1,3-Butadiene; CASRN 106-99-0

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 1,3-Butadiene

File First On-Line 03/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	11/05/2002
Inhalation RfC (I.B.)	yes	11/05/2002
Carcinogenicity Assessment (II.)	yes	11/05/2002

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

1,3-Butadiene
CASRN — 106-99-0
Last Revised — 11/05/2002

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as hemolysis. It is expressed in units of mg/kg/day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Documents for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An oral RfD is not calculated because 1,3-butadiene is a gas and causes hazard by inhalation only. The hazard by ingestion is unlikely since 1,3-butadiene is poorly soluble in water. When released in water, 1,3-butadiene rapidly evaporates.

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

Substance Name — 1,3-Butadiene
CASRN — 106-99-0
Last Revised — 11/05/2002

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and systems peripheral to the respiratory system. It is generally expressed in units of mg/m^3. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F, August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F, October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

A variety of reproductive and developmental effects have been observed in mice exposed to 1,3-butadiene by inhalation (U.S. EPA, 2002, Chapter 5). There are no human data on reproductive or developmental effects. Few adverse noncancer effects, other than reproductive and developmental effects, have been observed, except for hematological effects in mice exposed to higher concentrations (U.S. EPA, 2002, Section 6.1).

The most sensitive short-term developmental endpoint was decreased fetal weight in the mouse. Decreases were observed at the lowest exposure concentration (40 ppm, 6 hours/day, gestation days 6-15); thus there was not a no-observed-adverse-effect level (NOAEL) for this effect (Hacket et al., 1987). No developmental toxicity was observed in rats.

The most sensitive reproductive endpoint observed in subchronic exposure studies was fetal deaths in dominant lethal studies of mice (i.e., male mice were exposed to 1,3-butadiene and effects on litters were measured after mating to unexposed females) (Anderson et al., 1998; Brinkworth et al., 1998; Anderson et al., 1993; Adler and Anderson, 1994). Significant dominant lethal effects were observed at exposures of 65 ppm, 6 hours/day, 5 days/week, for 4 weeks. (The 12.5 ppm exposure level was a NOAEL.) Dominant lethal effects in humans would likely be manifested as infertility (due to reduced fertility or very early deaths) or spontaneous abortions. The dominant lethal responses are believed to represent a genotoxic effect.

From chronic exposure studies (2-year bioassays; NTP, 1993), the most sensitive reproductive effects were ovarian atrophy in female mice and testicular atrophy in male mice. Testicular atrophy was primarily a high-exposure effect. Ovarian atrophy, on the other hand, was observed at the lowest exposure level (6.25 ppm, 6 hours/day, 5 days/week, for 2 years). Uterine atrophy was also observed in the highest exposure groups; however, this is likely to be a secondary effect of the ovarian atrophy. The mechanisms of ovarian atrophy are unknown, although there is strong evidence that the effect is mediated by the diepoxide metabolite (U.S. EPA, 2002, Chapter 5).

Critical Effect	Experimental Doses*	UF	MF	RfC
Ovarian atrophy **2-year mouse inhalation study (NTP, 1993)**	$BMCL_{10} = 0.88$ ppm (HEC) $(BMC_{10} = 1.0$ ppm)	1000	1	0.9 ppb $(2 \times 10^{-3}$; mg/m^3)

*Conversion Factors and Assumptions — ppm equivalence across species was assumed (this is the same as using EPA's inhalation dosimetry methodology with $RGDR_r=1$ [U.S. EPA, 1994]); exposure concentrations were adjusted to 24-hour continuous daily exposure for the exposure period (i.e., exposure concentration $\times$ [6/24] $\times$ [5/7]). 1 ppm = 2.25 mg/m^3.

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

The chronic RfC of 0.9 ppb is based on ovarian atrophy. A $BMCL_{10}$ (0.88 ppm) was calculated from data from the 1993 NTP 2-year inhalation bioassay, including interim kill data, using benchmark concentration methodology (Weibull time-to-response model). In this bioassay, groups of 70 female B6C3F1 mice were exposed by inhalation 6 hours/day, 5 days/week to 0, 6.25, 20, 62.5, or 200 ppm 1,3-butadiene for up to 103 weeks; groups of 90 female mice were exposed to 625 ppm. Interim evaluations were conducted at 9 and 15 months on up to 10 mice per group. Significant concentration-related decreases in survival were seen in female mice exposed to concentrations >= 20 ppm, primarily due to the development of malignant neoplasms. Statistically significant increases in the incidence of ovarian atrophy were observed in all exposure groups, including the lowest exposure group (6.25 ppm), following lifetime exposures. In calculating the BMC_{10} and $BMCL_{10}$, lesion severity was not taken into account, and the 625 ppm group was excluded because of high early mortality. In addition, ovarian atrophy was modeled to reflect extra risks only until age 50, because 1,3-butadiene-induced ovarian atrophy is believed to result from follicular failure, and after menopause, follicles would no longer be available. Exposure concentrations were converted to 24-hour exposures by multiplying by (6/24) and (5/7).

Benchmark dose modeling and sample RfC calculations were also conducted for the endpoints of fetal weight (7 ppb), dominant lethal effects (20 ppb), and testicular atrophy (20 ppb) (U.S. EPA, 2002, Sections 10.3 and 10.4). Ovarian atrophy was selected as the critical effect because it yielded the lowest RfC. Ovarian atrophy also had the lowest BMC_{10} and was reported in a high-quality 2-year study.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 1000.

For ovarian atrophy, the uncertainty/modifying factors were: 3 for interspecies extrapolation, 10 for intraspecies variability, 3 for incomplete database, and 10 for extrapolation to a level below the 10% effect level (analogous to the LOAEL-to-NOAEL extrapolation factor). The $BMCL_{10}$ was estimated from a chronic bioassay; therefore, an acute/subchronic-to-chronic factor was not required. The factor of 10 used for effect level extrapolation was derived from a formula[1] that takes into account the benchmark response level as well as the slope of the exposure-response model at the benchmark concentration. However, because the model was supralinear at the BMC_{10}, a maximum factor of 10 for the 10% response level was used (U.S. EPA, 2002, Chapter 10). EPA is planning to develop guidance for applying an effect level extrapolation factor to a benchmark dose; the formula mentioned above was used in the interim. An extrapolation factor for effect level is applied because the 10% response level used as the point of departure is an adverse effect level. Therefore, a factor analogous to the LOAEL-to-NOAEL factor is needed to attempt to extrapolate to a level closer to a no effect

level. The default factors of 3 for interspecies extrapolation for inhalation exposures and of 10 for intraspecies variability were used. There is strong evidence that the diepoxide metabolite (1,2:3,4-diepoxybutane, DEB) is required to elicit ovarian atrophy (U.S. EPA, 2002, Chapter 5), and it is expected, based on pharmacokinetic data, that humans produce less DEB than mice (U.S. EPA, 2002, Chapter 3). However, DEB levels cannot be quantified without an adequate physiologically based pharmacokinetic (PBPK) model. Thus, default dosimetry (i.e., 1,3-butadiene exposure concentration) was used for dose-response modeling, and the default value of 1 for the pharmacokinetic portion of the interspecies uncertainty factor for inhalation exposures was retained. Finally, a factor of 3 was used to reflect an incomplete database, in particular the absence of a multigeneration study and a developmental neurotoxicity study. Dividing the $BMCL_{10}$ of 0.88 ppm by the composite UF of 1000 yields 0.9 ppb.

MF = 1.

[1] The formula is as follows: uncertainty factor = x × [(slope of the line from the BMC_x to 0)/(slope of the dose-response curve at the BMC_x)], where x% is the response level. Results of the formula are confined within a minimum value of 3 and a maximum value of x.

I.B.4. Additional Studies/Comments (Inhalation RfC)

A subchronic inhalation study showed that just 13 weeks of exposure to 1,000 ppm 1,3-butadiene was also sufficient to induce ovarian atrophy in female $B6C3F_1$ mice (Bevan et al., 1996).

In addition to deriving the chronic RfC, the Health Assessment Document also provides reference concentration values for acute and subchronic exposure scenarios, based on the mouse fetal weight data of Hackett et al. (1987) (see U.S. EPA, 2002, Chapter 10, Sections 10.3.2 and 10.4). These reference concentration values are not currently part of the IRIS file.

The EPA closely examined the physiologically-based pharmacokinetic (PBPK) models for 1,3-butadiene to determine if additional modeling could reduce uncertainties in the interspecies scaling between mice and humans for ovarian atrophy and other endpoints (U.S. EPA, 2002, Chapter 9). Despite advances in the models over the past decade, the current models are inadequate for this purpose. For example, the PBPK models do not yet accurately describe the distribution of the major metabolites in various compartments, they do not yet include the reportedly important epoxydiol metabolite, and they have not been adequately validated.

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — High
RfC — Medium

The overall confidence in this RfC assessment is medium. The RfC calculation was based on data from a high-quality NTP 2-year bioassay in which many exposure levels were used, although a NOAEL was not achieved. On the other hand, rat studies showed no such evidence of reproductive and developmental effects, and there are no human data on these effects; thus, it is uncertain how humans would respond.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 2002

This assessment was peer reviewed by external scientists (the Science Advisory Board). Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 2002.

Other documentation -- U.S. EPA, 1985

Agency Consensus Date — 9/13/2001

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,3-Butadiene
CASRN — 106-99-0
Last Revised — 11/05/2002

Section II provides information on three aspects of the carcinogenic assessment for the substance in question, the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per

(mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/m^3 air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000; 1 in 100,000; or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in *The Risk Assessment Guidelines of 1986* (EPA/600/8-87/045) and in the IRIS Background Documents. IRIS summaries developed since the publication of EPA's more recent *Proposed Guidelines for Carcinogen Risk Assessment* also utilize those guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

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

This weight-of-evidence carcinogenicity classification and quantitative estimate of carcinogenicity from inhalation exposure replace the previous classification of "B2; probable human carcinogen," and inhalation unit risk of 2.8×10^{-4} per µg/m^3, entered on IRIS on March, 31, 1987. The new classification and unit risk estimate are based on more recent data.

Under EPA's 1999 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), 1,3-butadiene is characterized as carcinogenic to humans by inhalation. This characterization is supported by the total weight-of-evidence provided by the following: (1) sufficient evidence from epidemiologic studies of the majority of U.S. workers occupationally exposed to 1,3-butadiene, either to the monomer or to the polymer by inhalation, showing increased lymphohematopoietic cancers and a dose-response relationship for leukemias in polymer workers (see Section II.A.2), (2) sufficient evidence in laboratory animal studies showing that 1,3-butadiene causes tumors at multiple sites in mice and rats by inhalation (see Section II.A.3), and (3) numerous studies consistently demonstrating that 1,3-butadiene is metabolized into genotoxic metabolites by experimental animals and humans (see Section II.A.4). The specific mechanisms of 1,3-butadiene-induced carcinogenesis are unknown; however, the scientific evidence strongly suggests that the carcinogenic effects are mediated by genotoxic metabolites of 1,3-butadiene, i.e., the monoepoxide, the diepoxide, and the epoxydiol.

II.A.2. Human Carcinogenicity Data

There is "sufficient evidence" from epidemiologic studies of exposed workers to consider 1,3-butadiene carcinogenic to humans. The exposure to 1,3-butadiene occurs in monomer production workers who produce 1,3-butadiene as a raw material or in polymer production workers who use 1,3-butadiene in styrene-butadiene rubber (SBR) production. Excesses of

lymphohematopoietic cancers have been observed in 1,3-butadiene polymer production workers and monomer production workers in North America. A significant excess of leukemias was observed in polymer production workers, and significant excesses of non-Hodgkin's lymphomas (previously diagnosed as lymphosarcoma and reticular sarcoma, but now included in non-Hodgkin's lymphomas [NHL] per the new classification in the *International Classification of Diseases of Oncology* [ICD-O]) have been observed in monomer workers. Under the previous, as well as the current, classification system adopted by the Revised European-American Lymphoma (REAL) and the Leukemia Society of America[2], both leukemia and lymphoma are lymphohematopoietic cancers, and thus the lymphohematopoietic system is considered to be the target organ for 1,3-butadiene.

The strongest evidence is provided by a retrospective cohort study of over 15,000 SBR workers in 8 plants studied by the University of Alabama at Birmingham (UAB cohort), with 49 years of follow-up (Delzell et al., 1996). Quantitative exposures (cumulative and peak) to 1,3-butadiene, styrene, and benzene were estimated for each worker (Macaluso et al., 1996). Limited validations of exposure estimates were attempted by various means. Significant excesses ranging from 43% to 336% were found for leukemia in ever hourly workers as compared with the general population, after adjusting for styrene and benzene. An internal comparison, using estimated ppm-years of 1,3-butadiene exposure, resulted in increasing risk ratios for leukemia with increasing exposures. This trend was statistically significant. A fairly consistent association between exposure to 1,3-butadiene and occurrence of leukemia across the six plants for which subanalyses were done was also found.

The major strengths of this study are the detailed and comprehensive quantitative exposure estimations for 1,3-butadiene, styrene, and benzene for each individual. The cohort was also large, and there was a long follow-up period of 49 years. In addition, both external and internal comparison showed similar results, adjustments for potential confounding factors were carried out, and analyses by duration of employment and for latency were conducted.

The study had some limitations. Some misclassifications of exposure may have occurred with respect to certain jobs, but these are unlikely to have occurred only in leukemia cases because the exposures were calculated a priori. Furthermore, the excess mortality observed for leukemia was based on death certificates and was not verified by medical records, thus, there may be misclassification of diagnosis. The histologic typing of leukemia was also not available, so currently it is not known whether a single cell type or more than one cell type is associated with the exposure to 1,3-butadiene. Two plants were eliminated from the final analysis due to the lack of work histories, which may have resulted in the loss of valuable data. Finally, an issue has been raised of potential confounding exposure to dithiocarbamates (DTC) (Irons and Pyatt, 1998). DTCs have been in use since the early 1940s as fungicides and treatments for parasitic skin diseases. The DTC disulfiram has also been in use since the early

1940s for the treatment of alcoholism. So far, there is not even a case report of leukemia in the literature in reference to any of the DTCs. In addition, available animal studies have not provided any evidence that DTCs cause carcinogenesis. Hence, at this time, it is conjecture that DTCs are causally associated with leukemia and, therefore, confound the results of Delzell et al.

Additional evidence is provided by the earlier cohort study of some of these polymer workers (13,500 individuals; Johns Hopkins University [JHU] cohort)[3] conducted by Matanoski and Schwartz (1987), as well as a nested case-control study by Santos-Burgoa et al. (1992). A significant excess of lymphohematopoietic cancer, but not of leukemia, was observed in the cohort study, while a significantly increased odds ratio of 7 for leukemia was observed in a nested case-control study, as was a significant trend of increasing risk of leukemia with increasing exposure level of 1,3-butadiene.

For 1,3-butadiene monomer production workers, two of three different cohort studies found significant increased risk of NHL (previously classified as lymphosarcoma and reticulosarcoma) (Divine and Hartman, 1996; Ward et al., 1995). The third study (Cowles et al., 1994) was small and had shorter follow-up times. The strongest evidence of human carcinogenicity from monomer production worker studies is provided by the largest cohort of approximately 2,800 workers in a Texaco plant studied by several investigators (Downs et al., 1987; Divine and Hartman, 1996). The only significant excess mortality observed was for lymphosarcoma (now included in NHL) in the wartime subcohort of workers (154% to 169% higher than the general population). The investigators estimated exposures for each individual in their last follow-up (Divine and Hartman, 1996) and found that, except for an excess observed for NHL (76% higher than the general population) in the wartime subcohort, there were no excesses in any cause-specific cancer mortality.

The major strengths of this study are a relatively large cohort of monomer workers, a long follow-up period of 52 years, analyses by duration of employment and latency, and adjustment for potential confounding factors. The exposures in each individual were estimated in the last follow-up. Except for "hire-age"[4] in survival analysis using the Cox model, after 52 years of follow-up, this study did not find any statistically significant excess in leukemia (as was observed in polymer workers), although an increase of 13% was reported. This study may not have enough statistical power to detect a significant leukemia increase.

Some of the limitations of the study are a lack of data or means available to the investigators to estimate the peak exposures that were hypothesized to be associated with the observed increase in lymphosarcomas in wartime workers. The authors' claim of the existence of extremely high peak exposures during the 1950s and 1960s cannot be validated in the absence of any information about the frequency or the variations in intensity of peak exposures for

these different time periods (as compared to prior to the 1950s). Although the cohort is relatively large, it had low power to detect excess leukemias. Nonetheless, the finding of excess mortality from lymphosarcoma is consistent with the findings of Ward et al. (1995).

Ward et al. (1995) studied a small cohort of 364 individuals who had potential exposure to 1,3-butadiene at three Union Carbide plants. A statistically significant excess for lymphosarcoma (477% higher than the general population) was found based on 4 cases. The main limitations of this study are that the cohort was small and that exposures were assumed based on department codes. In addition, there was no analysis for latency or adjustment for potential confounding by exposure to other chemicals.

These monomer and polymer production worker cohorts demonstrate an excess number of lymphohematopoietic cancers in occupationally exposed workers. Increased NHL (lymphosarcomas) are reported for monomer production workers, whereas excess leukemias occur predominantly in polymer production workers. There are several possible explanations for this apparent difference between the monomer and polymer workers. It has been hypothesized that the observed excess of NHL (lymphosarcomas) in the monomer production workers may be related to exposure intensity, i.e., the excess risk may result from the high (peak) exposures during wartime, rather than the much lower exposures currently encountered by monomer production workers or the likewise comparatively lower exposures encountered by the polymer production workers. The absence of a significant leukemia excess in these same monomer workers may be attributable to low statistical power in the monomer studies. There is some suggestion of excess leukemias in the monomer production workers, although these were not statistically significant. The Union Carbide cohort had a leukemia excess of 23% based on 2 cases, and the Texaco cohort had an elevated risk of leukemias of 13% based on 13 cases (it should be noted though, that with every follow-up of the Texaco cohort, investigators have observed additional leukemia deaths). Even the Texaco cohort, a relatively large monomer production cohort, has low power to detect a statistically significant excess for leukemias, and with every follow-up, the investigators of the Texaco cohort increased the calendar period for the worker inclusion criteria. This added many younger workers with little cumulative exposure, shorter follow-up periods, and inadequate latency periods, thereby diluting the risk. In addition, 1,3-butadiene is produced at the end of the monomer production process, and current 1,3-butadiene exposures are very low in these workers.

In fact, the apparent difference between monomer and polymer workers may be largely an artifact. Under the latest classification system for lymphohematopoietic cancers, all lymphomas not classified as Hodgkin's disease are now included under NHL (see footnote 1). Using this classification, an excess of NHL of 37% (based on 15 cases; not statistically significant) was reported for workers who had worked >= 10 years and with >= 20 years since hire in the UAB (polymer) cohort (Sathiakumar et al., 1998). (Previously lymphosarcomas and

NHL were reported separately for this cohort.) Furthermore, as these investigators report, their evaluation of NHL relations was limited by their reliance on death certificates. NHL has high survival rates and may, in later clinical stages, transform into leukemia. Therefore, leukemia may be reported on the death certificates. In addition, as discussed above, nonsignificant excesses of leukemia were observed in two monomer studies. Thus, excesses of both leukemia and NHL have been observed for both monomer and polymer workers, and it may be that the increased risk of NHL is primarily observed among workers exposed to high concentrations of 1,3-butadiene (mostly wartime monomer workers), whereas the polymer production studies have greater power to detect a significant leukemia excess among SBR workers who have modest to low exposures. In any event, leukemias and NHL are related tumor types and can both be classified as lymphohematopoietic cancers (see footnote 1).

Finally, an alternate explanation is that the monomer workers may lack exposure to a necessary co- or modifying factor that may be present in polymer production, resulting in the development of leukemias, although the findings of Delzell et al. (1996) and Macaluso et al. (1996) show no evidence of confounding by exposure to other chemicals.

In summary, the findings of excess lymphohematopoietic cancers in polymer and monomer production workers are consistent with a causal association with exposure to 1,3-butadiene. As demonstrated above, the causality criteria of *temporality, strength of association, specificity, biological gradient*, and *consistency* are satisfied. In addition, as discussed in the next sections, 1,3-butadiene is metabolized by humans and other species to genotoxic metabolites and is carcinogenic in mice and rats, thus fulfilling the criterion of *biological plausibility* as well. Therefore, the human evidence is considered sufficient.

[2] Under the previous classification (8th ICD, Adapted), lymphohematopoietic cancers comprised the following subcategories: lymphosarcoma and reticular sarcoma, Hodgkin's disease, leukemia, and other lymphatic tissue cancers. In 1994, the International Lymphoma Group's Revised European-American Lymphoma (REAL) classification was proposed for the lymphohematopoietic cancers, and is being adopted into the ICD-O (Berard and Hutchison, 1997). This classification is based on new ideas evolving in the fields of molecular biology, genetics, and immunology, which have rendered the old classification for lymphohematopoietic cancers obsolete. The REAL classification comprises the following subcategories: B-cell neoplasms, T-cell and putative natural killer (NK)-cell neoplasms, Hodgkin's disease, and unclassified lymphomas. It should be noted that both leukemias and lymphomas that are produced by B-cells are included under B-cell neoplasms, and leukemias and lymphomas produced by T-cells and NK-cells are included under T-cell and NK-cell neoplasms. Any lymphoma (such as B-cell, T-cell, and NK-cell) that is not classified as Hodgkin's disease is included under non-Hodgkin's lymphoma.

Furthermore, the Leukemia Society of America defines lymphohematopoietic cancers as follows: "Leukemia, Lymphoma, Hodgkin's disease, and Myeloma are cancers of the body's blood forming and immune systems: the bone marrow and lymph nodes. They are considered to be related cancers because they involve the uncontrolled growth of cells with similar functions."

[3] One Canadian plant and six U.S. plants were common in the JHU and the UAB cohorts.

[4] Survival analyses were conducted by the investigators using three different methods in their last follow-up. Two different risk factors were used for these analyses ([1] Exposure, i.e., cumulative exposure, and [2] Hire-age, i.e., age at which the employee was hired) to calculate risks for all lymphohematopoietic cancer, leukemia, lymphosarcoma, NHL, and multiple myeloma.

II.A.3. Animal Carcinogenicity Data

Sufficient. Several chronic inhalation bioassay studies have been conducted with 1,3-butadiene: a 2-year rat study (Hazleton Laboratories Ltd., 1981; Owen et al., 1987); two lifetime mouse studies (NTP, 1984, 1993), the first terminated early because of excessive mortality and the second using lower exposure concentrations; a 2-year stop-exposure study with male mice (NTP, 1993); and a 1-year study comparing the induction of thymic lymphomas in two different strains of male mice (Irons et al., 1989). These studies provide unequivocal evidence that 1,3-butadiene is a multisite carcinogen in both rats and mice, with the mouse being significantly more sensitive than the rat.

In the most recent mouse study (NTP, 1993), groups of 70 male and 70 female B6C3F1 mice were exposed by inhalation 6 hours/day, 5 days/week to 0, 6.25, 20, 62.5, or 200 ppm 1,3-butadiene for up to 103 weeks, while groups of 90 male and 90 female mice were exposed to 625 ppm. Interim evaluations were conducted at 9 and 15 months on up to 10 mice per group. Significant concentration-related decreases in survival were seen in male and female mice exposed to concentrations >= 20 ppm, primarily due to the development of malignant neoplasms. Significant concentration-related increases in survival-adjusted incidences were observed for the following primary neoplasms in both males and females: malignant lymphomas; histiocytic sarcomas; heart hemangiosarcomas; alveolar/bronchiolar adenoma, carcinoma, or adenocarcinomas; and forestomach squamous cell papilloma or carcinomas. Female mice also exhibited significant concentration-related increases in survival-adjusted incidences of benign or malignant granulosa cell tumors (ovary) and of adenocanthoma, carcinoma, or malignant mixed tumors of the mammary gland. Other tumor types that showed significant increases in some exposure groups versus controls for male and/or female mice were hepatocellular adenoma or carcinomas, Harderian gland adenoma or carcinomas, and

preputial gland carcinomas. The most sensitive site was the female mouse lung, which exhibited significantly increased tumor incidence at the lowest exposure concentration tested (6.25 ppm).

In the sole rat study (Hazleton Laboratories Ltd., 1981), Charles River CD rats (110/sex/group) were exposed by inhalation to 0, 1,000, or 8,000 ppm 1,3-butadiene 6 hours/day, 5 days/week for up to 111 weeks. There was a treatment-related increase in mortality, some of which was attributed to nephropathies in males. In exposed females, significant increases occurred in incidences of mammary gland carcinoma or fibroadenomas and thyroid follicular cell adenoma or carcinomas. In exposed males, there were also significant increases in thyroid follicular cell tumors, as well as in Leydig cell tumors and pancreatic exocrine adenomas. Although not significant by pairwise comparisons, significant exposure-response trends were observed for Zymbal gland carcinomas and uterine stromal sarcomas in females and for brain gliomas in males.

II.A.4. Supporting Data for Carcinogenicity

1,3-Butadiene is metabolized to at least three genotoxic metabolites: a monoepoxide (1,2-epoxy-3-butene, EB), a diepoxide (1,2:3,4-diepoxybutane, DEB), and an epoxydiol (3,4-epoxy-1,2-butanediol, EBD) (Himmelstein et al., 1997; Melnick and Kohn, 1995). Although there are quantitative differences in the metabolic rates for various pathways between different species, the metabolism of 1,3-butadiene is qualitatively similar among species. The enzymes responsible for the metabolic activation of 1,3-butadiene to these epoxide metabolites, as well as the enzymes responsible for the detoxification of these reactive metabolites, exist in humans as well as mice and rats. The genetic toxicology literature on 1,3-butadiene, EB, and DEB consists of more than 450 publications with positive genotoxic findings in viruses, bacteria, plants, and animals. EBD has been less extensively studied, but recent evidence suggests that most of the trihydroxybutyl-guanine adducts in mice and rats exposed to 1,3-butadiene are derived from EBD (Koc et al., 1999). In addition, 1,3-butadiene is structurally related to other (rodent) carcinogens, such as isoprene and chloroprene (NTP, 1997; Melnick et al., 1996; NTP, 1998).

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

None. 1,3-Butadiene is a gas at room temperature and pressure, making oral exposure unlikely.

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

II.C.1. Summary of Risk Estimates

II.C.1.1. Inhalation Unit Risk - 3×10^{-5} per $\mu g/m^3$ (0.08 per ppm).

II.C.1.2. Extrapolation Method - linear extrapolation from LEC_{01} (0.254 ppm); LEC_{01} derived from linear relative rate model (RR = 1 + bX) using lifetable analysis with leukemia incidence data; an adjustment factor of 2 was applied (see below).

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	$3 \, \mu g/m^3$
E-5 (1 in 100,000)	$0.3 \, \mu g/m^3$
E-6 (1 in 1,000,000)	$0.03 \, \mu g/m^3$

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

The Delzell et al. (1995) retrospective cohort study of more than 15,000 male styrene-butadiene rubber production workers provides high-quality epidemiologic data on leukemia risk from 1,3-butadiene exposure. In the Delzell et al. study, 1,3-butadiene exposure was estimated for each job and work area for each study year, and these estimates were linked to workers' work histories to derive cumulative exposure estimates for each individual worker. Subsequent to the Poisson regression analyses by Delzell et al., which used four different mathematical models (linear, log-linear, power, and square root) to fit the exposure-response data, Health Canada obtained the data on this cohort and performed their own analyses. The Health Canada (1998) analyses were similar to those of Delzell et al., but involved some minor refinements (e.g., finer stratification of age and other modifying variables, and use of the actual mean exposure in the highest exposure group rather than an arbitrary value). It is the Health Canada analyses that are used for this risk assessment.

The linear relative rate model reported by Health Canada was RR = 1 + 0.0099X, where X represents cumulative 1,3-butadiene exposure in ppm-years. The results were adjusted for age, calendar period, years since hire, and cumulative styrene exposure. Benzene exposure was also estimated for each worker but was not found to be a confounder, and hence, was not included in the models. Risk estimates were made using the relative rate models and an

actuarial program that accounts for the effects of competing causes of death. U.S. age-specific mortality rates for all race and gender groups combined (NCHS, 1993) were used to specify the leukemia and all-cause background rates. Risks were computed up to age 85 for continuous 1,3-butadiene exposures. The occupational exposures in the epidemiology study were converted to continuous exposures by adjusting for the differences in the number of days exposed per year (240/365 days) and differences in the amount of contaminated air inhaled per day (10/20 m^3). (10 m^3 is the default occupational ventilation volume for an 8-hour work shift; 20 m^3 is the default 24-hour ambient ventilation volume [U.S. EPA, 1994]).

Interpreting the proposed new carcinogen risk assessment guidelines (U.S. EPA, 1999), linear extrapolation from the LEC_{01} (i.e., the 95% lower confidence limit of the exposure concentration associated with a 1% increased risk) is warranted given the clear genotoxicity of 1,3-butadiene and the fact that a 1% increase in risk is within the range of the epidemiologic data. Using the linear relative rate model for modeling the epidemiologic data in the range of observation yields an LEC_{01} of 0.375 ppm. Using the LEC_{01} as the point of departure and extrapolating linearly to 0 increased risk at 0 exposure, a unit risk estimate of 0.03/ppm is obtained for the risk of leukemia mortality from the occupational data.

However, we actually wish to estimate cancer incidence, not mortality; therefore, another calculation was done using the linear relative rate model and age-specific leukemia incidence rates for 1994-1998 from SEER (Surveillance, Epidemiology and End Results program of the National Cancer Institute; NCI, 2001) in place of the leukemia mortality rates in the actuarial program. This calculation assumes that leukemia incidence and mortality have the same exposure-response relationship for 1,3-butadiene exposure and that the incidence data are for first occurrences of leukemia or that relapses provide a negligible contribution. The calculation also relies upon the fact that the leukemia incidence rates are small compared to the all-cause mortality rates. The result is an LEC_{01} of 0.254 ppm and a unit risk estimate of 0.04/ppm for leukemia incidence.

An adjustment factor of 2 was then applied to this unit risk estimate to reflect evidence from rodent bioassays suggesting that extrapolating the excess risk of leukemia in a male-only occupational cohort may underestimate the total cancer risk from 1,3-butadiene exposure in the general population. First, studies in both rats and mice indicate that 1,3-butadiene is a multisite carcinogen. It is possible that humans exposed to 1,3-butadiene may also be at risk of cancers other than leukemia and that the epidemiologic study had insufficient power to detect excess risks at other sites (see below). Second, both the rat and mouse studies suggest that females are more sensitive to 1,3-butadiene-induced carcinogenicity than males, and the female mammary gland was the only 1,3-butadiene-related tumor site common to both species. The mammary tumor unit risk estimated from the female mouse (most sensitive species) data is just slightly lower (maximum likelihood estimate [MLE] = 0.02/ppm, 95%

upper confidence limit [UCL] = 0.03/ppm) than the human (male) leukemia risk (0.04/ppm based on linear extrapolation from the LEC_{01}). Thus, EPA decided to apply an adjustment factor of 2 to the leukemia risk estimate, resulting in a unit risk estimate of 0.08/ppm intended to cover the combined risks for leukemia and mammary cancer and to provide additional protection to account for the fact that small increases in risk at other sites, particularly the lung, cannot be ruled out.

The Delzell et al. study was a large cohort study (over 15,000 subjects) with a long follow-up time (49 years; 25% of the subjects had died by the end of the follow-up), so for most tumor sites there should be sufficient power to detect an increased risk. The main tumor site that might be at issue is the lung, which was the most sensitive site in both male and female mice. Lung cancer is fairly common in humans; therefore, the epidemiology study may have lacked the power to detect an increase in lung cancer. A crude "power" calculation based on the average employment and exposure characteristics of the cohort, exposure estimates and number of subjects available for 6 of the 8 plants, and the MLE of lung cancer unit risk for the female mouse (i.e., 0.1/ppm), and assuming no confounding by smoking, suggests that if humans were as sensitive as mice to the lung cancer effects of 1,3-butadiene, one would have expected to see 26 excess lung cancer cases in the epidemiology study. In fact, only 2 excess lung cancer cases were observed in the workers from the 6 plants over a background of 312 expected cases. On the other hand, the study has low statistical power to detect such a small proportional excess (power to detect a statistically significant increase in risk if the true SMR = 338/312 = 108 is estimated to be 42% according to the method of Beaumont and Breslow [1981]), and an SMR of 107 (319 observed/297 expected) was observed for the ever hourly workers for the 8 plants (although there was no increased risk in the overall cohort [SMR=101] or in the subgroup of ever hourly workers with >= 10 years worked and >= 20 years since hire [SMR=100]).

The only process group associated with an increased lung cancer SMR was maintenance (SMR = 141 observed/114 expected = 124). However, 7 mesotheliomas were also observed in maintenance workers (9 among ever hourly workers in the total cohort), suggesting that these workers may have been exposed to asbestos, a known lung carcinogen. Furthermore, the evidence for the association between the increased lung cancers in the maintenance workers and 1,3-butadiene exposure is weakened by the fact that lung cancers are not increased in other process groups which exhibited increases in leukemia cases (e.g., 1,3-butadiene production), the absence of a positive relationship with number of years worked, the absence of a trend with increasing years since hire, and the fact that the increase was attenuated when state, rather than national, lung cancer rates were used for comparison (Sathiakumar et al., 1998). Thus, the overall evidence of an association between lung cancer and 1,3-butadiene exposure is tenuous.

On the other hand, because the background rate of lung cancer is high, the power of the study to detect small increases in lung cancer risk is low, and, without adjusting for amount of smoking, it is difficult to make firm conclusions. Workers are not allowed to smoke in the plants because of the explosive potential of 1,3-butadiene; therefore, the workers may have had lower cigarette consumption, and this could easily mask a small increase in lung cancer risk. Thus, while the study does not provide good evidence of an association between lung cancer and 1,3-butadiene exposure, one cannot rule out a small increase in risk.

Some increases were also observed for laryngeal cancer in the Delzell et al. study; however, these are based on small numbers (for the overall cohort: 17 observed, 15 expected). On the other hand, the increases are associated with process groups in which excess leukemias are observed. No data are provided for duration of exposure or other exposure characteristics. Thus, while the evidence for an association between laryngeal cancer and 1,3-butadiene exposure is meager, a small increase in laryngeal cancer cannot be ruled out.

II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

For comparison purposes, human unit cancer risk estimates based on extrapolation from the results of lifetime animal inhalation studies are also presented. These unit risk estimates are 95% upper confidence limits on unit cancer risk, calculated from incidence data on all significantly elevated tumor sites using a linearized low-dose extrapolation model, consistent with the 1986 guidelines (U.S. EPA, 1986). Exposure values were adjusted to 24-hour continuous equivalent exposures by multiplying by (6/24) and (5/7). The rat-based estimates are 4.2×10^{-3}/ppm from male rat data and 5.6×10^{-2}/ppm from female rat data. These estimates are from EPA's 1985 assessment and were derived using the linearized multistage model and estimates of absorbed dose (U.S. EPA, 1985). The mouse-based estimates were derived from the 1993 NTP study, including interim kill data, using a Weibull multistage time-to-tumor model and an assumption of ppm equivalence across species. Unit risk estimates for each tumor type were calculated separately and a Monte Carlo analysis was used to estimate the 95% upper bound on the sum of the MLEs (U.S. EPA, 2002, Section 10.2.2.2). A cancer unit risk estimate of 0.22/ppm was calculated from the male mouse data and 0.29/ppm from the female mouse data. The estimate of 0.3/ppm based on the female mouse data is the preferred animal-based upper bound on human risk.

Human health risk estimates based on extrapolation from high-quality epidemiologic results are preferable to those based on rodent data, because they avoid the uncertainties inherent in extrapolating across species and, typically, the human exposures in epidemiologic studies are closer to anticipated environmental exposures than the high exposures used in animal studies, thus reducing the extent of low-dose extrapolation. In the case of 1,3-butadiene, while the rat exposures were at least 100-fold higher than human exposures, the lowest exposure in the

1993 NTP mouse study (4.7 ppm, 8-h TWA) is within the range of occupational exposures (0.7-1.7 ppm median and 39-64 ppm max 8-hour TWAs for work-area groups). However, interspecies differences in tumor sites and susceptibilities between rats and mice are especially pronounced, and the biological bases for these differences are unresolved. A review of available pharmacokinetic data and models revealed that the state of the science is currently inadequate for explaining interspecies differences or improving on default dosimetry assumptions (see Section I.B.4 and U.S. EPA, 2002, Chapter 9). Therefore, the quantitative extrapolation of rodent risks to humans is highly uncertain for 1,3-butadiene.

II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Even though high-quality human data were used for the quantitative cancer risk estimation for 1,3-butadiene, there are inevitable uncertainties in the calculated risk estimate. First, there are uncertainties inherent in the epidemiologic study itself. In particular, there are uncertainties in the retrospective estimation of 1,3-butadiene exposures, which could have resulted in exposure misclassification. Nondifferential exposure misclassification would tend to bias estimates of effect toward the null, resulting in an underestimate of risk. Differential misclassification could bias results in either direction.

In fact, after completing their initial study, Delzell et al. raised some concerns about the accuracy of the exposure estimates (see U.S. EPA, 2002, Section 10.1.3). In 2000, Delzell et al. completed a re-assessment of the exposure estimates and concluded that the earlier a priori estimates were too low. The revised exposure estimates need to be critically evaluated before EPA can determine whether or not they are more credible than the a priori estimates. If the revised exposure estimates are valid, the leukemia portion of the cancer risk estimate would decrease somewhat (see U.S. EPA, 2002, Section 11.1).

Second, there are uncertainties regarding the appropriate dose metric for dose-response analysis. Although the dose surrogate of cumulative exposure (i.e., ppm × years) yielded highly statistically significant exposure-response relationships, cumulative exposure is strongly correlated with other possible exposure measures, and there may be a dose-rate effect (e.g., risk at high exposures may be more than proportionately greater than at lower exposures) obscured in the analysis, or operative at exposures below the observable range but relevant to low-dose extrapolation.

Third, there are uncertainties pertaining to which model to use for the epidemiologic data. Several mathematical models adequately fit the exposure-response data from the epidemiology study, and because the specific mechanisms of 1,3-butadiene carcinogenesis are unknown, there is no biological basis for choosing one model over another. The linear model was chosen

in this risk assessment to derive the "point of departure" for low-dose extrapolation because there was no compelling reason to deviate from historical approaches.

Fourth, it is uncertain which potential modifying or confounding factors should be included in the model. The linear model of Health Canada, which is used in this risk assessment, was adjusted for age, calendar year, years since hire, race, and exposure to styrene. Plant and benzene exposure were ruled out as potential confounders. However, there may be other relevant factors that were not included in the models.

Fifth, there are uncertainties in the parameter estimates used in the models. The study of Delzell et al. is large, providing some degree of reliability in the parameter estimates. However, especially given the large human variability that has been observed in metabolic activities that could affect cancer risk from 1,3-butadiene exposure, the generalizability of the occupational results is unclear.

Sixth, there are uncertainties in extending the relative rate models from the epidemiology study to derive lifetime excess leukemia incidence unit risk estimates for the U.S. population. Notwithstanding, the actuarial-type analysis that was used is a well-established methodology, and the background leukemia incidence rates and mortality rates used in the analysis are from large national databases.

Seventh, the precise model for low-dose extrapolation is unknown. The linear default extrapolation procedure in the 1999 proposed guidelines was used in this assessment because of the well-established genotoxicity of 1,3-butadiene via its metabolites.

In addition, there are important concerns raised by comparison with the rodent data. First, the rodent studies suggest that 1,3-butadiene is a multisite carcinogen. It is possible that humans may also be at risk of 1,3-butadiene-induced carcinogenicity at other sites and that the epidemiologic study had insufficient power to detect the other excess risks. In the mouse, for example, the lung is the most sensitive tumor site. Significant excesses of lung cancer may not have been detectable in the epidemiologic study because of the high background rates of lung cancer in humans (see also II.C.2 above). Delzell et al. did observe a slight increase in lung cancer among maintenance workers. The epidemiology-based excess cancer risk estimate of 0.04/ppm, which is based only on leukemias, may be an underestimate if other sites are also at risk.

Second, both the rat and mouse studies suggest that females are more sensitive to 1,3-butadiene-induced carcinogenicity than are males, and the mammary gland in females was the only tumor site common to both species. If female humans are also more sensitive than males, then the male-based risk estimates calculated from the epidemiology study would

underestimate risks to females. Because of these concerns, an adjustment factor of 2 is used, as discussed above, yielding a cancer unit risk estimate of 0.08/ppm.

Despite these uncertainties, confidence in the excess cancer risk estimate of 0.08/ppm is moderate. First, the estimate is based primarily on human data. Furthermore, these data are from a large, high-quality epidemiologic study in which 1,3-butadiene exposures were estimated for each individual a priori to conducting the exposure-response analysis. Although there are uncertainties in the exposure estimation, a serious attempt was made to reconstruct historical exposures for specific tasks and work areas at different time periods. It is virtually unprecedented to have such a comprehensive exposure assessment for individual workers in such a large occupational epidemiologic study. In addition, the assumption of linearity for low-dose extrapolation is reasonable given the clear evidence of genotoxicity by 1,3-butadiene metabolites.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA, 2002

This assessment was peer reviewed by external scientists. Their comments have been carefully evaluated and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to U.S. EPA, 2002.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 9/13/2001

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS in general at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (email address).

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

VI. Bibliography

Substance Name — 1,3-Butadiene
CASRN — 106-99-0

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

Adler, ID; Anderson, D. (1994) Dominant lethal effects after inhalation exposure to 1,3-butadiene. Mutat Res 309:295-297.

Anderson, D; Edwards, AJ; Brinkworth, MH. (1993) Male-mediated F_1 effects in mice exposed to 1,3-butadiene. In: Butadiene and styrene: assessment of health hazards. IARC Scientific Publications. Vol. 127. Sorsa, M; Peltonen, K; Vainio, H; et al., eds. Lyon, France: International Agency for Research on Cancer, pp. 171-181.

Anderson, D; Hughes, JA; Edwards, AJ; et al. (1998) A comparison of male-mediated effects in rats and mice exposed to 1,3-butadiene. Mutat Res 397:77-84.

Bevan, C; Stadler, JC; Elliot, GS; et al. (1996) Subchronic toxicity of 4-vinylcyclohexene in rats and mice by inhalation. Fundam Appl Toxicol 32:1-10.

Brinkworth, MH; Anderson, D; Hughes, JA; et al. (1998) Genetic effects of 1,3-butadiene on the mouse testis. Mutat Res 397:67-75.

Hackett, PL; Sikov, MR; Mast, TJ; et al. (1987) Inhalation developmental toxicology studies: teratology study of 1,3-butadiene in mice (final report). Richland, WA: Pacific Northwest Laboratory; PNL Report No. PNL-6412 UC-48; NIH Report No. NIH-401-ES-40131; 92. Prepared for NIEHS, NTP, under a Related Services Agreement with the U.S. Department of Energy under contract DE-AC06-76RLO-1830.

National Center for Health Statistics (NCHS). (1996) Vital statistics of the United States, 1992, vol. II, mortality, part A. Washington, DC: U.S. Public Health Service.

National Toxicology Program (NTP), U.S. Department of Health and Human Services. (1993) Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). NTP TR 434, NIH Pub. No. 93-3165. Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA). (1985) Mutagenicity and carcinogenicity assessment of 1,3-butadiene. Office of Health and Environmental Assessment, Office of Research and Development, Washington, DC. EPA/600/8-85/004F.

U.S. Environmental Protection Agency (U.S. EPA). (1994) Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington, DC. EPA/600/8-90/066F.

U.S. Environmental Protection Agency (U.S. EPA). (2002) Health assessment document for 1,3-butadiene. Office of Research and Development, Washington, DC. EPA/600/P-98/001.

VI.C. Carcinogenicity Assessment References

Beaumont, JJ; Breslow, NE. (1981) Power considerations in epidemiologic studies of vinyl chloride workers. Am J Epidemiol 114:752-34.

Berard, CW; Hutchison, RE. (1997) The problem of classifying lymphomas: an orderly prescription for progress. Ann Oncol (Suppl 2):53-59.

Cowles, SR; Tsai, SP; Snyder, PJ; et al. (1994) Mortality, morbidity, and haematologic results from a cohort of long-term workers involved in 1,3-butadiene monomer production. Occup Environ Med 51:323-329.

Delzell, E; Sathiakumar, N; Macaluso, M.; et al. (1995) A follow-up study of synthetic rubber workers. Submitted to the International Institute of Synthetic Rubber Producers. University of Alabama at Birmingham. October 2, 1995.

Delzell, E; Sathiakumar, N; Hovinga, M. (1996) A follow-up study of synthetic rubber workers. Toxicology 113:182-189.

Divine, BJ; Hartman, CM. (1996) Mortality update of butadiene production workers. Toxicology 113:169-181.

Downs, TD; Crane, MM; Kim, KW. (1987) Mortality among workers at a butadiene facility. Am J Ind Med 12:311-329.

Hazleton Laboratories Europe Ltd. (1981) The toxicity and carcinogenicity of butadiene gas administered to rats by inhalation for approximately 24 months. Prepared for the International Institute of Synthetic Rubber Producers, New York, NY. Unpublished.

Health Canada. (1998) Canadian Environmental Protection Act Priority Substances List Health Assessment: 1,3-Butadiene. Draft for second stage peer review. Ottawa. March 1998. Additional information was provided by Health Canada for calculation of the confidence intervals (personal communication from Michael Walker to Leslie Stayner, 18 June 1999).

Himmelstein, MW; Acquavella, JF; Recio, L; et al. (1997) Toxicology and epidemiology of 1,3-butadiene. Crit Rev Toxicol 27(1):1-108.

Irons, RD; Cathro, HP; Stillman WS; et al. (1989) Susceptibility to 1,3-butadiene-induced leukemogenesis correlates with endogenous ecotropic retroviral background in the mouse. Toxicol Appl Pharmacol 101:170-176.

Irons, RD; Pyatt, DW. (1998) Commentary: dithiocarbamates as potential confounders in butadiene epidemiology. Carcinogenesis 19(4):539-542.

Koc, H; Tretyakova, NY; Walker, VE; et al. (1999) Molecular dosimetry of N-7 guanine adduct formation in mice and rats exposed to 1,3-butadiene. Chem Res Toxicol 12:566-574.

Macaluso, M; Larson, R; Delzell, E. (1996) Leukemia and cumulative exposure to butadiene, styrene and benzene among workers in the synthetic rubber industry. Toxicology 113:190-202.

Matanoski, GM; Schwartz, L. (1987) Mortality of workers in styrene-butadiene polymer production. J Occup Med 29:675-680.

Melnick, RL; Kohn, MC. (1995) Mechanistic data indicate that 1,3-butadiene is a human carcinogen. Carcinogenesis 16(2):157-163.

Melnick, RL; Elwell, MR; Roycroft, JH; et al. (1996) Toxicity of inhaled chloroprene (2-chloro-1,3-butadiene) in F344 rats and B6C3F1 mice. Toxicology 113:247-252.

National Cancer Institute (NCI). (2001) SEER Cancer Statistics Review, 1973-1998, National Cancer Institute. Bethseda, MD, http://seer.cancer.gov/csr/19731998/index.html, 2001.

National Center for Health Statistics (NCHS). (1996) Vital statistics of the United States, 1992, vol. II, mortality, part A. Washington, DC: U.S. Public Health Service.

National Toxicology Program (NTP), U.S. Department of Health and Human Services. (1984) Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F1 mice (inhalation studies). NTP TR 288, NIH Pub. No. 84-2544. Research Triangle Park, NC.

NTP. (1993) Toxicology and carcinogenesis studies of 1,3-butadiene (CAS No. 106-99-0) in B6C3F$_1$ mice (inhalation studies). NTP TR 434, NIH Pub. No. 93-3165. Research Triangle Park, NC.

NTP. (1997) NTP Technical Report on the toxicology and carcinogenesis studies of isoprene in F344/N rats. Technical Report No. 486 (Draft), U.S. DHHS.

NTP. (1998) Toxicology and carcinogenesis studies of chloroprene in F344/N rats and B6C3F$_1$ mice. Technical Report No. 467, U.S. DHHS.

Owen PE; Glaister, JR; Gaunt, IF; et al. (1987) Inhalation toxicity studies with 1,3-butadiene. 3. Two-year toxicity/carcinogenicity study in rats. Am Ind Hyg Assoc J 48(5):407-413.

Santos-Burgoa, C; Matanoski, GM; Zeger, S; et al. (1992) Lymphohematopoietic cancer in styrene-butadiene polymerization workers. Am J Epidemiol 136:843-854.

Sathiakumar, N; Delzell, E; Hovinga, M; et al. (1998) Mortality from cancer and other causes of death among synthetic rubber workers. Occup Environ Med 55:230-235.

U.S. Environmental Protection Agency (U.S. EPA). (1985) Mutagenicity and carcinogenicity assessment of 1,3-butadiene. Office of Health and Environmental Assessment, Office of Research and Development, Washington, DC. EPA/600/8-85/004F.

U.S. EPA. (1999) Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July 1999. Risk Assessment Forum. http://www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm.

U.S. EPA. (2002) Health assessment document for 1,3-butadiene. Office of Research and Development, Washington, DC. EPA/600/P-98/001.

Ward, EM; Fajen, JM; Ruder, A. (1995) Mortality study of workers in 1,3-butadiene production units identified from a chemical workers cohort. Environ Health Perspect 103:598-603.

VII. Revision History

Substance Name — 1,3-Butadiene
CASRN — 106-99-0

Date	Section	Description
11/05/2002	All	Complete revision based on new health assessment document

VIII. Synonyms

Substance Name — 1,3-Butadiene
CASRN — 106-99-0
Last Revised — 11/05/2002

- 106-99-0
- BIETHYLENE
- BIVINYL
- BUTADIEEN
- BUTA-1,3-DIEEN
- BUTADIEN
- BUTA-1,3-DIEN
- BUTADIENE
- 1,3-Butadiene
- Butadiene, 1,3-
- alpha,gamma-BUTADIENE
- DIVINYL
- ERYTHRENE
- NCI-C50602
- PYRROLYLENE
- VINYLETHYLENE