenicity of 1,4-dichloro-2-butene in female ICR/Ha Swiss mice (Van Duuren et al., 1975). No tumors were detected following repeated dermal applications. The chemical did not initiate tumors when applied to the skin, followed by repeated application of the tumor promoter, phorbol myristate acetate. Repeated intraperitoneal injections of a relatively low (0.05 mg) dose of 1,4-dichloro-2-butene did not result in significantly increased incidences of tumors. A significant increase in the incidence of injection site sarcomas was observed following repeated subcutaneous injections of 1,4-dichloro-2-butene.

Available test results consistently demonstrate the genotoxicity of 1,4-dichloro-2-butene. The chemical was mutagenic in some strains of *S. typhimurium* (E.I. DuPont, 1992b; Bartsch et al., 1980; Mukai and Hawryluk, 1973), *E. coli* (Mukai and Hawryluk, 1973) and Chinese hamster ovary cells (E.I. DuPont, 1992c). 1,4-Dichloro-2-butene elicited mitotic gene conversion in *S. cerevisiae* (E.I. DuPont, 1992b), sex-linked recessive-lethal mutations in male *D. melanogaster* (Vogel, 1979) and chromosomal damage in bone marrow cells of rats repeatedly exposed to the chemical through inhalation (Nalbandyan and Gizhlaryan, 1985). Mutagenic responses were elicited in *S. typhimurium* by individual cis- and trans- isomers of 1,4-dichloro-2-butene (Seifried et al., 2006). A mutagenic response was also elicited by each isomer in mouse lymphoma assays (Seifried et al., 2006). However, the available data are insufficient to clearly define a specific mode of action

Based on U.S. EPA (2005) cancer guidelines, 1,4-dichloro-2-butene is considered with a descriptor of "*suggestive evidence of carcinogenic potential*." The human study did not prove carcinogenicity and only one animal species (rat) demonstrated a clearly carcinogenic response; mouse was negative.

Quantitative Estimates of Carcinogenic Risk

The available data for increased incidences of nasal tumors in rats chronically exposed to 1,4-dichloro-2-butene are vapors are considered suitable for quantitative cancer assessment. The available data are insufficient to clearly define a specific mode of action. Therefore,

consistent with U.S. EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), a linear (non-threshold) extrapolation is indicated.

Oral Exposure

Derivation of quantitative estimates of cancer risk following oral exposure to 1,4-dichloro-2-butene is precluded by the lack of suitable data.

Inhalation Exposure

Data for 1,4-dichloro-2-butene are sufficient to perform dose-response modeling. Modeling was performed based on incidences of nasal adenomas and combined nasal adenomas and carcinomas in male Crl:CD® (SD)BR rats exposed to 1,4-dichloro-2-butene vapors for 6 hours/day, 5 days/week for up to 19 months and observed for up to 24 months (Mullin et al., 2000; E.I. DuPont, 1985b). Weaknesses in this principal study include a concurrent *C. kutscheri* infection that resulted in early mortality in control and 1,4-dichloro-2-butene-exposed rats and incomplete histopathological examinations of nasal tissues from many of the rats at all exposure levels for reasons the study authors described as tissue autolysis, fragmentation during tissue extraction, insufficient nasal tissue or no nasal tissue. Due to the concurrent *C. kutscheri* infection and early mortality, the study authors performed a statistical adjustment (Kaplan and Meier, 1958) to account for mortality in estimating lifetime tumor incidences. Adjusted incidences were expressed in percent (see Table 3). Based on the data presented in the study reports (Mullin et al., 2000; E.I. DuPont, 1985b), the numbers of animals that contributed to the incidence data could not be accurately determined. Furthermore, the study authors included animals for which only partial histopathological examinations of nasal tissues were possible. Due to these weaknesses, the following quantitative assessment of carcinogenic risk based on incidences of nasal tumors in the rats of the principal study (Mullin et al., 2000; E.I. DuPont, 1985b) includes two major adjustments to the reported data. Based on early mortality, all rats that died or were sacrificed prior to detection of the first nasal adenoma at exposure month 10 were eliminated from the assessment. Furthermore, all rats with only partial histopathological examination of the nasal tissue were eliminated unless a nasal adenoma or carcinoma was detected. This adjustment was considered necessary to eliminate the uncertainty concerning lack of tumor detection in partial histopathological assessments. The resulting nasal tumor incidence data that were modeled are presented in Table 5.

Exposure concentrations used in the principal study (Mullin et al., 2000; E.I. DuPont, 1985b) included 0, 0.1, 0.3 and 1.0 ppm levels. These concentrations were converted to 0, 0.511, 1.53 and 5.11 mg/m^3, respectively, and adjusted from intermittent exposure (6 hours/day, 5 days/week) to a continuous exposure scenario as follows:

$$Conc_{[ADJ]} = Conc \times \frac{5\ days/\ week}{7\ days/\ week} \times \frac{6\ hours/\ day}{24\ hours/\ day}$$

The duration-adjusted exposure concentrations were 0, 0.091, 0.27 and 0.91 mg/m^3, respectively.

Table 5. Incidences of Nasal Tumors in Rats Exposed to 1,4-Dichloro-2-Butene Vapor 6 Hours/Day, 5 Days/Week for up to 19 Months and Observed for up to 24 Months[a,b]

Reported concentration (ppm)	**0**	**0.1**	**0.3**	**1.0**
Converted concentration (mg/m^3)	**0**	**0.511**	**1.53**	**5.11**
Duration-adjusted concentration (mg/m^3)	**0**	**0.091**	**0.27**	**0.91**
Benign tumors				
Adenoma	0/78	3/72	12/54[c]	23/65[c]
Malignant tumors				
Adenocarcinoma	0/78	0/73	2/52	11/64[c]
Mixed carcinoma	0/78	0/73	0/52	3/64
Carcinosarcoma	0/78	0/73	0/52	3/64
Spindle cell sarcoma	0/78	1/73	0/52	0/64
Rhabdomyosarcoma	0/78	0/73	0/52	1/64
Metastatic neoplasm	0/78	1/73	1/52	0/64
Combined	0/78	2/73	3/52	18/64[c]
Benign or Malignant Tumors (Combined Incidence)	0/78	5/74[d]	15/56[c]	35/68[c]

[a]E.I. DuPont, 1985b (Appendix G).
[b]Rats from which complete assessment of nasal tissues was not possible due to deterioration, damage or loss were excluded from incidence data unless tumors could be identified in partial histopathological examination. Rats that died or were sacrificed prior to exposure month 10 (at which time the first nasal adenoma was detected) were also excluded from the tumor incidence data.
[c]Significantly different ($p < 0.01$) from controls by Fisher's Exact test, performed for this review
[d]Significantly different ($p < 0.05$) from controls by Fisher's Exact test, performed for this review
[e]exposure was 6 hours/day 5 days/week

The incidence data for nasal tumors (benign and malignant tumors combined) in male rats (Table 5) were analyzed using the cancer multistage model in the Benchmark Dose Modeling Software (BMDS) program (version 1.4.1c) (U.S. EPA, 2000). Risk was calculated as extra risk. Confidence bounds were automatically calculated by the BMDS software using a maximum likelihood profile method. The $BMCL_{10}$ (lower bound on the exposure concentration estimated to produce a 10% increase in tumor incidence over background) for nasal tumors in the rats was estimated at 0.098 mg/m^3. Output from the BMDS program was evaluated using the criteria described in U.S. EPA (2000). The overall model fit to the cancer data was evaluated based on goodness-of-fit *p*-values and visual inspection of the dose response curve. Goodness-of-fit was evaluated using the chi-square statistic calculated by the BMDS program. Acceptable global goodness-of-fit is indicated by a *p*-value greater than or equal to 0.1. Local fit is evaluated visually on the graphic output by comparing the observed and estimated results at each data point.

Modeling results are shown in Table 6 and Figure 1.

Table 6. Benchmark Dose Modeling Results for Combined Incidences of Benign and Malignant Nasal Tumors in Male Rats Exposed to 1,4-Dichloro-2-Butene Vapors 6 Hours/Day, 5 Days/Week for up to 19 Months and Observed for up to 24 Months

Model	AIC	*p*-Value	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Multistage[a]	199.347	0.6773	0.12145	0.09767

[a]Betas restricted to ≥0; polydegree = 1 (higher degree polynomials revert to the 1-degree)

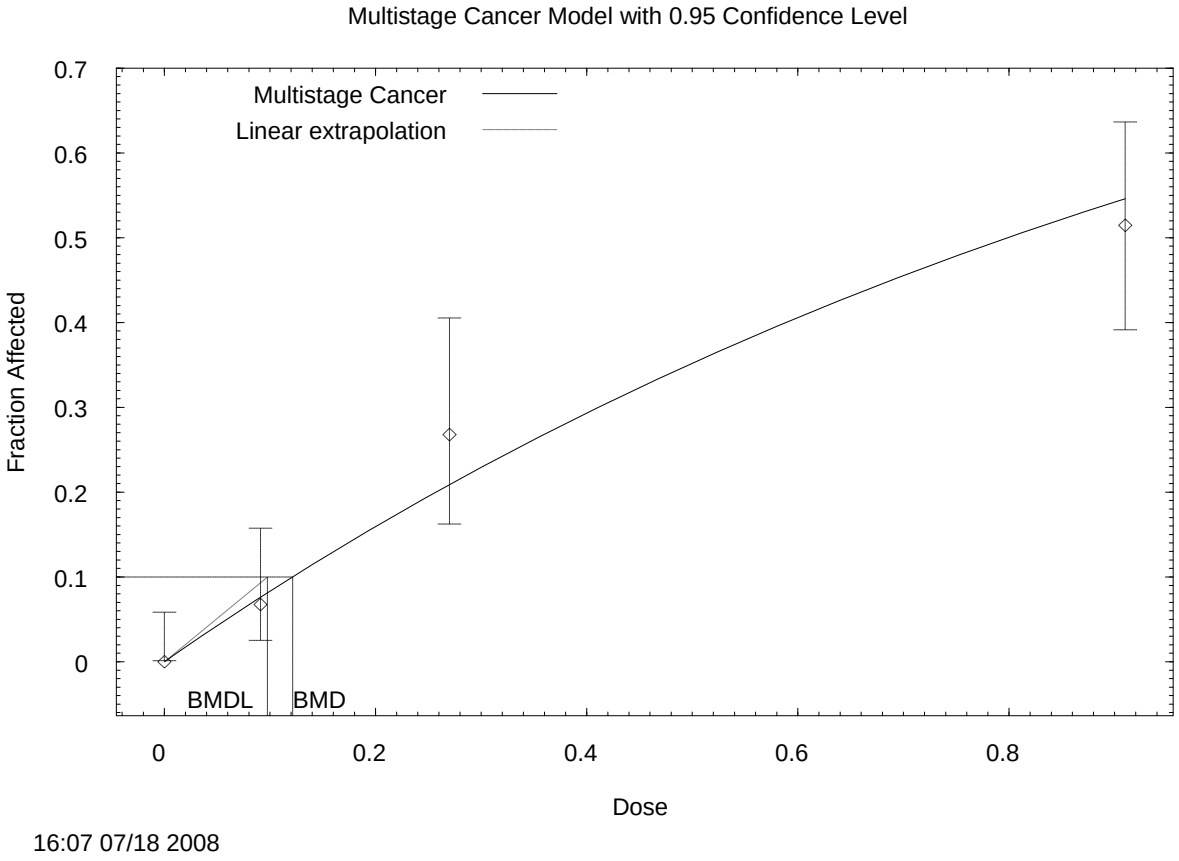

Figure 1. Observed and Predicted Incidences of Combined Nasal Tumors in Male Rats Exposed to 1,4-Dichloro-2-Butene Vapors for 6 Hours/Day, 5 Days/Week for up to 19 Months and Observed for up to 24 Months (Mullin et al., 2000; E.I. DuPont, 1985b)

The human equivalent concentration (HEC) of the $BMCL_{10}$ ($BMCL_{10\ HEC}$) for nasal tumors was calculated using the methodology for extrathoracic respiratory effects of a Category 1 gas by multiplying the duration-adjusted $BMCL_{10}$ by the regional gas ratio for the extrathoracic region of the respiratory tract ($RGDR_{ET}$). The $RGDR_{ET}$ was calculated according to Equation 4-18 of U.S. EPA (1994b) as follows:

$$RGDR_{ET} = \frac{(\frac{V_E}{SA_{ET}})A}{(\frac{V_E}{SA_{ET}})H}$$

$RGDR_{ET}$	=	regional gas dose ratio for extrathoracic respiratory effects
SA_{ET}	=	surface area for extrathoracic portion of respiratory tract (rat: 15 cm^2, human: 200 cm^2; U.S. EPA, 1994b)
V_E	=	minute volume (rat: 254 cm^3/min, human: 13,800 cm^3/min; U.S. EPA, 1994b)
A	=	animal
H	=	human

For the male rat:

$$RGDR_{ET} = \frac{(\frac{254}{15})A}{(\frac{13,800}{200})H} = \frac{(16.93)}{(69)} = 0.245$$

The $BMCL_{10\ HEC}$ = duration-adjusted $BMCL_{10}$ x $RGDR_{ET}$
= 0.098 mg/m^3 x 0.245
= 0.024 mg/m^3

A linear extrapolation from the $BMCL_{10\ HEC}$ to the origin (0.1/0.024) provides a cancer **inhalation unit risk (IUR) of 4.2 $(mg/m^3)^{-1}$ or 4.2x10^{-3} $(\mu g/m^3)^{-1}$** for 1,4-dichloro-2-butene as indicated below:

p-IUR = $0.1/BMCL_{10\ HEC}$
= 0.1/0.024 $(mg/m^3)^{-1}$
= **4.2 $(mg/m^3)^{-1}$ or 4.2 x 10^{-3} $(\mu g/m^3)^{-1}$**

The inhalation unit risk for 1,4-dichloro-2-butene should not be used with exposures exceeding the point of departure ($BMCL_{10\ HEC}$ = 0.024 mg/m^3), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of 1,4-dichloro-2-butene.

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