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Occupational Safety and Health Administration

29 CFR Part 1910, et al.

Occupational Exposure to 1,3-Butadiene; Final Rule

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Parts 1910, 1915 and 1926

[Docket No. H–041]

RIN 1218–AA83

Occupational Exposure to 1,3-Butadiene

AGENCY: Occupational Safety and Health Administration (OSHA), Department of Labor.

ACTION: Final rule.

SUMMARY: This final standard amends the Occupational Safety and Health Administration's (OSHA) occupational standard that regulates employee exposure to 1,3-Butadiene (BD). The basis for this action is a determination by the Assistant Secretary, based on animal and human data, that OSHA's current permissible exposure limit (PEL) which permits employees to be exposed to BD in concentrations up to 1,000 parts BD per million parts of air (1,000 ppm) as an eight-hour time-weighted average (TWA) does not adequately protect employee health. OSHA's new limits reduce the PEL for BD to an 8-hour TWA of 1 ppm and a short term exposure limit (STEL) of 5 ppm for 15 minutes. An ''action level'' of 0.5 ppm as an 8-hour TWA is included in the standard as a mechanism for exempting an employer from some administrative burdens, such as employee exposure monitoring and medical surveillance, in instances where the employer can demonstrate that the employee's exposures are consistently at very low levels. In order to reduce exposures and protect employees, OSHA's BD standard includes requirements such as engineering controls, work practices and personal protective equipment, measurement of employee exposures, training, medical surveillance, hazard communication, regulated areas, emergency procedures and recordkeeping.

DATES: The effective date of these amendments is February 3, 1997. Start-up date for engineering controls is November 4, 1998, and for the exposure goal program November 4, 1999. Affected parties do not have to comply with the information collection requirements in § 1910.1051(d) exposure monitoring, § 1910.1051(f) methods of compliance, § 1910.1051(g) exposure goal program, § 1910.1051(h) respiratory protection, § 1910.1051(j) emergency situations, § 1910.1051(k) medical screening and surveillance, § 1910.1051(l) communication of BD hazards to employees; and § 1910.1051(m) recordkeeping until the Department of Labor publishes a Federal Register notice informing the public that OMB has approved these information requirements under the Paperwork Reduction Act of 1995.

Other Dates: Written comments on the paperwork requirements of this final rule must be submitted on or before January 3, 1997.

ADDRESSES: In accordance with 28 U.S.C. 2112(a), the Agency designates the following party to receive petitions for review of this regulation: Associate Solicitor for Occupational Safety and Health, Office of the Solicitor, Room S–4004, U.S. Department of Labor, 200 Constitution Ave., NW., Washington, DC 20210. These petitions must be filed no later than the 59th calendar day following promulgation of this regulation; see section 6(f) of the Occupational Safety and Health Act of 1970 (OSH Act), 29 CFR 1911.18(d), and *United Mine Workers of America* v. *Mine Safety and Health Administration,* 900 F.2d 384 (D.C. Circ. 1990).

Comments regarding the paperwork burden of this regulation, which are being solicited by the Agency as required by the Paperwork Reduction Act of 1995, are to be submitted to the Docket Office, Docket No. ICR 96–13, U.S. Department of Labor, Room N–2625, 200 Constitution Ave., NW., Washington, DC 20210, telephone (202) 219–7894. Written comments limited to 10 pages or less in length may also be transmitted by facsimile to (202) 219–5046.

FOR FURTHER INFORMATION CONTACT: Ms. Anne Cyr, OSHA Office of Public Affairs, United States Department of Labor, Room N–3641, 200 Constitution Avenue, NW., Washington, DC. 20210, Telephone (202) 219–8151. Copies of the referenced information collection request are available for inspection and copying in the Docket Office and will be mailed to persons who request copies by telephoning Vivian Allen at (202) 219–8076. For electronic copies of the 1,3–Butadiene Information Collection Request, contact OSHA's WebPage on Internet at http://www.osh.gov/.

I. Collection of Information; Request for Comment

This final 1,3–Butadiene standard contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA95) 44 U.S.C. 3501 *et seq.* (see also 5 CFR part 1320). PRA95 defines collection of information to mean, ''the obtaining, causing to be obtained, soliciting, or requiring the disclosure to third parties or the public of facts or opinions by or for an agency regardless of form or format.'' (44 U.S.C. 3502(3)(A))

The title, the need for and proposed use of the information, a summary of the collections of information, description of the respondents, and frequency of response required to implement the required information collection is described below with an estimate of the annual cost and reporting burden (as required by 5 CFR 1320.5(a)(1)(iv) and 1320.8(d)(2)). Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

OSHA invites comments on whether the proposed collection of information:

- Ensures that the collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility;
- Estimates the projected burden accurately, including whether the methodology and assumptions used are valid;
- Enhances the quality, utility, and clarity of the information to be collected; and
- Minimizes the burden of the collection of information on those who are to respond, including the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submissions of responses.

Title: 1,3–Butadiene, 29 CFR 1910.1051.

Description: The final 1,3-Butadiene (BD) Standard is an occupational safety and health standard that will minimize occupational exposure to BD. The standard's information collection requirements are essential components that will protect employees from occupational exposure. The information will be used by employers and employees to implement the protection required by the standard. OSHA will use some of the information to determine compliance with the standard.

Summary of the Collection of Information: The collections of information contained in the standard include the provisions concerning objective data; exposure monitoring records and employee notification of exposure monitoring results; written plans for compliance, respiratory protection, exposure goal, emergency situations; information to the physician; employee medical exams and medical

records; respirator fit-testing records; record of training program; employee access to monitoring and medical records; and transfer of records to NIOSH.

Respondents: The respondents are employers whose employees may have occupational exposure to BD above the action level. The main industries affected are 1,3-Butadiene Polymer Production, Monomer purification of 1,3-Butadiene, Stand-Alone Butadiene Terminals, and Crude 1,3-Butadiene Producers.

Frequency of Response: The frequency of monitoring and notification of monitoring results will be dependent on the results of the initial and subsequent monitoring events and the number of different job classifications with BD exposure. The Compliance Plan is required to be established and updated as necessary and reviewed at least annually. The Exposure Goal Program, Respiratory Protection Program, and Emergency Plans are required to be established and updated as necessary. For those using respirators, respirator fit testing is required initially, and at least annually thereafter. The frequency of the medical examinations will be dependent on the number of employees who will be exposed at or above the action level, or in emergency situations. A record of the training program is required to be maintained. Those employers using objective data in lieu of monitoring must maintain records of the objective data relied upon. The employer must maintain exposure monitoring and medical records, which includes information provided to the physician or other licensed health care professional, in accordance with 29 CFR 1910.20. Fit-Test records must be maintained for respirator users until the next fit test is administered.

Total Estimated Cost: First Year $820,388; Second Year $658,949; and Third and Recurring Years $75,890.

Total Burden Hours: The total burden hours for the first year is estimated to be *8,077;* for the second year, the burden is estimated to be *5,342;* and for the third and recurring years, the burden is estimated to be *1,587.* The Agency has submitted a copy of the information collection request to OMB for its review and approval. Interested parties are requested to send comments regarding this information collection to the OSHA Docket Office, Docket No. ICR 96–13, U.S. Department of Labor, Room N–2625, 200 Constitution Avenue, NW, Washington, DC 20210. Written comments limited to 10 pages or fewer may also be transmitted by facsimile to (202) 219–5046.

Comments submitted in response to this notice will be summarized and included in the request for Office of Management and Budget approval of the final information collection request; they will also become a matter of public record.

Copies of the referenced information collection request are available for inspection and copying in the OSHA Docket Office and will be mailed to persons who request copies by telephoning Vivian Allen at (202) 219–8076. Electronic copies of the 1,3-Butadiene information collection request are available on the OSHA WebPage on the Internet at http://www.osha.gov/.

Federalism

This standard has been reviewed in accordance with Executive Order 12612, 52 FR 41685 (October 30, 1987), regarding Federalism. This Order requires that agencies, to the extent possible, refrain from limiting State policy options, consult with States prior to taking any actions only when there is clear constitutional authority and the presence of a problem of national scope. The Order provides for preemption of State law only if there is a clear Congressional intent for the Agency to do so. Any such preemption is to be limited to the extent possible.

Section 18 of the Occupational Safety and Health Act (OSH Act), expresses Congress' clear intent to preempt State laws with respect to which Federal OSHA has promulgated occupational safety or health standards. Under the OSH Act, a State can avoid preemption only if it submits, and obtains Federal approval of, a plan for the development of such standards and their enforcement. Occupational safety and health standards developed by such State Plan-States must, among other things, be at least as effective in providing safe and healthful employment and places of employment as the Federal standards. Where such standards are applicable to products distributed or used in interstate commerce, they may not unduly burden commerce and must be justified by compelling local conditions. (See section 18(c)(2).)

The final BD standard is drafted so that employees in every State will be protected by general, performance-oriented standards. States with occupational safety and health plans approved under section 18 of the OSH Act will be able to develop their own State standards to deal with any special problems which might be encountered in a particular state. Moreover, the performance nature of this standard, of and by itself, allows for flexibility by States and employers to provide as much leeway as possible using alternative compliance.

This final rule of BD addresses a health problem related to occupational exposure to BD which is national in scope.

Those States which have elected to participate under section 18 of the OSH Act would not be preempted by this regulation and will be able to deal with special, local conditions within the framework provided by this performance-oriented standard while ensuring that their standards are at least as effective as the Federal Standard.

State Plans

The 23 States and 2 territories with their own OSHA-approved occupational safety and health plans must adopt a comparable standard within 6 months of the publication of this final standard for occupational exposure to 1,3-butadiene or amend their existing standards if it is not ''at least as effective'' as the final Federal standard. The states and territories with occupational safety and health state plants are: Alaska, Arizona, California, Connecticut (for State and local government employees only), Hawaii, Indiana, Iowa, Kentucky, Maryland, Michigan, Minnesota, Nevada, New Mexico, New York (for State and local government employees only), North Carolina, Oregon, Puerto Rico, South Carolina, Tennessee, Utah, Vermont, Virginia, the Virgin Islands, Washington, and Wyoming. Until such time as a State standard is promulgated, Federal OSHA will provide interim enforcement assistance, as appropriate, in these states and territories.

SUPPLEMENTARY INFORMATION:

I. Table of Contents

The preamble to the final standard on occupational exposure to BD discusses events leading to the final rule, physical and chemical properties of BD, manufacture and use of BD, health effects of exposure, degree and significance of the risk presented, an analysis of the technological and economic feasibility, regulatory impact and regulatory flexibility analysis, and the rationale behind the specific provisions set forth in the proposed standard. The discussion follows this outline:

II. Pertinent Legal Authority

The purpose of the Occupational Safety and Health Act, 29 U.S.C. 651 *et seq.* (''the Act'') is to ''assure so far as possible every working man and woman in the nation safe and healthful working conditions and to preserve our human resources.'' 29 U.S.C. 651(b). To achieve this goal, Congress authorized the Secretary of Labor to promulgate and enforce occupational safety and health standards. U.S.C. 655(a) (authorizing summary adoption of existing consensus and federal standards within two year of Act's enactment), 655(b) (authorizing promulgation of standards pursuant to notice and comment), 654(b) (requiring employers to comply with OSHA standards.)

A safety or health standard is a standard ''which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment or places of employment.'' 29 U.S.C. 652(8).

A standard is reasonably necessary or appropriate within the meaning of Section 652(8) if it substantially reduces or eliminates significant risk, and is economically feasible, technologically feasible, cost effective, consistent with prior Agency action or supported by a reasoned justification for departing from prior Agency actions, supported by substantial evidence, and is better able to effectuate the Act's purposes than any national consensus standard it supersedes. See 58 FR 16612–16616 (March 30, 1993).

The Supreme Court has noted that a reasonable person would consider a fatality risk of 1/1000 over a 45-year working lifetime to be a significant risk. Industrial Union *Dep't* v. *American Petroleum Institute, 448 U.S. 607,* 646 (1980) (benzene standard). OSHA agrees that a fatality risk of 1/1000 over a working lifetime *is well within the range of risk that* reasonable people would consider significant. See e.g., *International Union, UAW* v. *Pendergrass,* 878 F.2d 389 (D.C. Cir. 1989) (formaldehyde standard); *Building and Constr. Trades Dep't, AFL–CIO* v. *Brock,* 838 F.2d 1258, 1265 (D.C. Cir. 1988) (asbestos standard).

A standard is technologically feasible if the protective measures it requires already exist, can be brought into existence with available technology, or can be created with technology that can reasonably be expected to be developed. *American Textile Mfrs. Institute* v. *OSHA,* 452 U.S. 490, 513 (1981) (''ATMI''), *American Iron and Steel Institute* v. *OSHA,* 939 F.2d 975, 980 (D.C. cir. 1991) (''AISI'').

A standard is economically feasible if industry can absorb or pass on the cost of compliance without threatening its long term profitability or competitive structure. See *ATMI,* 452 U.S. at 530 n. 55; *AISI,* 939 F. 2d at 980.

A standard is cost effective if the protective measures it requires are the least costly of the available alternatives that achieve the same level of protection. ATMI, 453 U.S. at 514 n. 32; *International Union, UAW* v. *OSHA,* 37 F. 3d 665, 668 (D.C. Cir. 1994) (''LOTO III'').

All standards must be highly protective. See 58 FR 16614–16615; *LOTO III,* 37 F. 3d at 668. However, health standards must also meet the ''feasibility mandate'' of Section 6(b)(5) of the Act, 29 U.S.C. 655(b)(5). Section 6(b)(5) requires OSHA to select ''the most protective standard consistent with feasibility'' that is needed to reduce significant risk when regulating health hazards. *ATMI,* 452 U.S. at 509.

Section 6(b)(5) also directs OSHA to base health standards on ''the best available evidence,'' including research, demonstrations, and experiments. 29 U.S.C. 655(b)(5). OSHA shall consider ''in addition to the attainment of the highest degree of health and safety protection * * * the latest scientific data * * * feasibility and experience gained under this and other health and safety laws.'' *Id.*

Section 6(b)(7) of the Act authorizes OSHA to include among a standard's requirements labeling, monitoring, medical testing and other information gathering and transmittal provisions. 29 U.S.C. 655(b)(7).

Finally, whenever practical, standards shall ''be expressed in terms of objective criteria and of the performance desired.'' *Id.*

III. Events Leading to the Final Standard

The standard adopted for BD by OSHA in 1971 pursuant to Section 6(a) of the OSH Act, 29 U.S.C. 655 from an existing Walsh-Healey Federal Standard required employers to assure that employee exposure does not exceed 1,000 ppm determined as an 8-hour TWA (29 CFR 1910.1000, Table Z–1). The source of the Walsh-Healey Standard was the Threshold Limit Value (TLV) for BD developed in 1968 by the American Conference of Governmental Industrial Hygienists (ACGIH). This TLV was adopted by the ACGIH to prevent irritation and narcosis.

In 1983, the National Toxicology Program (NTP) released the results of an animal study indicating that BD causes cancer in rodents. (Ex. 20) Based on the strength of the results of this animal study, ACGIH in 1983 classified BD as an animal carcinogen and in 1984 recommended a new TLV of 10 ppm. (Ex. 2–4) Based on the same evidence, on February 9, 1984, the National Institute for Occupational Safety and Health (NIOSH) published a Current Intelligence Bulletin (CIB) recommending that BD be regarded as a potential occupational carcinogen, teratogen and a possible reproductive hazard. (Ex. 23–17) On January 5, 1984, OSHA published a Request for Information (RFI) jointly with the Environmental Protection Agency. (EPA) (49 FR 844) EPA also announced the initiation of a 180 day review under the authority of section 4(f) of the Toxic Substance Control Act (TSCA) (49 FR 845) to determine ''whether to initiate appropriate action to prevent or reduce the risk from the chemical or to find that the risk is not unreasonable.'' Comments were to be submitted to OSHA by March 5, 1984. On April 4, 1984, OSHA extended the comment period until further notice. (49 FR 13389)

Petitions for an Emergency Temporary Standard (ETS) of 1 ppm or less for workers' exposure to BD were submitted to OSHA on January 23, 1984, by the United Rubber, Cork, Linoleum and

Plastic Workers of America (URW), the Oil, Chemical and Atomic Workers (OCAW), the International Chemical Workers Union (ICWU), and the American Federation of Labor and Congress of Industrial Organizations (AFL–CIO). (Ex. 6–4) On March 7, 1984, OSHA denied the petitions on the ground that the Agency was still evaluating the health data to determine whether regulatory action was appropriate.

Based on its 180-day review of BD, EPA published, on May 15, 1984, an Advance Notice of Proposed Rulemaking (ANPR) (49 FR 20524) to announce the initiation of a regulatory action by the EPA to determine and implement the most effective means of controlling exposures to the chemical BD under the TSCA. EPA was working with OSHA because available evidence indicated that exposure to BD occurs primarily within the workplace.

Information received in response to this ANPR was used by EPA to develop risk assessments. Subsequently, EPA identified BD as a probable human carcinogen (Group B2) according to EPA's classification of carcinogens, and concluded that current exposures during the manufacturing of BD and its processing into polymers presented an unreasonable risk of injury to human health. (Ex. 17–4) Additionally, EPA determined that the risks associated with exposure to BD may be reduced to a sufficient extent by action taken under the OSH Act. Following these findings, EPA, in accordance with section 9(a) of TSCA, on October 10, 1985 (50 FR 41393), referred BD to OSHA to give this Agency an opportunity to regulate the chemical under the OSH Act. EPA requested that OSHA determine whether the risks described in the EPA report may be prevented or reduced to a sufficient extent by action taken under the OSH Act and then if such a determination is made, OSHA issue an order declaring whether the manufacture and use of BD described in the EPA report present the risk therein described. EPA asked OSHA to respond within 180 days, by April 8, 1986. (50 FR 41393)

On December 27, 1985, OSHA published a notice soliciting public comments on EPA's referral report. (50 FR 52952) Based on all the available information, OSHA, on April 11, 1986, responded to the EPA referral report by making a preliminary determination (50 FR 12526) that a revised OSHA standard limiting occupational exposure to BD could prevent or reduce the risk of exposure to a sufficient extent and that such risks had been accurately described by EPA in the report. On October 1, 1986, OSHA published an ANPR (51 FR 35003) to initiate a rulemaking within the meaning of section 9(a) of TSCA. The Agency requested that comments be submitted by December 30, 1986. Twenty-four comments, some of them containing new information, were received in response to the ANPR. (Ex. 28–1 to 28–24) Six additional comments were received after the deadline. (Ex. 29–1 to 29–6)

OSHA reviewed the available data and conducted risk assessment, regulatory impact and flexibility analyses. These analyses demonstrate that the proposed standard was technologically and economically feasible and substantially reduced the significant risk of cancers and other adverse health effects.

On August 10, 1990, OSHA published its proposed rule to regulate occupational exposure to 1,3-butadiene. (55 FR 32736) Based on the Agency's review of studies of exposed animals and epidemiologic studies and taking into account technologic and economic feasibility considerations, OSHA proposed a permissible exposure limit (PEL) of 2 ppm as an 8-hour time-weighted average and a short term exposure limit (STEL) of 10 ppm for a 15 minute sampling period. Also included in the proposal was an ''action level'' of 1 ppm which triggered certain provisions of the standard such as medical surveillance and training.

OSHA convened public hearings in Washington, DC., on January 15–23, 1991, and in New Orleans, Louisiana, on February 20–21, 1991. The post-hearing period for the submission of briefs, arguments and summations was to end July 22, 1991, but was extended by the Administrative Law Judge to December 13, 1991, in order to give participants time to review new data on low-dose exposures submitted by NTP and a quantitative risk assessment done by NIOSH. The comment period closed February 10, 1992.

In the Fall of 1992, the International Agency for Research on Cancer (IARC) published the results of the Working Group on the Evaluation of Carcinogenic Risks to Humans, which reviewed the carcinogenic potential of BD and concluded that:

> There is limited evidence for the carcinogenicity in humans of 1,3-butadiene * * * There is sufficient evidence for the carcinogenicity in experimental animals * * * (Ex. 125)

IARC stated that its overall evaluation led it to conclude that ''1,3-butadiene is probably carcinogenic to humans (Group 2A).'' (Ex. 125)

To assist OSHA in issuing a final rule for BD, representatives of the major unions and industry groups involved in the production and use of BD submitted the outline of a voluntary agreement reached by the parties dated January 29, 1996, outlining provisions that they agreed upon and recommended be included in the final rule. The letter transmitting the agreement was signed by J.L. McGraw for the International Institute of Synthetic Rubber Producers (IISRP), Michael J. Wright for the United Steelworkers of America (USWA), and Michael Sprinker (CWU). The committee that worked on the issues also included Joseph Holtshouser of the Goodyear Tire and Rubber Company, Carolyn Phillips of the Shell Chemical Company, representing the Chemical Manufacturers Association, Robert Richmond of the Firestone Synthetic Rubber and Latex Company, and Louis Beliczky (formerly of the URW) and James L. Frederick of the SWA.

The agreement proposed a change in the permissible exposure limits, additional provisions for exposure monitoring, and an exposure goal program designed to reduce exposures below the action level. It also set forth other modifications to the scope, respiratory protection, communication of hazards, medical surveillance, and start-up dates sections of the final rule.

On March 8, 1996 OSHA published the labor/industry joint recommendations and re-opened the record for 30 days to allow the public to comment. (61 FR 9381) In response to requests from the parties to the agreement, the comment period was extended to April 26, 1996. (61 FR 15205)

At the beginning of the comment period, OSHA placed in the rulemaking record an epidemiologic study of BD exposed workers by Delzell, et al. sponsored by IISRP, along with IARC volume 127 ''Butadiene and Styrene Assessment of Health Hazards,'' a published paper by Santos-Burgoa, et al. entitled ''Lymphohematopoietic Cancer in Styrene-Butadiene Polymerization Workers,'' and abstracts from a symposium entitled ''Evaluation of Butadiene and Isoprene Health Risks.'' (Ex. 117–1; 117–2; 117–3; 117–4) The epidemiological study had also been submitted to the EPA in compliance with provisions of the Toxic Substances Control Act.

In response to the re-opening of the BD record, 18 sets of comments were received. The parties to the labor/industry agreement submitted a draft regulatory text which put their recommendations into specific requirements. The outline and the

subsequent draft regulatory text are solely the work product of the negotiating committee. OSHA was neither a party to nor present at the negotiations.

While the responses to the record re-opening helped clarify the intent of the negotiating parties, the rationales behind several of the changes were not fully explained.

On September 16, 1996, Judge John M. Vittone, for Judge George C. Pierce who presided over the BD hearings, closed the record of the public hearing on the proposed standard for 1,3-butadiene and certified it to the Assistant Secretary of Labor. (Ex. 135)

IV. Chemical Identification, Production and Use

A. Monomer

The chemical 1,3-butadiene (BD) (Chemical Abstracts Registry Number 106–99–0) is a colorless, noncorrosive, flammable gas with a mild aromatic odor at standard ambient temperature and pressure. It has a chemical formula of C_4H_6, a molecular weight of 54.1, and a boiling point of −4.7 °C at 760 mm Hg, a lower explosive limit of 2%, and an upper explosive limit of 11.5%. Its vapor density is almost twice that of air. It is slightly soluble in water, somewhat soluble in methanol and ethanol, and readily soluble in less polar organic solvents such as hexane, benzene, and toluene. (Ex. 17–17) It is highly reactive, dimerizes to 4-vinylcyclohexene, and polymerizes easily. Because of its low odor threshold, high flammability and explosiveness, BD has been handled with extreme care in the industry.

In the United States BD has been produced commercially by three processes: Catalytic dehydrogenation of n-butane and n-butene, oxidative dehydrogenation of n-butene, and recovery as a by-product from the C_4 co-product stream from the steam cracking process used to manufacture ethylene, which is the major product of the petrochemical industry. For economic reasons, almost all BD currently made in the U.S. is produced by the ethylene co-product process.

In the steam cracking process for ethylene, a hydrocarbon feedstock is diluted with steam then heated rapidly to a high temperature by passing it through tubes in a furnace. The output stream, containing a broad mixture of hydrocarbons from the pyrolysis reactions in the cracking tubes plus unreacted components of feedstock, is cooled and then processed through a series of distillation and other separation operations in which the various products of the cracking operation are separated for disposal, recycling or recovery.

The cracking process produces between 0.02 to 0.3 pounds of BD per pound of ethylene, depending upon the composition of the feedstock. BD is recovered from the C_4 stream by the separation operations. The C_4 stream contains from 30 to 50% BD plus butane, butenes and small fractions of other hydrocarbons. This crude BD stream from the ethylene unit may be refined in a unit on site, or transferred to another location, a monomer plant, owned by the same or a different company, to produce purified BD.

Regardless of the source of the crude BD-ethylene co-product, (dehydrogenation, or blending of C_4 streams from other sources), the processes used by different companies to refine BD for subsequent use in polymer production are similar. Extractive distillation is used to effect the basic separation of BD from butanes and butenes and fractional distillation operations are used to accomplish other related separations. A typical monomer plant process is described below.

C_3 and C_4 acetylene derivatives, present in the C_4 co-product stream, are converted to olefins by passing the stream through a hydrogenation reactor. The stream is then fed to an extractive distillation column to separate the BD from butanes and butenes. Several different solvents have been employed for this operation, including n-methylpyrrolidone, dimethylformamide, furfural, acetonitrile, dimethylacetamide, and cuprous ammonium acetate solution. The BD, extracted by the solvent, is stripped from it in the solvent recovery column, then fed to another fractionation column, the methylacetylene column, to have residual acetylene stripped out. The bottom stream from the methylacetylene column, containing the BD, is fed to the BD rerun column, from which the purified BD product is taken off overhead. The solvent, recovered in the solvent recovery column, is recycled to the extractive distillation column with part of it distilled to keep down the level of polymer. (Ex. 17–17)

A stabilizer is added to the monomer to inhibit formation of polymer during storage. It is stored as a liquid under pressure, sometimes refrigerated to reduce the pressure, generally stored in a tank farm in diked spheres. It is shipped to polymer manufacturers and other users by pipeline, barge, tank car, or tank truck.

BD is a major commodity product of the petrochemical industry. Total U.S. production of BD in 1991 was 3.0 billion pounds. Although BD is a toxic flammable gas, its simple chemical structure with low molecular weight and high chemical reactivity make it a useful building block for synthesizing other products. In ''1,3-Butadiene Use and Substitutes Analysis,'' EPA identified 140 major, minor and potential uses of BD in the chemical industry. (Ex. 17–15)

Over 60% of the BD consumed in the United States is used in the manufacture of rubber, about 12% in making adiponitrile which in turn is used to make hexamethylenediamine (HMDA), a component of Nylon, approximately 8% in making styrene-butadiene copolymer latexes, approximately 7% in producing polychloroprene, and about 6% in producing acrylonitrile-butadiene-styrene (ABS) resins. Lesser amounts are consumed in the production of rocket propellants, specialty copolymer resins and latexes for paint, coatings and adhesive applications, and hydrogenated butadiene-styrene polymers used as lubricating oil additives. Some nonpolymer applications include the manufacture of the agricultural fungicides, Captan and Captofol, the industrial solvent sulfolane, and anthroquinone dyes.

B. Polymers

BD based synthetic elastomers are manufactured by polymerizing BD by itself, by polymerizing BD with other monomers to produce copolymers, and by producing mixtures of these polymers. The largest-volume product is the copolymer of styrene and BD, styrene-butadiene rubber, followed in volume by polybutadiene, polychloroprene, and nitrile rubber. Polybutadiene is the polymer of BD monomer by itself. Polychloroprene is made by polymerizing chloroprene, produced by chlorination of BD. Nitrile rubbers are copolymers of acrylonitrile and BD.

Four general types of processes are used in polymerizing BD and its copolymers: emulsion, suspension, solution and bulk polymerization. In emulsion and suspension polymerization, the monomers and the many chemicals used to control the reaction are finely dispersed or dissolved in water. In solution polymerization, the monomers are dissolved in an organic solvent such as hexane, pentane, toluene. In bulk polymerization, the monomer itself serves as solvent for the polymer. The polymer product, from which end-use products are manufactured, is produced in the form of polymer crumb (solid particles), latex (a milky suspension in water), or cement (a solution).

Emulsion polymerization is the principal process used to make synthetic rubber. A process for the manufacture of styrene-butadiene crumb is typical of emulsion processes. Styrene and BD are piped to the process area from the storage area. The BD is passed through a caustic soda scrubber to remove the inhibitors which were added to prevent premature polymerization. The fresh BD monomer streams are mixed with styrene, aqueous emulsifying agents, activator, catalyst, and modifier, and then fed to the first of a train of reactors. The reaction proceeds stepwise in the series of reactors to around 60% conversion of monomer to polymer. In the cold process, the reactants are chilled and the reactor temperature is maintained at 4°C to 7°C (40°F to 45°F) and pressure at 0 to 15 psig; in the hot rubber process, temperature and pressure are around 50°C (122°F) and 40 to 60 psig, respectively.

The latex from the reactor train is flashed to evaporate unreacted BD which is compressed, condensed and recycled. Uncondensed vapors are absorbed in a kerosene absorber before venting and the absorbed BD is steam stripped or recovered from the kerosene by some other operation. The latex stream is passed through a steam stripper, operated under vacuum, to remove and recover unreacted styrene. The styrene and water in the condensate are separated by decanting. The styrene phase is recycled to the process. Noncondensibles from the stripping column contain some BD and are directed through the BD recovery operations.

Stripped latex, to which an antioxidant has been added, is pumped to coagulation vessels where dilute sulfuric acid and sodium chloride solution are added. The acid and brine mixture breaks the emulsion, releasing the polymer in the form of crumb. Sometimes carbon black and oil are added during the coagulation step since better dispersion is obtained than by mixing later on.

The crumb and water slurry from the coagulation operation is screened to separate the crumb. The wet crumb is pressed in rotary presses to squeeze out most of the entrained water then dried with hot air on continuous dry belt dryers. The dried product is baled and weighed for shipment.

Production of styrene-butadiene latex by the emulsion polymerization process is similar to that for crumb but is usually carried out on a smaller scale with fewer reactors. For some but not all products, the reaction is run to near completion, monomer removal is simpler and recovery may not be practiced.

Polybutadiene rubber is usually produced by solution polymerization. Inhibitor is removed from the monomer by caustic scrubbing. Both monomer and solvent are dried by fractional distillation, mixed in the desired ratio and dried in a desiccant column. Polymerization is conducted in a series of reactors using initiators and catalysts and is terminated with a shortstop solution. The solution, called rubber cement, is pumped to storage tanks for blending. Crumb is precipitated by pumping the solution into hot water under violent agitation. Solvent and monomer are recovered by stripping and distillation similar to those previously described. The crumb is screened, dewatered, dried and baled.

Polychloroprene (neoprene) elastomers are manufactured by polymerizing chloroprene in an emulsion polymerization process similar to that used for making styrene-butadiene rubber. The monomer, chloroprene (2-chloro-BD), is made by chlorination of BD to make 3,4-dichlorobutene, and dehydrochlorination of the latter.

Nitrile rubbers, copolymers of acrylonitrile and BD, are produced by emulsion polymerization similar to that used to make styrene-butadiene rubber.

Substantial amounts of BD are used in the production of two other large volume polymers: Nylon resins and ABS resin. Dupont manufactures adiponitrile from BD and uses the product to make hexamethylenediamine which is polymerized in making Nylon resins and fibers, including Nylon 6,6. Acrylonitrile, BD and styrene are the monomers used to make ABS resin which is a major thermoplastic resin. Chemically complex emulsion, suspension and bulk polymerization processes are used by different producers to make ABS polymer.

V. Health Effects

A. Introduction

The toxicity of BD was long considered to be low and non-cumulative. Thus, the OSHA standard for BD was 1,000 ppm on the basis of its irritation of mucous membranes and narcosis at high levels of exposure. However, in the 1980s, carcinogenicity studies indicated BD is clearly a carcinogen in rodents. In 1986, the American Conference of Governmental Industrial Hygienists (ACGIH) was prompted by these studies to lower the workplace threshold limit value (TLV) from 1,000 to 10 ppm. (Ex. 2–5)

Rodent studies are now conclusive that BD is an animal carcinogen. Further, a consistent body of epidemiologic studies have also shown increased mortality from hematopoietic cancers associated with BD exposure among BD-exposed production and styrene/BD rubber polymer workers. Complementary studies of metabolic products and genotoxicity support these cancer findings. OSHA was also concerned about evidence that BD affects the germ cell as well as the somatic cell, and what potential reproductive toxicity might result from exposure to BD. Since BD itself does not appear to be carcinogenic, but must be metabolized to an active form, OSHA also reviewed studies on the metabolism of BD to determine wether they might help explain the observed differences in cancer incidence among species.

The following sections discuss the effects of BD exposure, both in human and animal systems.

B. Carcinogenicity

1. Animal Studies

In the proposed BD rule, OSHA discussed the results of two lifetime animal bioassays, one on the Sprague-Dawley rat and one in the $B6C3F_1$ mouse. (55 FR 32736 at 32740) Both studies found evidence of BD carcinogenicity, with the greater response in the mouse. The rat study involved exposure levels of 0, 1000, or 8000 ppm BD, starting at five weeks of age, to groups of 100 male and 100 female Sprague-Dawley rats for 6 hours per day, five days per week, for 105 weeks. Mortality was increased over controls in the 1,000 ppm exposed female rats and in both of the male rat exposure groups. Significant tumor response sites in the male rats included exocrine adenomas and carcinomas (combined) of the pancreas in the highest exposure group (3, 1, and 11 tumors in the 0, 1000, and 8000 ppm groups, respectively); and Leydig-cell tumors of the testis (0, 3, and 8 in the same groups, respectively). In the female rats, the significantly increased tumor response also occurred in the highest exposure group; cancers seen included follicular-cell adenomas and carcinomas (combined) of the thyroid gland (0,4, and 11 tumors in the three exposure groups, respectively), and benign and malignant (combined) mammary gland tumors (50, 79, and 81 in the same exposure groups). To a lesser degree there were also sarcomas of the uterus (1, 4, 5 tumors in the three exposure groups), and Zymbal gland (0, 0, 4 tumors in the same exposure groups, respectively). While only high

exposure group tumor response for some of these sites was statistically significant, trend tests were also significant.

In contrast to the generally less than 10% increase in tumor response seen in the Sprague-Dawley rat at levels far above BD metabolic saturation, the carcinogenic response to BD in the $B6C3F_1$ mouse in the National Toxicology Program study (NTP I) was extensive. (Ex. 23–1) In this study, groups of 50 male and 50 female mice were exposed via inhalation to 0, 625 or 1250 ppm BD for 6 hours per day, 5 days per week in a study originally designed to last 2 years. However, the high carcinogenic response included multiple primary cancers, with short latent periods, and led to early study termination (60–61 weeks) due to high cancer mortality in both the 625 ppm and 1250 ppm exposure groups of both sexes. This mortality was due mainly to lymphocytic lymphomas and hemangiosarcomas of the heart, both of which were typically early occurring and quickly fatal. This large and rapidly fatal carcinogenic response led to both the NTP and industry to undertake additional studies to better understand the mechanisms involved.

Some commenters have associated qualitative or quantitative differences in mouse and rat BD carcinogenicity with the differences in rat and mouse BD metabolism. Many studies published and submitted to the BD record since the proposed rule have sought to better characterize the metabolic, distributional, and elimination processes involved, and some have attributed species differences (at least in part) to the metabolic differences. These will be addressed separately in the metabolism section.

Another factor hypothesized to account for differences between mouse and rat BD carcinogenicity was the role of activation of ecotropic retrovirus in hematopoietic tissues on tumor response in the $B6C3F_1$ mouse. This virus is endogenous to the $B6C3F_1$ mouse and was hypothesized to potentiate the BD lymphoma response in this strain. To study this hypothesis Irons and co-workers exposed both (60) $B6C3F_1$ male (those with the endogenous virus) and (60) NIH Swiss male (those without the endogenous virus) mice to either 0 or 1250 ppm BD, for 6 hours./day, 5 days per week for 52 weeks. (Ex. 32–28D) A third group of 50 $B6C3F_1$ male mice received 1250 ppm for 12 weeks only and was observed until study termination at 52 weeks. The results of the study showed significantly increased thymic lymphomas in all exposed groups but significantly greater response in the $B6C3F_1$ mouse—1 tumor/60 (2%) in the control (zero exposure) group, 10/48 (21%) in the 12 week exposure group, and 34/60 (57%) in the 52 week exposure group—vs. the NIH Swiss mice, which developed 0 tumors/60 in the control group, and 8 tumors/57 (14%) in the BD exposed group. Hemangiosarcomas of the heart were also observed in both strains exposed to BD for 52 weeks—5/60 (8%) in the $B6C3F_1$ mice vs. 1/57 in the NIH Swiss mice. (Ex. 32–28D). The $B6C3F_1$ response was very similar to the NTP I high exposure group response, verifying that earlier study. The qualitatively similar lymphoma responses of the two strains also confirmed that the mouse hematopoietic system is highly susceptible to the carcinogenic effects of BD, although quantitatively the strains may differ. The 21% 1-year lymphoma response in the 12-week stop-exposure $B6C3F_1$ group also increased concerns about high concentration, short duration exposures.

NTP II Study

Concurrent with the industry studies, the NTP, in order to better characterize the dose-response and lifetime experience, conducted a second, much larger research effort over a much broader dose range. (Ex. 90; 96) These toxicology and carcinogenesis studies included a 100-fold lower (6.25 ppm) low exposure group than NTP I, several intermediate exposure groups, a study of dose-rate effects using several high-concentration partial lifetime (stop-) exposure groups, and planned interim sacrifice groups. Other parts of the study included clinical pathology studies (with the 9- and 15-month interim sacrifices, metabolism studies, and examination of tumor bearing animals for activated oncogenes).

For the lifetime carcinogenesis studies, groups of 70 $B6C3F_1$ mice of each sex were exposed via inhalation to BD at levels of 0, 6.25, 20, 62.5, 200, or 625 ppm (90 of each sex in this highest group) for 6 hours per day, 5 days per week for up to 2 years. Up to 10 randomly selected animals in each group were sacrificed after 9 and 15 months of exposure, and these animals were assessed for both carcinogenicity and hematologic effects.

For the stop-exposure study, different groups of 50 male mice were exposed 6 hours per day, 5 days per week to concentrations of either 200 ppm for 40 weeks, 625 ppm for 13 weeks, 312 ppm for 52 weeks, or 625 ppm for 26 weeks. Following the BD exposure period, the exposed animals were then observed for the remainder of the 2-year study. The first two stop-exposure groups received a total exposure (concentration times duration) of 8,000 ppm-weeks, while the latter two groups received approximately 16,000 ppm-weeks of exposure. For the analysis discussed below, groups are compared both with each other for dose-rate effects and with the lifetime (2 year) exposure groups for recovery effects.

Methodology

Male mice were 6–8 weeks old and female mice were 7–8 weeks old when the exposures began. Animals were exposed in individual wire mesh cage units in stainless steel Hazelton 2000 chambers (2.3 m^3). The exposure phase extended from January, 1986 to January, 1988. Animals were housed individually; water was available *ad libitum;* NIH–07 diet feed was also available *ad libitum* except during exposure periods. Animals were observed twice daily for moribundity and mortality; animals were weighed weekly for the first 13 weeks and monthly thereafter. Hematology included red blood cell count (RBC), and white blood cell count (WBC). The study was conducted in compliance with the Food and Drug Administration (FDA) Good Laboratory Practice Regulations with retrospective quality assurance audits.

The results of the study are presented below for the two-year and stop-exposure study. Between study group comparisons are made where it is deemed appropriate. Emphasis is placed on the neoplastic effects.

Results

Two-Year Study

While body weight gains in both exposed male and female mice were similar to those of the control groups, exposure related malignant neoplasms were responsible for decreased survival in all exposure groups of both sexes exposed to concentrations of 20 ppm or above. Excluding the interim sacrificed animals, the two-year survival decreased uniformly with increasing exposure for females (37/50, 33/50, 24/50, 11/50, 0/50, 0/70), and nearly uniformly for males (35/50, 39/50, 24/50, 22/50, 4/50, 0/70). As with the earlier NTP study, all animals in the 625 ppm group were dead by week 65, mostly as a result of lymphomas or hemangiosarcomas of the heart. The 200 ppm exposure groups of both sexes also had much higher mortality, but significantly less than that of the 625 ppm group. The survival of the lowest exposure group (6.25 ppm) was slightly better than controls for the male mice, slightly less for the female mice. Mean

survival for the males was an exposure-related 597, 611, 575, 558, 502, and 280 days; for the females it was similarly 608, 597, 573, 548, 441, and 320 days. This decreased survival with increasing exposure was almost totally due to tumor lethality.

Carcinogenicity

Nine different sites showed primary tumor types associated with butadiene exposures, seven in the male mice and eight in the female mice. These were lymphoma, hemangiosarcoma of the heart, combined alveolar-bronchiolar adenoma and carcinoma, combined forestomach papilloma and carcinoma, Harderian gland adenoma and adenocarcinoma, preputial gland adenoma and carcinoma (males only), hepatocellular adenoma and carcinoma, and mammary and ovarian tumors (females only). These are shown in Table V–1 adapted from Melnick et al. (Ex. 125) From this table it is seen that six of these tumor sites are statistically significantly increased in the highest exposed males and five were statistically significantly increased in the highest exposed females. Two additional sites which showed significant increases at lower exposures showed decline at the highest exposures because other tumors were more rapidly fatal. At 200 ppm preputial gland adenoma and carcinoma combined were significantly increased in males ($p<.05$; 0/70 (0%) control vs. 5/70 (7%) in the 200 ppm group) and hepatocellular adenoma and carcinoma were increased for both exposed males and females. At the lowest exposure concentration, 6.25 ppm, only female mouse lung tumors (combined adenoma and carcinoma) showed statistical significance ($p<.05$; 4/70 (6%) in controls vs. 15/70 (21%) in the 6.25 ppm group); these tumors in female mice showed a monotonic increase with increasing exposure up to 200 ppm. At 20 ppm female mouse lymphomas and liver tumors also reached statistical significance (lymphomas, $p<.05$; 10/70 (15%) in controls vs. 18/70 (26%) in the 20 ppm group; liver tumors, $p<.05$; 17/70 (24%) in controls vs. 23/70 (33%) in the 20 ppm group), and at 62.5 ppm, tumors at several other sites were also significantly increased. In general, while there were some differences in amount of tumor response between the male and female mice, there is fairly consistent pattern of tumor type in mice of both sexes for the six non-sexual organ sites.

TABLE V–1.—TUMOR INCIDENCES (I) AND PERCENTAGE MORTALITY-ADJUSTED TUMOR RATES (R) IN MICE EXPOSED TO 1,3-BUTADIENE FOR UP TO 2 YEARS.

[Adapted from Ex. 125]

Tumor	Sex	Exposure concentration (ppm)											
		0		6.25		20		62.5		200		625	
		I	R[c]	I	R	I	R	I	R	I	R	I	R
Lymphoma	M	4/70	8	3/70	6	8/70	19	11/70	[a]25	9/70	[a]27	69/90	[a]97
	F	10/70	20	14/70	30	[a]18/70	41	10/70	26	19/70	[a]58	43/90	[a]89
Heart—Hemangiosarcoma	M	0/70	0	0/70	0	1/70	2	5/70	[a]13	20/70	[a]57	6/90	[a]53
	F	0/70	0	0/70	0	0/70	0	1/70	3	20/70	[a]64	26/90	84
Lung—Alveolar-bronchiolar adenoma and carcinoma.	M	22/70	46	23/70	48	20/70	45	33/70	[a]72	42/70	[a]87	12/90	[a]73
Forestomach—Papilloma and carcinoma	F	4/70	8	15/70	[a]32	19/70	[a]44	27/70	[a]61	32/70	[a]81	25/90	[a]83
Harderian gland—Adenoma and adenocarcinoma	M	1/70	2	0/70	0	1/70	2	5/70	13	12/70	[a]36	13/90	[a]75
	F	2/70	4	2/70	4	3/70	8	4/70	12	7/70	[a]31	28/90	[a]85
Preputial gland—Adenoma and carcinoma	M	6/70	13	7/70	15	11/70	25	24/70	[a]53	33/70	[a]77	7/90	[a]58
	F	9/70	18	10/70	21	7/70	17	16/70	[a]40	22/70	[a]67	7/90	48
Liver—Hepatocellular adenoma and carcinoma	M	0/70	0	0/70	0	0/70	0	0/70	0	5/70	[a]17	0/90	0
Mammary gland—Adenocarcinoma	M	31/70	55	27/70	54	35/70	68	32/70	69	40/70	[a]87	12/90	75
Ovary—Benign and malignant granulosa-cell tumors.	F	17/70	35	20/70	41	23/70	[a]52	24/70	[a]60	20/70	[a]68	3/90	28
	F	0/70	0	2/70	4	2/70	5	6/70	[a]16	13/70	[a]47	13/90	[a]66
	F	1/70	2	0/70	0	0/70	0	9/70	[a]24	11/70	[a]44	6/90	44

[a] Increased compared with chamber controls (0 ppm), $p < 0.05$, based on logistic regression analysis.
[b] The Working Group noted that the incidence in control males and females was in the range of that in historical controls (Haseman et al., 1985).
[c] Mortality adjusted tumor rates are adjusted for competing causes of mortality, such as death due to other tumors, whose rates differ by exposure group.

Hemangiosarcoma of the heart, with metastases to other organs was first observed at 20 ppm in 1 male (the historical controls for this strain are 1/2373 in males and 1/2443 in females), in 5 males and 1 female at 62.5 ppm and in 20 males and 20 females at 200 ppm; at 625 ppm these tumor rates leveled off as other tumors, especially lymphomas became dominant. Lymphatic lymphomas increased to statistical significance first in females at 20 ppm and were usually rapidly fatal, the first tumor appearing at week 23, most likely preempting some of the later appearing tumors in the higher exposure groups. Because of the plethora of primary tumors and the different time patterns observed to onset of each type, several tumor dose-response trends do not appear as strong as they would otherwise be.

Non-Neoplastic Effects

Several non-cancer toxic effects were noted in the exposed groups, reflecting many of the same target sites for which the neoplastic effects were seen. (Ex. 90; 96; 125).

Although the reported numbers differ slightly in the different exhibits, generally dose-related increases in hyperplasia were observed in the heart, lung, forestomach, and Harderian gland, both in the two-year study (both sexes) and in the stop-exposure study (conducted in males only). In addition, testicular atrophy was observed in both the two-year and stop-exposure male mice, but remained in the 6%–10% range except for the 2-year, 625 ppm

group where it was 74%. Ovarian germinal hyperplasia (2/49 (control), 3/49 (6.25 ppm), 8/48 (20 ppm), 15/50 (62.5 ppm), 15/50 (200 ppm), 18/79 (625 ppm), ovarian atrophy (4/49, 19/49, 32/48, 42/50, 43/50, 69/79), and uterine atrophy (1/50, 0/49, 1/50, 1/49, 8/50, 41/78) were also dose related, with ovarian atrophy significantly increased at the lowest BD exposure of 6.25 ppm. These toxic effects to the reproductive organs are discussed in greater detail in the reproductive effects section of this preamble. Bone marrow atrophy was noted only in the highest exposure groups, occurring in 23/73 male mice and 11/79 female mice.

Stop-Exposure Study

As with the 2-year study, the body weights of the four treated groups in the stop-exposure study were similar to controls. All exposure groups exhibited markedly lower survival than controls, and only slightly better survival than that of the comparable full lifetime exposure groups. Mortality appeared to be more related to total dose than to exposure concentration. Most deaths were caused by tumors.

Neoplastic Effects

All of these stop-exposure groups exhibited a very similar tumor profile to that of the lifetime high exposure groups, with the lone exception of liver tumors, which were increased only in the lifetime exposure group; all the other multiple primary tumors were observed at significantly increased levels in both the stop- and lifetime-exposure groups, Table V–2. (Ex. 125) In addition, the 625 ppm, 26 week exposure group had higher rates for several of the tumor types compared to the lifetime 625 ppm group, possibly because of the shorter exposure group's slightly better survival. The most prevalent tumor type, lymphoma, also showed a dose-rate effect, as the tumor incidence was greater for exposure to short-term higher concentrations compared with a lower long-term exposure ($p=.01$; 24/50 at 625 ppm for 13 weeks vs. 12/50 at 200 ppm for 40 weeks: $p<.0001$; 37/50 at 625 ppm for 26 weeks vs. 15/50 at 312 ppm for 52 weeks). The same pattern was seen with forestomach tumors and preputial gland carcinomas. Conversely, the hemangiosarcomas of the heart and alveolar-bronchiolar tumors showed an opposite trend, as lower exposures for a longer time yielded a significantly higher incidence of these tumors than the same cumulative exposures over a shorter time (survival-adjusted, as opposed to the raw incidence lung tumor rates actually suggest no dose-response trends). These inconsistent trends with the different tumor sites may be the result of multiple mechanisms of carcinogenicity or partially due to the rapid fatality caused by lymphocytic lymphomas in the short-term high-exposure groups. As with the lifetime study, angiosarcomas of the heart and lymphomas presented competing risks in the highly exposed mice.

TABLE V–2.—TUMOR INCIDENCES (I) AND PERCENTAGE MORTALITY-ADJUSTED TUMOR RATES (R) IN MALE MICE EXPOSED TO 1,3-BUTADIENE IN STOP-EXPOSURE STUDIES. (AFTER EXPOSURES WERE TERMINATED, ANIMALS WERE PLACED IN CONTROL CHAMBERS UNTIL THE END OF THE STUDY AT 104 WEEKS.)

[Adapted from Ex. 125]

Tumor	Exposure									
	0		200 ppm, 40 wk		625 ppm, 13 wk		312 ppm, 52 wk		625 ppm, 26 wk	
	I	R[c]	I	R	I	R	I	R	I	R
Lymphoma	4/70	8	12/50	[a]35	24/50	[a]61	15/50	[a]55	37/50	[a]90
Heart—Hemang-iosarcoma	0/70	0	7/50	[a]47	7/50	[a]31	33/50	[a]87	13/50	[a]76
Lung—Alveolar-bronchiolar adenoma and carcinoma	22/70	46	35/50	[a]88	27/50	[a]87	32/50	[a]88	18/50	[a]89
Forestomach—Squamous-cell papilloma and carcinoma	1/70	2	6/50	[a]20	8/50	[a]33	13/50	[a]52	11/50	[a]63
Harderian gland—Adenoma and adenocarcinoma	6/70	13	27/50	[a]72	23/50	[a]82	28/50	[a]86	11/50	[a]70
Preputial gland—Carcinoma	0/70	0	1/50	3	5/50	[a]21	4/50	[a]21	3/50	[a]31
Kidney—Renal tubular adenoma	0/70	0	5/50	[a]16	1/50	5	3/50	[a]15	1/50	11

From Melnick et al (1990).

AA[a]Increased compared with chamber controls (0ppm), $p<0.05$, based on logistic regression analysis.

[c]Mortality adjusted tumor rates are adjusted for competing causes of mortality, such as death due to other tumors, whose rates differ by exposure group.

Activated Oncogenes

The presence of activated oncogenes in the exposed groups which differ from those seen in tumors in the control group can help in identifying a mechanistic link for BD carcinogenicity. Furthermore, certain activated oncogenes are seen in specific human tumors and K-*ras* is the most commonly detected oncogene in humans. In independent studies, tumors from this study were evaluated for the presence of activated protooncogenes. (Ex. 129) Activated K-*ras* oncogenes were found in 6 of 9 lung adenocarcinomas, 3 of 12 hepatocellular cancers and 2 of 11 lymphomas in BD exposed mice. Nine of these 11 K-*ras* mutations, including all six of those seen in lung tumors, were G to C conversions in codon 13. Activation of K-*ras* genes by codon 13 mutations has not been detected in lung or liver tumors or lymphomas in unexposed $B6C3F_1$ mice, but activation by codon 12 mutation was observed in 1 of 10 lung tumors in unexposed mice. (Ex. 129)

Conclusion

All of the four animal bioassays (one rat, three mouse) find a clear carcinogenic response; together they provide sufficient evidence to declare BD a known animal carcinogen and a probable human carcinogen. The three mouse studies, all with a positive lymphoma response, further support a finding that the mouse is a good model for BD related lymphatic/hematopoietic and other site tumorigenicity. The most recent NTP II study confirms and strengthens the previous NTP I and Irons et al. mouse studies, and presents clear evidence that BD is a potent multisite carcinogen in $B6C3F_1$ mice of both sexes. (Ex. 23–1;32–28D, Irons) The finding of lung tumors at exposures as low as 6.25 ppm, 100 fold lower than the lowest exposure of the NTP I study and a level that is in the occupational exposure range, increases concern for workers' health. Two other concerns

raised by both the second NTP and the Irons et al. studies are, (1) substantial carcinogenicity is found with less-than-lifetime exposures (as low as 12 or 13 weeks) for lymphomas and hemangiosarcomas, at least at higher concentrations, and, (2) for lymphomas and at least two other sites, there appears to be a dose-rate effect, where exposure to higher concentrations for a shorter time yields higher tumor response (by a factor of as much as 2–3) than a comparable total exposure spread over a longer time. These findings suggest that even short-term exposures should be as low as possible. Positive studies for genotoxicity and the detection of activated K-*ras* oncogenes in several of these tumors induced in mice, including lymphomas, liver, and lung, suggest a mutagenic mechanism for carcinogenicity, and support reliance on a linear low-dose extrapolation procedure (on the basis of the multistage mutagenesis theory of carcinogenicity), at least for these tumor sites. The finding of activated K-*ras* oncogenes in these mouse tumors may also be relevant to humans, because K-*ras* is the most commonly detected oncogene in humans.

The different dose-rate trends for different tumor sites suggest that different mechanisms are involved at different sites. The observation of a highly nonlinear exposure-response for lymphomas at exposure levels of 625 ppm and above suggests a secondary high-exposure mechanism as well, not merely a metabolic saturation, as is suspected with the high-exposure saturation seen in Sprague-Dawley rats. (Ex. 34–6, Owen and Glaister) The picture emerges of BD as a potent genotoxic multisite carcinogen in mice, far more potent in mice than in rats.

With respect to appropriate tumor sites for risk extrapolation from mouse to humans, Melnick and Huff have presented information comparing animal tumor response for five known or suspected human carcinogens—BD, benzene, ethylene oxide, vinyl chloride, and acrylonitrile. (Ex. 117–2) BD, benzene, and ethylene oxide all have strong occupational epidemiology evidence of increased lymphatic/hematopoietic cancer (LHC) mortality and all three cause both LHC, lung, Harderian gland, and mammary gland tumors in mice, plus several other primary tumors (see Table V–3). Only BD and vinyl chloride cause mouse hemangiosarcomas, BD in the heart and vinyl chloride in the liver. In rats, while all five carcinogens cause tumors at multiple sites, only brain and Zymbal gland tumors are associated with as many as four of the compounds. In general mice and rats are affected at different tumor sites by these carcinogens. LHC, lung, Harderian gland, mammary gland and, possibly hemangiosarcomas are sites in mice which correlate well with human LHC. This suggests that mice, rats and humans may have different target sites for the same carcinogen, but that compounds which are multisite carcinogens in the mouse and rat are likely to be human carcinogens as well. Based on BD's strong LHC association in humans, and its multisite carcinogenicity in the mouse, including occurrence at several of the same target sites seen with other carcinogens, OSHA concludes that the mouse is a good animal model for predicting BD carcinogenesis in humans.

TABLE V–3.—SITES AT WHICH NEOPLASMS ARE CAUSED BY 1,3-BUTADIENE IN MICE AND RATS: COMPARISON WITH RESULTS OF STUDIES WITH BENZENE, ETHYLENE OXIDE, VINYL CHLORIDE AND ACRYLONITRILE

[From Ex. 117–2]

Site	1,3–Butadiene		Benzene		Ethylene oxide		Vinyl chloride		Acrylonitrile	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
Lymphatic/hematopoietic	•		•		•	•			NS	
Lung	•		•		•		•			
Heart	[f]•									
Liver	•		•				[a]•	[a]•		
Forestomach	•		•	•				•		•
Harderian gland	•		•		•					
Ovary	•		•							
Mammary gland	•	•	•		•		•			•
Preputial gland	•		•							
Brain		•				•		•		•
Zymbal gland		•	•	•				•		•
Uterus		•		•	•					
Pancreas		•								
Testis		•								
Thyroid gland		•								

NS, not studied.
Hemangiosarcoma.

2. Epidemiologic Studies

(i) *Introduction.* OSHA has concluded that the epidemiologic studies contained in this record, as well as the related hearing testimony and record submissions, show that occupational exposure to BD is associated with an increased risk of death from cancers of the Lymphohematopoietic (LH) system. However, in contrast to the available toxicologic data, our understanding of BD epidemiology is based on observational studies, not experimental ones. In other words, the investigators who conducted these epidemiologic studies did not have control over the exposure status of the individual workers. They were, nonetheless, able to select the worker populations and the observational study design.

Cohort and case control studies are two types of observational study designs. Each of these designs has strengths and weaknesses that should be considered when the results are interpreted. Cohort studies, for example, have the advantages of decreasing the chance of selection bias regarding exposure status and providing a more complete description of all health outcomes subsequent to exposure. The disadvantages of cohort studies include the large number of subjects that are needed to study rare diseases and the potentially long duration required for follow-up. By comparison, case control studies are well suited for the study of rare diseases and they require fewer

subjects. The disadvantages of case control studies, however, include the difficulty of selecting an appropriate control group(s), and the reliance on recall or records for information on past exposures. Regardless of the selected observational study design, the greatest limitation of occupational epidemiologic studies is their ability to measure and classify exposure.

In spite of the inherent limitations of observational epidemiologic studies, guidelines have been developed for judging causal association between exposure and outcome. Criteria commonly used to distinguish causal from non-causal associations include: Strength of the association as measured by the relative risk ratio or the odds ratio; consistency of the association in different populations; specificity of the association between cause and effect; temporal relationship between exposure and disease which requires that cause precede effect; biologic plausibility of the association between exposure and disease; the presence of a dose-response relationship between exposure and disease; and coherence with present knowledge of the natural history and biology of the disease. These criteria have been considered by OSHA in the development of its conclusion regarding the association between BD and cancer of the LH system.

As stated previously, each type of epidemiologic study design has strengths and weaknesses. Since epidemiologic studies are observational and not experimental, each study will also have inherent strengths and weaknesses; there is no perfect epidemiologic study. The most convincing evidence of the validity and reliability of any epidemiologic study comes with replication of the study's results.

There are six major epidemiologic studies in the record that have examined the relationship between occupational exposure to BD and human cancer. These studies include: A North Carolina study of rubber workers (Ex. 23–41; 23–42; 23–4; 2–28; 23–27; 23–3); a Texaco study of workers at a BD production facility in Texas (Ex. 17–33; 34–4; 34–4); a NIOSH study of two plants in the styrene-butadiene rubber (SBR) industry (Ex. 2–26; 32–25); the Matanoski cohort study of workers in SBR manufacturing (Ex. 9; 34–4); the nested case-control study of workers in SBR manufacturing conducted by Matanoski and Santos-Burgoa (Ex. 23–109); and a follow-up study of synthetic rubber workers recently completed by Delzell et al. (Ex. 117–1). Several comments in the record have concluded that these studies demonstrate a positive association between occupational exposure to BD and LH cancers. However, OSHA has been criticized by the Chemical Manufacturers Association (CMA) and the International Institute of Synthetic Rubber Producers, Inc. (IISRP) for its interpretation of these studies as showing a positive association; the chief criticisms will be discussed below. (Ex. 112 and 113)

OSHA's final consideration of the BD epidemiologic studies is organized and presented according to what have been identified as key issues. These are the epidemiologic issues that were raised and considered throughout the rulemaking. They are also the issues most pertinent to OSHA's conclusions. These key issues surrounding BD exposure and LH cancer are: Evidence of an association; observation of a dose-response relationship; observation of short latency periods; the potential role of confounding exposures and the observed study results; the biological basis for grouping related LH cancers; relevance of subgroup analyses; and appropriateness of selected reference populations.

(ii) *Evidence of an Association Between BD and LH Cancer.* Each of the studies listed above contributes to the epidemiologic knowledge upon which OSHA's conclusion regarding the relationship of BD exposure and LH cancer has been developed.

(a) *North Carolina Studies.* This series of studies was undertaken to examine work-related health problems of a population of workers in a major tire manufacturing plant. They were not designed to look specifically at the health hazards of BD. (Tr. 1/15/91, p. 117) However, in a work area that involved the production of elastomers, including SBR, relative risks of 5.6 for lymphatic and hematopoietic malignancies and 3.7 for lymphatic leukemia were found among workers employed for more than five years. The International Agency for Research on Cancer (IARC) evaluation concluded that this study suggests an association between lymphatic and hematopoietic malignancy and work in SBR manufacturing. (Tr. 1/15/91, p. 117) However, the IISRP asserted that these studies do not provide ''meaningful evidence of an association between butadiene and cancer.'' (Ex. 113, p. A–23) OSHA recognizes that the researchers who conducted these studies acknowledged that the workers may have had exposures to organic solvents, including benzene, a known leukemogen, as pointed out by the IISRP. (Ex. 113, p. A–24)

(b) *Texaco Study.* The two Texaco studies examined mortality of a population of workers in a BD manufacturing facility in Texas. (Ex. 17–33; 34–4 Vol. III, H–2; Divine 34–4, Vol. III, H–1) A qualitative method of exposure classification, based on department codes and expert consensus judgement, was used in the Downs study. (Ex. 17–33; 34–4, Vol. III, H–2) From this methodology four exposure groups were defined: Low exposure, which included utility workers, welders, electricians, and office workers; routine exposure, which included process workers, laboratory personnel, and receiving, storage and transport workers; non-routine exposure, which included skilled maintenance workers; and unknown exposure, which included supervisors and engineers. It is OSHA's opinion that although this is a crude approach to exposure classification, there are important findings in this study that contribute to our understanding of BD epidemiology.

In the Downs study (Ex. 34–4, Vol. III, H–2) the standardized mortality ratio (SMR) for all causes of death in the entire study cohort was low (SMR 80; $p < .05$) when compared to national population rates. However, a statistically significant excess of deaths was observed for lymphosarcoma and reticulum cell sarcoma combined (SMR 235; 95% confidence interval (CI) = 101,463) when compared with national population rates. (The issue of reference population selection is discussed below in paragraph (viii).)

When analyzed by duration of employment, the SMR for the category of all LH neoplasms was higher in workers with less than five years employment (SMR = 167) than for those with more than five years employment (SMR = 127). (Ex. 34–4, Vol. III, H–2) However, neither of these findings was statistically significant. Alternatively, it has been suggested that perhaps the short-term workers were wartime workers, and that these workers were actually exposed to higher levels of BD, albeit for a shorter time. (Tr. 1/15/91, p. 119)

Analyses of the four exposure groups also showed elevated but not statistically significant SMRs. The routine exposure group had a SMR of 187 for all LH neoplasms, explained primarily by excesses in Hodgkin's disease (SMR = 197) and other lymphomas (SMR = 282). (Ex. 34–4, Vol. III, H–2) Those workers in the non-routine exposure group also had an elevated SMR for all LH neoplasms (SMR = 167), with excess mortality for Hodgkin's disease (SMR = 130), leukemias (SMR = 201), and other

lymphomas (SMR = 150) (Ex. 34–4, Vol. III, H–2).

These data were updated by Divine by extending the period of follow-up from 1979 through 1985. (Ex. 34–4, Vol. III, H–1) The SMR for all causes of mortality remained low (SMR = 84, 95% CI = 79,90), as it did for mortality from all cancers (SMR = 80, 95% CI = 69,94). (Ex. 34–4, Vol. III, H–1) However, the SMR for lymphosarcoma and reticulosarcoma combined was elevated and statistically significant (SMR = 229, 95% CI = 104,435). This finding was consistent with the previous analyses done by Downs. (Tr. 1/15/91, p. 120).

Exposure group analyses were also consistent with the previous findings by Downs. The highest levels of excess mortality from lymphatic and hematopoietic malignancy were again seen in the routine and non-routine exposure groups. The routine exposure group that was ''ever employed'' had a statistically significant excess of lymphosarcoma (SMR = 561, 95% CI = 181,1310), that accounted for most of the LH excess. (Ex. 34–4, Vol. III, H–1) The cohort of workers employed before 1946 (wartime workers) also demonstrated a statistically significant excess of mortality due to lymphosarcoma and reticulosarcoma combined (SMR = 269, 95% CI = 108,555). (Ex. 34–4, Vol. III, H–2)

In summary, the Texaco study provides several notable results. The first of these is the consistently elevated mortality for lymphosarcoma. This finding is consistent with excess lymphomas observed in experimental mice. (Ex. 23–92) Second, the excess risk of mortality was found in the routine and non-routine exposure groups. Based on the types of jobs held by workers in these two exposure groups, this finding suggests that the incidence of lymphatic malignancy is highest in the groups with the heaviest occupational exposure to BD. (Tr. 1/15/91, p. 121) The third notable result of this study was the significantly elevated rate of malignancy in workers employed for fewer than 10 years.

(c) *NIOSH Study.* The NIOSH study was undertaken in January 1976 in response to the report of deaths of two male workers from leukemia. (Ex. 2–26; 32–25) These workers had been employed in two adjacent SBR facilities (Plant A and Plant B) in Port Neches, Texas. The hypothesis tested by this study is that:

> Employment in the SBR production industry was associated, specifically, with an increased risk of leukemia and, more generally, with an increased risk of other malignancies of hematopoietic and lymphatic tissue. (Ex. 2–26)

This study did not specifically examine the association between BD and all LH cancers. Thus, OSHA agrees with the criticism that this study by itself did not demonstrate that occupational exposure to BD *causes* cancer. (Ex. 113, pp. A–13, A–19) However, the findings in this study are consistent with the patterns observed in the other epidemiologic studies discussed in this section. In Plant A, the overall mortality was significantly decreased (SMR=80, $p<0.05$). (Ex. 2–26) The SMR for all malignant neoplasms was also decreased (SMR=78), but this result was not statistically significant. (Ex. 2–26) The SMR for LH cancers was elevated (SMR=155), as it was for lymphosarcoma and reticulum cell sarcoma (SMR=181) and leukemia (SMR=203), but none of these results was statistically significant. (Ex. 2–26)

The pattern of mortality for a subgroup of wartime workers was also examined for the Plant A population. For this subgroup of white males, employed at least six months between the beginning of January 1943 and the end of December 1945, there was an elevated SMR for lymphatic and hematopoietic neoplasms (SMR = 212) that was statistically significant at the level of $0.05<p<0.1$. (Ex. 2–26) Likewise, the SMR for leukemia was increased (SMR=278), also with statistical significance at the level of $0.05<p<0.1$. (Ex. 2–26)

At Plant B, the overall mortality was low (SMR=66, $p<0.05$), as was death from all malignant neoplasms (SMR=53, $p<0.05$). (Ex. 2–26) The SMR for LH cancer was also low (SMR=78), but this finding was not statistically significant. (Ex. 2–26)

When this study was updated, the mortality patterns remained unchanged. (Ex. 32–25) The most remarkable findings of the NIOSH study are the excess mortality for malignancies of the LH system, and the excess of these cancers in workers employed during the wartime years.

(d) *Matanoski Cohort Study.* The cohort study conducted by Matanoski et al. is comprised of two follow-up periods: In the original study, completed in June 1982, the cohort was followed from 1943 to 1979; and in the update, completed in March 1988, the cohort follow-up period was extended to 1982. (Ex. 9; 23–39; 34–4, Vol. III, H–3 and H–6, respectively) The original study analyzed mortality data for 13,920 male workers employed for more than one year in eight SBR production plants in the United States and Canada. Although historical quantitative exposure data were not available, creation of a job dictionary made it possible to designate four general work activities as surrogates for exposure: Production; utilities; maintenance; and a combined category of all other jobs. The work activities with the highest BD exposures were production and maintenance. (Ex. 16–39) The total duration worked was measured by the dates of first and last employment.

The mortality experience for the original study cohort, as compared with death rates for males in the United States, was low for all causes (SMR=81) and all cancers (SMR=84). (Ex. 9; 23–39) The SMR for all LH cancers was also low (SMR=85). (Ex. 9; 23–39) The mortality rate for Hodgkin's disease was slightly elevated (SMR=120), but it was not statistically significant. (Ex. 9; 23–39) In fact, there were no statistically significant excesses in mortality from cancer at any site found in this original cohort study.

These initial data were also analyzed according to major work area. There were not any elevations of mortality rates for the category of all LH cancers. (Ex. 9; 23–39) For production workers, the SMR for other lymphatic cancers was elevated (SMR=202), but it was not statistically significant. (Ex. 9; 23–39) The SMR for leukemia in the utilities work group was also elevated (SMR=198), but it was based on only two deaths and was not statistically significant. (Ex. 9; 23–39) Slight excesses, none of which was statistically significant, were seen for Hodgkin's disease in each of the four work group categories. (Ex. 9; 23–39)

OSHA has been criticized for its opinion, expressed in the preamble of the BD proposed rule, that the original Matanoski cohort study did not have sufficient power to detect a difference in the cancer SMR if one actually existed. (Ex. 113, pp. A–10–11) Statistical power of at least 80% is the accepted rule-of-thumb for epidemiologic research study design. Calculations provided by Matanoski indicate that, for the outcomes of greatest concern to OSHA, statistical power was often below the 80% level. (Ex. 9) For leukemia, statistical power to detect 25% and 50% increases in mortality was only 27% and 62%, respectively. (Ex. 9) The power to detect a 25% increase in mortality for all lymphohematopoietic cancers was only 49%. (Ex. 9) However, the study did have a statistical power of 93% to detect a SMR of 150 for all LH cancers. (Ex. 9) Thus, for the cancers of most interest to OSHA, this study had limited statistical power to detect mortality excesses that were less than two-fold. OSHA does not consider this to be an ''unrealistically strict standard of acceptability,'' as alleged by the

IISRP, but rather part of a thorough critique of an epidemiologic study with purportedly ''negative results.'' (Ex. 113, p. A–11)

The update of Matanoski's original study extends the period of cohort follow-up from 1979 to 1982, providing a full 40 years of mortality experience for analysis. The update study cohort differed from the original cohort in two additional ways: Canadian workers with relatively short-term exposure were removed from the cohort; and the proportion of workers lost to follow-up was reduced. The extension of follow-up resulted in findings of excess mortality from lymphatic and hematopoietic cancers that had not been observed in the original analyses. (Ex. 34–4, Vol. III, H–6)

The SMR for all causes of mortality remained low (SMR=81, 95% CI=78,85), as it did for death from all cancers (SMR=85, 95% CI=78,93). (Ex. 34–4, Vol. III, H–6) For lymphatic and hematopoietic cancers, the overall SMR for white males was not increased (SMR=92, 95% CI=68,123). (Ex. 34–4, Vol. III, H–6) However, for black males, the SMR for all LH cancers was elevated (SMR=146, 95% CI=59,301). (Ex. 34–4, Vol. III, H–6) Specific increases were also found for lymphosarcoma (SMR=132), leukemia (SMR=218, 95% CI=59,560), and other lymphatic neoplasms (SMR=116, 95% CI=14,420). (Ex. 34–4, Vol. III, H–6) These increases were based on small numbers of observed deaths.

Analyses conducted on the four exposure groups also produced some evidence of excess mortality. For the total cohort of production workers, an elevated SMR was observed for all lymphopoietic cancers (SMR=146, 95% CI=88,227). (Ex. 34–4, Vol. III, H–6) For white production workers, the SMR for that category was 110, explained principally by excess mortality from other lymphatic neoplasms (SMR=230, 95% CI=92,473). (Ex. 34–4, Vol. III, H–6) Although based on small numbers, the results for black production workers were more pronounced and statistically significant: The SMR for all lymphatic and hematopoietic cancers was 507 (95% CI=187,1107). (Ex. 34–4, Vol. III, H–6) That overall increase in black workers reflected excess mortality from lymphosarcoma (SMR=532), leukemia (SMR=656, 95% CI=135,1906), and other lymphatic cancers (SMR=482, 95% CI=59,1762). (Ex. 34–4, Vol. III, H–6)

A pattern of excess mortality for all LH cancers was also seen in utility workers (SMR=203, 95% CI=66,474). (Ex. 34–4, Vol. III, H–6) That elevated SMR may be explained by elevated rates for leukemia (SMR=192, 95% CI=23,695) and other lymphatic cancers (SMR=313, 95% CI=62,695). (Ex. 34–4, Vol. III, H–6) No increases in LH malignancy were seen in the other exposure groups, i.e., maintenance or other workers.

From these study results Matanoski et al. concluded:

> Deaths from cancers of the hematopoietic and lymphopoietic system are higher than expected in production workers with significant excesses for leukemias in black workers and other lymphomas in all (production) workers. (Ex. 34–4, Vol. III, H–6, p. 116)

In response to criticism from the IISRP that OSHA placed too much emphasis on the findings in the group of black production workers, OSHA is aware of the statement offered by the researchers that because of the potential for bias from misclassification of race: ''* * * the total SMRs are probably the most correct representation of risk.'' (Ex. 34–4, Vol. III, H–6) However, OSHA also agrees with the authors that the risk of death from LH cancers seems to be higher in this SBR industry population than in the general population, and these causes of death seem to be associated with different work areas. These cohort study findings stimulated the design and implementation of the Santos-Burgoa and Matanoski nested case-control study.

(e) *Santos-Burgoa and Matanoski Nested Case-Control Study.* To further investigate the findings of the cohort study, Santos-Burgoa and Matanoski et al. designed and conducted a case-control study of LH cancers in workers in the styrene-butadiene polymer manufacturing industry. (Ex. 23–109; 34–4, Vol. III, H–4) The specific questions addressed by this research study are: ''Is there a risk of any lymphatic or hematopoietic cancer which is associated with exposure to (BD) or styrene or both?''; and ''is there a risk of these cancers related to exposure to jobs within the industry?'' (Ex. 34–4, Vol. III, H–4) This is the first study to specifically investigate the association between LH cancers and individual worker exposure to BD, which is why, contrary to the opinion of IISRP, OSHA places so much ''weight'' on these results. (Ex. 113, pp. A–25–34)

The subjects in this case-control study were ''nested,'' or contained, within the population of the original cohort study. ''Cases'' in this study were defined as males who worked one year or more at any of eight synthetic rubber polymer producing plants and who died of or with a lymphopoietic cancer. These cancers included: Lymphosarcoma and reticulum cell sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, all leukemias, multiple myeloma, polycythemia vera, and myelofibrosis. Sixty-one cases were identified, but two cases were omitted from data analyses, resulting in a total of 59 cases. One case was omitted because he could not be matched to controls, and the other case lacked job records from which exposure could be identified.

Eligible ''controls'' included workers who were either alive or had died of any cause other than malignant neoplasms, who had been employed at one of the eight SBR plants, and who had not been lost to follow-up. These controls were individually matched to cases on the following criteria: Plant; age; hire year; employment as long or longer than the case; and survival to the death of the case. The study aim was to select four controls per case. Even though this was not always possible, there were, on average, just over three controls per case in each group of lymphopoietic cancer. The total number of controls was 193.

Unlike the previous studies, in this research study an exposure measurement value for BD (and also for styrene) was determined for each case and control. This value was determined by a multi-step process. First, the job records of each subject were reviewed and the number of months that each job was held was determined. Second, the level of BD (and styrene) associated with the job was estimated by a panel of five industrial experts, i.e., engineers with long term experience in SBR production. The exposure level for BD (and styrene) for each job was based on a scale of zero to ten, with ten being the rank given to the job with the highest exposure. The next step in the development of each individual job-exposure matrix was to add all of the exposures to the chemicals for all the months a specific job was held and then sum the exposures over a working lifetime. This procedure resulted in a cumulative BD exposure value for each case and control.

The distribution of the cumulative exposure estimates for the study population was not normally distributed, i.e., there were some extreme values. In order to approximate a normal distribution, a required assumption for many statistical analyses, a logarithmic transformation of these values was done. (Ex. 34–4, Vol. III, H–4) Exposure was analyzed as a dichotomous variable, i.e., ever/never exposed. ''Exposed'' workers were defined as those with a log rank cumulative exposure score above the mean of the scores for the entire population of cases and controls within

a cancer subtype; ''non-exposed'' workers were those with a score below the mean.

There were several important findings in this study. First, in the unmatched analysis of cases and controls, the leukemia subgroup had a significant excess risk of 6.8 fold for exposure to BD among cases compared to controls (Odds Ratio (OR)=6.82, 95% CI=1.10,42.23). (Ex. 34–4, Vol. III, H–4) The results were even stronger in the matched-pair analyses. In that analysis for exposure to BD, the OR was 9.36 (95% CI=2.05,22.94) in the leukemia subgroup. (Ex. 34–4, Vol. III, H–4) This result can be interpreted to mean that cases with leukemia were more than nine times as likely as their controls to be exposed to BD. Additionally, the data in this analysis indicate that BD exposure above the group mean is 2.3 times (OR=2.30, 95% CI=1.13,4.71) more common among cases with all lymphopoietic cancers when compared to a similar exposure in the controls. (Ex. 34–4, Vol. III, H–4)

This case-control study has been the subject of criticism that has centered on both validity and reliability. (Ex. 23–68; 113) For example, the data from this study have been criticized as being ''inconsistent'' with the results of the Matanoski cohort study. (Ex. 23–68; 113, p. A–25) Further, it has been suggested that ''the study results are not reliable and should not be relied upon by OSHA.'' (Ex. 113, p. A–25) OSHA rejects these criticisms for the reasons discussed below.

First, regarding the issue of inconsistency, a nested case control study does not test the same hypotheses or make the same comparisons as a cohort study. (Ex. 32–24; Tr. 1/15/91, p. 161; Tr. 1/16/91, p. 347) In fact, as presented in the above discussions of the studies, they ask and answer different research questions. For example, the cohort study asked whether all of the SBR workers have a different risk of leukemia from the general population, and the case control study asked whether workers with leukemia have different exposures within the industrial setting from workers without leukemia. (Ex. 32–24) Thus, the criticism that the results of these two studies are incompatible, and therefore invalid, is not relevant. (Ex. 32–24)

Second, the challenge directed at the reliability of the case-control study does not hold up under close scrutiny. This criticism is based on four issues: Log transformation of the exposure data; instability of the results; irregular dose-response pattern; and selection criteria for ''controls.'' (Ex. 113, A–29–34)

Regarding the log transformation of the exposure data, the IISRP asserts that there is not a sound rationale for this approach to data analyses. (Ex. 113, A–29–30) However, Santos-Burgoa offered the following explanation of this procedure in his testimony:

> For analysis, exposures were categorized in advance above and below the mean of the cumulative exposure for the study subjects. This cutpoint was defined from the very beginning of the analysis design as follows. The total cumulative exposures, as happens in most environmental exposures, showed a skewed distribution with many observations at the low levels and few at the high levels. Since the geometric mean is the best estimate of the central tendency point in log normal data, such as exposure data, the cumulative exposures were transformed by the logarithm, and then the mean was calculated. (Ex. 40, pp. 12–13)

It is OSHA's opinion that, given the log normal distribution of the exposure data, Santos-Burgoa chose the best approach for data analyses.

The case-control study has also been criticized for producing ''highly unstable and therefore unreliable'' results. (Ex. 113, A–30) For example, the leukemia subgroup (matched-pair analysis) OR of 9.36 with a 95% confidence interval of 2.05–22.94 has been used to illustrate statistical instability of the data. (Ex. 113, A–31) However, as previously discussed, the disease category of ''all lymphopoietic cancers'' (matched-pair analysis) had an OR of 2.30 with a confidence interval of 1.13–4.71. Thus, it is OSHA's opinion that, while some specific odds ratios may have wide confidence intervals, the study results as a whole are not ''unreliable.''

The IISRP has also criticized the case-control study for ''* * * fail(ing) to demonstrate a dose-response relationship * * *'' (Ex. 113, A–32) However, the test for linear trend, i.e., test for dose-response, shows a statistically significant, but irregular, trend in the odds of leukemia with increasing levels of exposure to BD. Specifically, as exposure levels increase the pattern of odds ratios is: 7.2; 4.9; 13.0; 2.5; and 10.3. (Ex. 23–109, Table 10) Although this is not a compelling linear dose-response, in OSHA's opinion, it is suggestive of a pattern of increasing disease risk at increasing exposure levels.

Inconsistent application of the control selection criteria is the final criticism directed at the case-control study by the IISRP. (Ex. 113, A–33) However, careful review of docket exhibits related to the case-control study reveals this criticism to be unfounded. In his dissertation, Santos-Burgoa clearly states the protocol for control selection:

> All cohort subjects were arranged into groups by plants, date of birth, date of hire, duration of work and duration of follow-up. A two and a half year period around each time variable was relaxed in a few instances when no more controls were available. One lymphosarcoma case was lost since no match was found for his date of birth, even allowing for three and a half years around the date. This was the only case lost to analysis because of lack of a matched control. (Ex. 32–25, p. 80)

With only 59 cases, Santos-Burgoa was correctly concerned about loss of valuable data should any additional cases need to be eliminated due to lack of a match. Also, regarding the potential for bias, abstractors were blinded to case or control status when employment data were being collected. (Ex. 34–4, Vol. III, App. H–5) Thus, it is most likely that any misclassification bias would be nondifferential, biasing the study results towards the null.

(f) *Delzell et al. Follow-up Study for the IISRP.* The most recent study of synthetic rubber workers was conducted by Delzell et al. (Ex. 117–1) This study updated and expanded the research on SBR workers conducted by NIOSH, Matanoski et al., and Santos-Burgoa. More specifically, the Delzell et al. study consists of workers at seven of eight plants previously studied by The Johns Hopkins University (JHU) investigators, and the two plants included in the NIOSH study.

This retrospective cohort study evaluated the associations between occupational exposure to BD, styrene, and benzene and mortality from cancer and other diseases among the SBR workers. There were five study objectives:

> (1) To evaluate the overall and cause-specific mortality experience of SBR workers relative to that of the USA and Canadian general populations;
>
> (2) To assess the cancer incidence experience of Canadian synthetic rubber workers relative to that of the general population of Ontario;
>
> (3) To determine if overall and cause-specific mortality patterns vary by subject characteristics such as age, calendar time, plant, period of hire, duration of employment, time since hire and payroll status (hourly or salaried);
>
> (4) To examine relationships between work areas within the SBR study plants and cause-specific mortality patterns;
>
> (5) To evaluate the relationship between exposure to BD and [styrene] and the occurrence of leukemia and other lymphopoietic cancers among SBR workers. (Ex. 117–1 p. 10)

The study population for this investigation included 17,964 male synthetic rubber workers employed in one of eight plants in either the USA or Canada. In order to be eligible for

inclusion, a worker had to be employed for a total of at least one year before the closing date of the study, January 1, 1992. Additional eligibility criteria were developed for selected plants due to limitations in availability of plant records and follow-up of subjects. The eligibility criteria in this study were considered by the investigators to be more restrictive than in either the JHU or NIOSH studies. (Ex. 117–1, p. 13) Most of the exclusions were based on less than one year of employment. During the study period of 1943 through 1991, there were 4,665 deaths in the study population.

The methods used in this study included development of work history information and retrospective quantitative exposure estimates for individual members of the study population. Complete work history information was available for approximately 97% of the study cohort. There was a total of 8,281 unique ''work area/job'' combinations for all of the plants combined, with a range of 199 to 4,850 in specific plants. Additionally, 308 work area groups were defined based on individual plant information regarding production, maintenance, and other operations, as well as jobs and tasks within each type of operation. Five ''process groups'' and seven ''process subgroups'' were derived from the work area groups. The process groups include: Production of SBR, solution polymerization (SP), liquid polymerization (LP), and latex production; maintenance; labor; laboratories; and other operations.

Six plants had sufficiently detailed individual work history information for use in development of retrospective quantitative exposure estimates for BD and styrene. The process used to produce these exposure estimates included: In-depth walk-through surveys of each plant; meetings with plant management; interviews with key plant experts, such as individuals with long-term employment. The interviews were used to collect information regarding the production process, specific job tasks, and exposure potential. Additionally, the results of industrial hygiene monitoring from these plants were obtained. The actual exposure estimation was based on:

Specification of the exposure model; the estimation of exposure intensities for specific tasks in different time periods; the estimation of exposure intensities for generic (nonspecific) job titles (e.g., ''laboratory worker'') in different time periods; validation of exposure intensity estimates; the computation of job- and time period specific summary indices; and the compilation of job-exposure matrices (JEMs) for BD, [styrene], and [benzene] and linkage with subjects' work histories. (Ex. 117–1, pp. 27–28)

A limited validation of the quantitative exposure estimations was conducted, which resulted in revision of the estimates used in analyses presented in the Delzell et al. study. (Ex. 117–1)

The major findings of this study have been reported by Delzell et al. in five categories: General mortality patterns; mortality among USA subjects compared to state populations; cancer incidence; mortality patterns by process group; and mortality patterns by estimated monomer exposure. Key results from each of these categories, especially as they relate to leukemia and other LH cancers, are briefly presented.

First, regarding general mortality patterns, there were deficits in both all causes (SMR=87, 95% CI=85,90) and all cancers (SMR=93, 95% CI=87,99) for the entire cohort. (Ex. 117–1, p. 53) Of the LH cancers, excess mortality was only observed for leukemia (SMR=131, 95% CI=97–174). (Ex. 117–1, p. 53) In a cohort subgroup having 10 or more years of employment and 20 or more years since hire, the excess of leukemia deaths was even greater (SMR=201, 95% CI=134,288). (Ex. 117–1, p. 54)

Analyses were also conducted to explore the possibility of racial differences in the general mortality patterns. Regarding mortality from leukemia, the SMRs were higher for blacks than for whites. In a subgroup of ''ever hourly'' workers with 10 or more years of work and 20 or more years since hire, the SMRs for leukemia were 192 (95% CI=119,294) for whites and 436 (95% CI=176,901) for blacks. (Ex. 117–1, p. 55)

Additionally, analyses were done by specific groups of LH cancers: Lymphosarcoma; leukemia; and other lymphopoietic cancer. For the overall cohort, there was an excess of mortality from lymphosarcoma in those members who died in 1985 and beyond (SMR=215, 95% CI=59,551). (Ex. 117–1, p. 116) This excess was observed in ''ever hourly'' white men; there were no lymphosarcoma deaths in blacks. (Ex. 117–1, p. 119)

In the ''other lymphopoietic cancer'' category, the overall cohort had a slight deficit of mortality (SMR=97, 95% CI=70,132). (Ex. 117–1, p. 116) When analyzed according to racial groups, whites were also observed to have a deficit of mortality from this group of cancers (SMR=91, 95% CI=63,127). (Ex. 117–1, p. 118) Blacks, however, had an increase in mortality from ''other lymphopoietic'' cancers (SMR=142, 95% CI=61,279). (Ex. 117–1, p. 120)

The analyses for leukemia mortality in the overall cohort showed a modest increase (SMR=131, 95% CI=97,174). (Ex. 117–1, p. 116) The increase in mortality was found primarily in the subgroups of workers who died in 1985 or later, those that worked for 10 or more years, and those with 20 or more years since hire. A dose-response type of pattern was observed among ''ever hourly'' subjects in the analysis of the relationship of leukemia and duration of employment: Less than 10 years worked, the SMR=95 (95% CI=53,157); 10–19 years worked, the SMR=170 (95% CI=85,304); and 20 or more years worked, the SMR=204 (95% CI=123,318). (Ex. 117–1, p. 117)

Leukemia mortality was also analyzed for racial difference among ''ever hourly'' men. Overall, the SMR was higher for black subjects (SMR=227, 95% CI=104,431) than for white (SMR=130, 95% CI=91,181). (Ex. 117–1, p. 122) In fact, there were statistically significant elevations in the leukemia SMR for black ''ever hourly'' men with 20 or more years worked (SMR=417, 95% CI=135,972), and 20 to 29 years since hire (SMR=446, 95% CI=145,1042). (Ex. 117–1, p. 122)

Second, Delzell et al. analyzed the mortality data of the USA cohort subgroup using both state general population rates and USA general population rates for comparison. The overall pattern of these analyses was that of ''slightly lower'' SMRs when the state general population rates were used. (Ex. 117–1, p. 60) For example, in the analysis for leukemia mortality, the SMR using the USA rates was 131 (95% CI not provided), and it decreased to 129 (95% CI=92,176) when state rates were applied. (Ex. 117–1, pp. 61, 136)

Third, the results of the Delzell et al. study include an analysis of the cancer incidence in the Canadian plant (plant 8). Regardless of whether the cancer experience of terminated workers was included or excluded, the overall cancer incidence was not elevated in this cohort subgroup (SIR=105, 95% CI=93,117; SIR=106, 95% CI=94,119, respectively). (Ex. 117–1, pp. 61–62) However, analysis of this cohort subgroup, with the terminated workers included, ''revealed an excess of leukemia cases before 1980 (overall cohort, 6 observed/3.0 expected; ever hourly, 6 observed/2.9 expected)'' (further data were not provided). (Ex. 117–1, p. 62)

Fourth, Delzell et al. examined mortality patterns by work process group. These analyses produced elevated SMRs for both lymphosarcoma and leukemia. There was excess lymphosarcoma mortality in field maintenance workers (SMR=219, 95% CI=88,451), production laborers

(SMR=263, 95% CI=32,951), and maintenance laborers (SMR=188, 95% CI=39,548). (Ex. 117–1, pp. 65–66) However, these results were not statistically significant, and may be due to chance. For leukemia, the results were more striking: Polymerization workers had a SMR of 251 (95% CI=140,414); workers in coagulation had a SMR of 248 (95% CI=100,511); maintenance labor workers had a SMR of 265 (95% CI=141,453); and workers in laboratories had a SMR of 431 (95% CI=207,793). (Ex. 117–1, pp. 66,151) It should be noted that excess mortality by work process group was also observed for other cancers, i.e., lung cancer and larynx cancer.

Fifth, the final set of analyses performed by Delzell et al. was designed to examine mortality patterns by estimated monomer exposure, i.e., BD, styrene, and benzene. Poisson regression analyses conducted to explore the association between ''BD ppm-years'' and leukemia indicated a positive dose-response relationship, after controlling for styrene ''ppm-years'', age, years since hire, calendar period, and race. Specifically, in the cohort group that included all person-years and leukemia coded as either underlying or contributing cause of death, the rate ratios (RRs) were: 1.0, 1.1 (95% CI=0.4,5.0), 1.8 (95% CI=0.6,5.4), 2.1 (95% CI=0.6,7.1), and 3.6 (95% CI=1.0,13.2) for BD ppm-year exposure groups of 0, >0–19, 20–99, 100–199, and 200+, respectively. (Ex. 117–1, pp. 68–69; 158) Poisson regression analyses were also conducted using varying exposure categories of BD ppm-years. These analyses demonstrated a stronger and more consistent relationship between BD and leukemia than between styrene and leukemia. (Ex. 117–1, p. 69, 159) Although a clearly positive relationship between BD ''peak-years'' and leukemia was observed from additional Poisson regression analyses, even after controlling for BD ppm-years, styrene ppm-years, and styrene peak-years, the dose-response relationship was less clear. (Ex. 117–1, pp. 71, 162)

In summary, one of the most important findings of the research of Delzell et al. was strong and consistent evidence that employment in the SBR industry produced an excess of leukemia. In the authors own words:

> This study found a positive association between employment in the SBR industry and leukemia. The internal consistency and precision of the result indicate that the association is due to occupational exposure. The most likely causal agent is BD or a combination of BD and [styrene]. Exposure to [benzene] did not explain the leukemia excess. (Ex. 117–1, p. 85)

(g) *Summary.* These studies provide a current body of scientific evidence regarding the association between BD and LH cancers. As previously discussed, two of the criteria commonly used to determine causal relationships are consistency of the association and strength of the association. The consistency criterion for causality refers to the repeated observation of an association in different populations under different circumstances. Consistency is perhaps the most striking observation to be made from this collection of studies: ''[E]very one of these studies to a greater or lesser extent finds excess rates of deaths from tumors of the lymphatic and hematopoietic system.'' (Tr. 1/15/91, p. 129)

Strength of the association is determined by the magnitude and precision of the estimate of risk. In general, the greater the risk estimate, e.g., SMR or odds ratio, and the narrower the confidence intervals around that estimate, the more probable the causal association. In the nested case-control study, although the confidence intervals were wide, the odds ratios provide evidence of a strong association between leukemia and occupational exposure to BD.

(iii) *Observation of a Dose-Response Relationship.* A dose-response relationship is present when an increase in the measure of effect (response), e.g., SMR or odds ratio, is positively correlated with an increase in the exposure, i.e., estimated dose. When such a relationship is observed, it is given serious consideration in the process of determining causality. However, the absence of a dose-response relationship does not necessarily indicate the absence of a causal relationship.

OSHA has been criticized for its conclusion that the epidemiologic data suggest a dose-response relationship. (Ex. 113) The IISRP offers a different interpretation of the data. In their opinion, the data provide a ''consistent finding of an inverse relationship between duration of employment and cancer mortality.'' (Ex. 113, A–34) This observation is further described by John F. Acquavella, Ph.D., Senior Epidemiology Consultant, Monsanto Company, as ''the paradox of butadiene epidemiology.'' (Ex. 34–4, Vol. I, Appendix A) This interpretation assumes that cumulative occupational exposure to BD will increase with duration of employment, and, thus, cancer mortality will increase with increasing duration of employment. (Ex. 113, A–35–39)

In OSHA's opinion, this is an erroneous assumption; the epidemiologic data for BD tell a different story. For the workers in these epidemiologic studies, it is unlikely that occupational exposure to BD was constant over the duration of employment. According to Landrigan, BD exposures were most likely higher during the war years than they were in subsequent years. (Tr. 1/15/91, p.146) It is logical that exposures would be especially intense during this time period because of wartime production pressures, the process of production start-up in a new industry, and the general lack of industrial hygiene controls during that phase of industrial history. Unfortunately, without quantitative industrial hygiene monitoring data, the true levels of BD exposure for wartime workers cannot be ascertained. In the absence of such data, however, OSHA believes it is reasonable to consider wartime workers as a highly exposed occupational subgroup. (Tr. 1/15/91, p. 121; Tr. 1/16/91, pp. 225–227) Thus, the excess mortality seen among these workers provides another piece of the evidence to support a dose-response relationship between occupational exposure to BD and LH cancers.

Additional support that excess mortality, among workers exposed to BD, is dose-related can be found in the analyses of the work area exposure groups. The studies by Divine, Matanoski, and Matanoski and Santos-Burgoa all provide evidence that excess mortality is greatest among production workers. (Ex. 34–4, Vol. III, H–1; 34–4, Vol. III, H–6; 23–109, respectively) Production workers are typically the most heavily exposed workers to potentially toxic substances. (Ex. 34–4)

The most compelling data that support the existence of a dose-response relationship for occupational exposure to BD and LH cancers are those in the study by Delzell et al. (Ex. 117–1) Analysis of the cumulative time-weighted BD exposure in ppm-years indicates a relative risk for all leukemias that increases positively with increasing exposure. This relationship is present even with statistical adjustment for age, years since hire, calendar period, race, and exposure to styrene. It is OSHA's opinion that identification of a positive dose-response in an epidemiologic study is a very powerful observation in terms of causality.

(iv) *Observation of Short Latency Periods.* Short latency periods, i.e., time from initial BD exposure to death, were seen in two epidemiologic studies. In the NIOSH study, three of the six leukemia cases had a latency period from three to four years. (Ex. 2–26) Additionally, five of these six workers were employed prior to 1945. (Ex. 2–26)

In the Texaco study update, a latency of less than 10 years was seen in four of the nine non-Hodgkin's lymphoma (lymphosarcoma) cases, and seven of these workers were also employed during the wartime years. (Ex. 34–4, Vol. III, H–1)

According to OSHA's expert witness, Dr. Dennis D. Weisenburger,

> these findings are contrary to the accepted belief that, if a carcinogen is active in an environment, one should expect the * * * SMRs to be higher for long-term workers than for short-term workers (i.e., larger cumulative dose). (Ex. 39, p. 9)

Thus, it has been argued that these findings appear to lack coherence with what is known of the natural history and biology of LH cancers. (Ex. 113, A–40–42) Furthermore, these findings have been interpreted as evidence against a causal association between BD and these LH cancers. (Ex. 113, A–42)

In OSHA's opinion, there are other possible explanations for these observations. First, as proffered by Dr. Weisenburger, a median latency period of about seven years has been found for leukemia in studies of atomic bomb victims, radiotherapy patients, and chemotherapy patients who have received high-dose, short-term exposures. (Ex. 39) In contrast, Dr. Weisenburger points out that low-dose exposure to an environmental carcinogen, such as benzene, has a median latency period for leukemia of about 15–20 years. (Ex. 39) He concludes that short-term, high-dose exposures may be associated with a short latency period, whereas long-term, low-dose exposures may be associated with a long latency period.

Second, the occurrence of short latency periods for LH cancer mortality in these two studies was concentrated in workers first employed during the wartime years. As previously discussed, it is possible that exposure to BD during the wartime years was greater than in subsequent years. (Ex. 39; Tr. 1/15/91, p. 121) Dr. Weisenburger suggests that the ''short latency periods for LH cancer in these studies may be explained by intense exposures to BD over a relatively short time period.'' (Ex. 39, p. 10)

In his testimony, Dr. Landrigan, another OSHA expert witness, makes the point that ''duration of employment is really only a crude surrogate for total cumulative exposures, not itself a measure of exposure.'' (Tr. 1/15/91, p. 121) In other words, it is possible that short-term workers employed during the wartime years may have actually had heavier exposures to BD than long-term workers. (Tr. 1/15/91, pp. 115–205) On cross-examination, Dr. Landrigan cautioned against ''assuming that duration of exposure directly relates to total cumulative exposure.'' (Tr. 1/15/91, p. 180) He also emphatically stated that an increased cancer risk in short-term workers would not be inconsistent with a causal association. (Tr. 1/15/91, p. 204)

(v) *The Potential Role of Confounding Exposures and Observed Results.* In epidemiologic studies ''confounding'' may lead to invalid results. Confounding occurs when there is a mixing of effects. More specifically, confounding may produce a situation where a measure of the effect of an exposure on risk, e.g., SMR, RR, is distorted because of the association of the exposure with other factors that influence the outcome under study.

For example, the IISRP has suggested that confounding exposures from other employment were responsible for the LH cancers observed in the studies of BD epidemiology. (Ex. 113, A–43) This argument is based on the past practice of using petrochemical industry workers, who may have also been exposed to benzene, to start up the SBR and BD production plants. The IISRP finds support for this position in the observation of elevated SMRs in short-term workers employed during the wartime years, precisely those most likely to be cross-employed. (Ex. 113, A–43)

However, there are a number of research methods in occupational epidemiology that are available to control potential confounding factors. Research methods that eliminate the effect of confounding variables include: Matching of cases and controls; adjustment of data; and regression analyses. In the nested case-control study, for example, cases and controls were matched on variables that otherwise might have confounded the study results. In the testimony provided by Santos-Burgoa, he states that the ''matching scheme allowed us to control for potential confounders and concentrate only on exposure variations.'' (Ex. 40, p. 12)

On cross-examination, Landrigan also addressed the potential role of confounding exposures and the observed study results. First, he observed that Dr. Philip Cole, Professor, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, one of the outspoken critics of OSHA's proposed rule, found no evidence for confounding in his review of the Matanoski study. (Tr. 1/15/91, p. 178) Second, Dr. Landrigan dismissed the notion of previous exposure to benzene as the causative agent for the observed results in the short-term workers. (Tr. 1/15/91, p. 178–179)

In their analyses of mortality patterns by estimated monomer exposure, Delzell et al. used Poisson regression to control for potential confounding factors. (Ex. 117–1) As previously stated, the analyses conducted to determine the association between BD ppm-years and leukemia indicated a positive dose-response relationship, even after controlling for styrene ppm-years, age, years since hire, calendar period, and race. In the opinion of the investigators, benzene exposure did not explain the excess of leukemia risk, and BD is the most likely causal agent. (Ex. 117–1, p. 85)

(vi) *The Biological Basis for Grouping Related LH Cancers.* The epidemiologic studies that have examined the association between occupational exposure to BD and excess mortality have grouped related LH cancers in their analyses. This approach has been criticized as evidence of a lack of ''consistency with respect to cell type'' which ''argues against a common etiologic agent.'' (Ex. 113, A–45) In other words, these critics suggest that the relationship between BD and excess mortality does not meet the specificity of association requirement for a causal relationship. This requirement states that the likelihood of a causal relationship is strengthened when an exposure leads to a single effect, not multiple effects, and this finding also occurs in other studies.

More specifically, OSHA has been criticized for its position that ''broad categories such as 'leukemia' or 'all LHC' should be used to evaluate the epidemiologic data.'' (Ex. 113, A–46) Dr. Cole, for example, commented that:

> It is a principle of epidemiology—and of disease investigation in general—that entities should be divided as finely as possible in order to maximize the prospect that one has delineated a homogeneous etiologic entity. Entities may be grouped for investigative purposes only when there is substantial evidence that they share a common etiology. (Ex. 63, p. 11)

It is Dr. Cole's opinion that LH cancers are ''distinct diseases'' with ''heterogeneous and multifactorial'' etiologies. (Ex. 63, p. 47)

Dr. Weisenburger, OSHA's expert in hematopathology, provided testimony to the contrary. (Ex. 39, pp. 7–8) According to Dr. Weisenburger, ''LH (cancer) cannot be readily grouped into 'etiologic' categories, since the precise etiologies and pathogenesis of LH (cancer) are not well understood.'' (Ex. 39, p. 7) In his opinion, because LH cancers are ''closely related to one

another and arise from common stem cells and/or progenitor cells, it is valid to group the various types of LH (cancer) into closely-related categories for epidemiologic study.'' (Ex. 39, p.7)

The issue of grouping related LH cancers to observe a single effect was also addressed by Dr. Landrigan in his testimony. (Tr. 1/15/91, pp. 131–133) The first point raised by Dr. Landrigan is that the ''diagnostic categories [for LH cancers] are imprecise and * * * overlapping.'' (Tr. 1/15/91, p. 131) For example, he explained that in clinical practice transitions of lymphomas and myelomas into leukemias may be observed. In such a case, one physician may record the death as due to lymphoma and another may list leukemia as the cause of death. (Tr. 1/15/91, p. 131–132) Additionally, Dr. Landrigan testified that ''some patients with lymphomas or multiple myeloma may subsequently develop leukemia as a result of their treatments with radiation or cytotoxic drugs.'' (Tr. 1/15/91, p. 132)

These recordings of disease transition are further complicated by the historical changes that have occurred in nomenclature and The International Classification of Diseases (ICD) coding. According to Dr. Landrigan,

> certain lymphomas and * * * leukemias, such as chronic lymphatic leukemia are now considered by some investigators * * * to represent different clinical expressions of the same neoplastic process. There have been recent immunologic and cytogenetic studies which indicate that there are stem cells which appear to have the capacity to develop variously into all the various sorts of hematopoietic cells including T-lymphocytes, plasma cells, granulocytes, erythrocytes, and monocytes. (Tr. 1/15/91, p. 132)

Dr. Landrigan summarized his testimony on this issue by stating that ''these different types of cells share a common ancestry * * * there is good biologic reason to think that they would have etiologic factors in common.'' (Tr. 1/15/91, pp. 132–133)

OSHA maintains the opinion, which is well supported by the record, that there is a biological basis and a methodologic rationale for grouping related LH cancers. Furthermore, OSHA rejects the criticism that the observation of different subtypes of LH cancers argues against the consistency and specificity of the epidemiologic findings.

(vii) *Relevance of Worker Subgroup Analyses.* OSHA has been criticized for focusing on and emphasizing the ''few positive results'' seen in the results of worker subgroup analyses. (Ex. 113, A–48) It has been pointed out, for example, that in the update of the Matanoski cohort study ''there were hundreds of SMRs computed in that study and it's not surprising that one or two or even more would be found to be statistically significant even when there is in fact nothing going on.'' (Tr. 1/22/91, p. 1444) Additionally, it has been suggested that OSHA has ignored the ''clearly overall negative results'' of the epidemiologic studies. (Ex. 113, A–48)

OSHA agrees with the observation that when many statistical analyses are done on a database, it is possible that some positive results may be due to chance. However, OSHA rejects criticism that the Agency has inappropriately concentrated on the positive results and disregarded the negative results. It is OSHA's opinion that there is a compelling pattern of results in the epidemiologic studies.

Furthermore, a reasonable explanation for the elevated SMR for black production workers in the update of the Matanoski cohort study is that this subset of the population actually had heavy exposure to BD. Support for this explanation can be found in the industrial hygiene survey results of Fajen et al. (Ex. 34–4) In this case, then, the risk for excess mortality would be concentrated in a small subset of otherwise very healthy and unexposed workers that would be diluted when analyses are based on the entire group being studied. The only way to observe the risk in the most highly exposed subset would be to analyze the data by subgroups of the population.

(viii) *Appropriateness of Selected Reference Populations.* OSHA also has been criticized for ''ignor[ing] the fact that most of the epidemiologic studies of butadiene-exposed workers only used U.S. cancer mortality rates for comparison to worker mortality.'' (Ex. 113, A–49) The significance of this criticism is based on the observation by Downs that ''use of local (mortality) rates (for comparison) tended to bring the SMRs closer to 100.'' (Ex. 17–33, p.14) This finding results from cancer rates along the Texas Gulf coast that are higher than national rates. (Ex. 17–33) In other words, it has been argued that national comparison rates artificially inflate the SMRs, while local rates provide a more accurate picture of the mortality experience of workers with occupational exposure to BD. (Ex. 113, A–50)

Dr. Landrigan captured the essence of this issue in his testimony on cross-examination,

> This is a perennial debate in epidemiology of whether to use local comparison rates or regional or national, and there's [sic] arguments [to] go both ways. (Tr. 1/15/91, p. 154)

He presented several arguments for using national rates. First, U.S. mortality rates are based on the entire population, so they are more stable. Second, national rates are more commonly used, so it is easier to compare results from different studies.

On the other hand, the argument in favor of using local rates centers on the fact that people in a local area may truly be different from the total population or a regional population(s). Thus, comparing a local subpopulation with the entire local population may provide more accurate results. However, the weakness in this argument was highlighted by Dr. Landrigan when he said that,

> * * * if there are factors acting in the local population, such as environmental pollution that may elevate rates in the local area so that they are closer to the rates in the occupationally exposed population, then theoretically at least one could argue that the local population is overmatched, too similar to the employee population and that the use of the national comparison group actually give [sic] a better reflection of reality. (Tr. 1/15/91, p. 155)

In fact, he went on to point out that the BD plants have been identified by the Environmental Protection Agency (EPA) as ''major'' polluters of the local environment with BD. (Tr. 1/15/91, p. 155)

OSHA acknowledges that there are pros and cons to both approaches of reference population selection. However, in the study by Delzell et al. mortality data of the USA cohort subgroup were analyzed using both state, i.e., local, general population rates and USA general population rates. (Ex. 117–1) As previously stated, there was little difference in the overall pattern of these analyses. (Ex. 117–1, p. 60) Additionally, the Santos-Burgoa and Matanoski nested case control study used the most appropriate comparison group of all: Those employed at the same facilities. (Ex. 23–109 and 34–4, Vol. III, H–4) Thus, given the available data in the record, OSHA is of the opinion that it cannot ignore the findings of excess mortality that are based on national comparison rates.

(ix) *Summary and Conclusions.* (a) *Summary.* Table V–4 lists the criteria that can be used to judge the presence of a causal association between occupational exposure to BD and cancer of the lymphohematopoietic system. When the available epidemiologic study results are examined in this way, there is strong evidence for causality. The data fulfill all of the listed criteria: Temporal relationship; consistency;

strength of association; dose-response relationship; specificity of association; biological plausibility; and coherence.

In his testimony, OSHA's epidemiologist expert witness agreed that there is ''definite evidence for the fact that occupational exposure to 1,3–Butadiene can cause human cancer of the hematopoietic and lymphatic organs.'' (Tr. 1/15/91, p. 133) Dr. Weisenburger, OSHA's expert witness in hematopathology, also concluded that ''it would be prudent to treat BD as though it were a human carcinogen.'' (Ex. 39, p. 11)

TABLE V–4.—EVIDENCE THAT 1,3-BUTADIENE IS A HUMAN CARCINOGEN

Criterion for causality	Met by BD
Temporal relationship	Yes.
Consistency	Yes.
Strength of association	Yes.
Dose-response relationship	Yes.
Specificity of association	Yes.
Biological plausibility	Yes.
Coherence	Yes.

(b) *Conclusion.* On the basis of the foregoing analysis, OSHA concludes that there is strong evidence that workplace exposure to BD poses an increased risk of death from cancers of the lymphohematopoietic system. The epidemiologic findings supplement the findings from the animal studies that demonstrate a dose-response for multiple tumors and particularly for lymphomas in mice exposed to BD.

C. Reproductive Effects

In addition to the established carcinogenic effects of BD exposure, various reports have led to concern about the potential reproductive and developmental effects of exposure to BD. The term reproductive effects refers to those on the male and female reproductive systems and the term developmental refers to effects on the developing fetus.

Male reproductive toxicity is generally defined as the occurrence of adverse effects on the male reproductive system that may result from exposure to chemical, biological, or physical agents. Toxicity may be expressed as alterations to the male reproductive organs and/or related endocrine system. For example, toxic exposures may interfere with spermatogenesis (the production of sperm), resulting in adverse effects on number, morphology, or function of sperm. These may adversely affect fertility. Human males produce sperm from puberty throughout life and thus the risk of disrupted spermatogenesis is of concern for the entire adult life of a man.

Female reproductive toxicity is generally defined as the occurrence of adverse effects on the female reproductive system that may result from exposure to chemical, biological, or physical agents. This includes adverse effects in sexual behavior, onset of puberty, ovulation, menstrual cycling, fertility, gestation, parturition (delivery of the fetus), lactation or premature reproductive senescence (aging).

Developmental toxicity is defined as adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Developmental effects induced by exposures prior to conception may occur, for example, when mutations are chemically induced in sperm. If the mutated sperm fertilizes an egg, adverse developmental effects may be manifested in developing fetuses. Mutations may also be induced in the eggs. The major manifestations of developmental toxicity include death of the developing fetus, structural abnormality, altered growth and function deficiency.

To determine whether an exposure condition presents a developmental or reproductive hazard, there are two categories of research studies on which to rely: Epidemiologic, or studies of humans, and toxicologic, or experimental studies of exposed animals or other biologic systems.

Many outcomes such as early embryonic loss or spontaneous abortion are not easily detectable in human populations. Further, some adverse effects may be quite rare and require very large study populations in order to have adequate statistical power to detect an effect, if in fact one is present. Often, these populations are not available for study. In addition, there are fewer endpoints which may be feasibly measured in humans as compared to laboratory animals. For example, early embryonic loss is difficult to measure in the study of humans, but can be measured easily in experimental animals. There are no human studies available to address reproductive and developmental effects of BD exposure to workers. Thus, evidence on the reproductive and developmental toxicity of BD comes from toxicologic studies performed using primarily mice.

Animal studies have proved useful for studying reproductive/developmental outcomes to predict human risk. A very important advantage to the toxicological approach is the ability of the experimenter to fully quantitate the exposure concentration and conditions of exposure. Although extrapolation of risk to humans on a qualitative basis is accepted, quantitative extrapolation of study results is more complex.

In his testimony, OSHA's witness, Dr. Marvin Legator, an internationally recognized genetic toxicologist from the University of Texas Medical Branch in Galveston, cautioned that in assessing risk ''humans in general have proven to be far more sensitive than animals * * * to agents characterized as developmental toxicants.'' (Ex. 72) He also noted that ''of the 21 agents considered to be direct human developmental toxins, in 19 * * * the human has been shown to be more sensitive than the animal * * *'' He also pointed to the possibility that sub-groups of the human population may be even more highly sensitive than the population average.

OSHA believes that the animal inhalation studies designed to determine the effect of BD on the reproduction and development of these animals indicate that BD causes adverse effects in both the male and female reproductive systems and produces adverse developmental effects. These studies are briefly summarized and discussed below.

Toxicity to Reproductive Organs

In the first NTP bioassay, an increased incidence of testicular atrophy was observed in male mice exposed to BD atmospheric concentrations of 625 ppm. (Ex. 23–1) In female mice, an increased incidence of ovarian atrophy was observed at 625 and 1,250 ppm. These adverse effects were confirmed in reports of the second NTP study, which used lower exposure concentrations. The latter lifetime bioassay exposed male and female B3C6F1 mice to 0, 6.25, 20, 62.5, 200, and 625 ppm BD. (Ex. 114, p 115) See Table V–5. Testicular atrophy in males was significantly increased at the highest dose tested, 625 ppm, and reduced testicular weight was observed from BD exposures of 200 ppm. (Ex. 96) These latter data are not shown in the Table. In female mice at terminal sacrifice, 103 weeks, ovarian atrophy was significantly increased at all exposure levels including the lowest dose tested, 6.25 ppm, compared with controls. Evidence of ovarian toxicity was also seen during interim sacrifices, but in these cases was the result of higher exposure levels. After 65 weeks of exposure, 90% of the mice exposed to 62.5 ppm experienced ovarian atrophy.

TABLE V–5.—OVARIAN AND TESTICULAR ATROPHY IN MICE EXPOSED TO BD

Lesion	Weeks of exposure	Exposure concentration (ppm)					
		0	6.25	20	62.5	200	625
		Incidence (%)					
Testicular atrophy	40	0/10(0)	NE	NE	NE	0/10(0)	6/10(60)
	65	0/10(0)	NE	NE	NE	0/10(0)	4/7(57)
	103	1/50(2)	3/50(6)	4/50(8)	2/48(4)	6/49(12)	53/72(74)
Ovarian atrophy	40	0/10(0)	NE	NE	0/10(0)	9/10(90)	8/8(100)
	65	0/10(0)	0/10(0)	1/10(10)	9/10(90)	7/10(70)	2/2(100)
	103	4/49(8)	19/49(39)	32/48(67)	42/50(84)	43/50(86)	69/79(87)

NE, not examined microscopically.
Source: Ex. 114.

Extensive comments on the BD induced ovarian atrophy were received from Dr. Mildred Christian, a toxicologist who offered testimony on behalf of the Chemical Manufacturers Association. She questioned the relevance of using the data from studies of mice to extrapolate risk of ovarian atrophy to humans because most of the evidence was observed among the animals who were sacrificed after the completion of the species reproductive life and only after prolonged exposure to 6.25 ppm and 20 ppm (Ex. 118–13, Att 3, p. 4) On the other hand, Drs. Melnick and Huff, toxicologists from the National Institute of Environmental Health Sciences stated that: ''Even though ovarian atrophy in the 6.25 ppm group was not observed until late in the study when reproductive senescence likely pertains, the dose-response data clearly establish the ovary as a target organ of 1,3-butadiene toxicity at concentrations as low as 6.25 ppm, the lowest concentration studied.'' (Ex. 114, p. 116) In addition, it should be noted that an elevated incidence of ovarian atrophy was observed at periods of interim sacrifice of female mice exposed to 20 ppm that took place at the 65 week exposure period, a time prior to the ages when senescence would be expected to have occurred. NIOSH also accepted Dr. Melnick's view that mice exposed to 6.25 ppm BD demonstrated ovarian atrophy. (Ex. 32–35) OSHA remains concerned about the ovarian atrophy demonstrated at low exposure levels in the NTP study. Thus, OSHA concludes that exposure to relatively low levels of BD resulted in the induction of ovarian atrophy in mice.

Sperm-Head Morphology Study

NTP/Battelle investigators also described sperm head morphology findings using $B6C3F_1$ mice exposed as described in the dominant lethal study mentioned below, e.g., exposures to 200, 1000 and 5000 ppm BD. The mice were sacrificed in the fifth week post-exposure and examined for gross lesions of the reproductive system. (Ex. 23–75) The study authors chose this interval as having the highest probability for detecting sperm abnormalities. Epididymal sperm suspensions were examined for morphology. The percentage of morphologically abnormal sperm heads was significantly increased in the mice exposed at 1,000 ppm and 5,000 ppm, but not for those exposed to 200 ppm. The study authors concluded that ''these significant differences in the percentage of abnormalities between control mice and males exposed to 1000 and 5000 ppm [BD] indicated that their late spermatogonia or early spermatocytes were sensitive to this chemical.'' (Ex. 23–75, p. 16)

In reviewing this study, Dr. Mildred Christian stated that these results are not necessarily correlated with developmental abnormalities or reduced fertility and are ''reversible in nature'' and that the observed differences are ''biologically insignificant.'' (Ex. 76, p. 14) In its submission, the Department of Health Services of California said: ''A conclusion as to the reproductive consequences of these abnormalities cannot be made from this study.'' (Ex. 32–168) In reviewing Dr. Christian's comments, OSHA is in agreement that the observation of a significant excess of sperm head abnormalities as a result of BD exposure is not necessarily correlated with the development of abnormal fetuses or of reduced fertility; however, the Anderson study, which did evaluate fetal abnormality and reduced fertility, demonstrated a significant excess of both fetal abnormality plus early and late fetal mortality as a result of male mice exposure to BD. (Ex. 117–1, P. 171) These observations of fetal mortality could only occur as a result of an adverse effect on the sperm. In response to Dr. Christian's comment that the sperm head abnormality observed in the study is reversible, the reversibility would be dependent upon cessation of exposure. Since workers may be exposed to BD on a daily basis, the significance of reversibility may be moot.

Developmental Toxicity

Dominant Lethal Studies

A dominant lethal study was conducted by Battelle/NTP to assess the effects of a 5-day exposure of male CD–1 mice to BD atmospheric concentrations of 0, 200, 1,000 and 5,000 ppm BD for 6 hours per day on the reproductive capacity of the exposed males during an 8-week post-exposure period. (Ex 23–74) If present, dominant lethal effects are expressed as either a decrease in the number of implantations or as an increase in the incidence of intrauterine death, or both, in females mated to exposed males. Dominant lethality is thought to arise from lethal mutations in the germ cell line that are dominantly expressed through mortality to the offspring. In this study, the only evidence of toxicity to the adult male mouse was transient and occurred over a 20 to 30 minute period following exposure at 5,000 ppm. Males were then mated to a different female weekly for 8 weeks. After 12 days, females were killed and examined for reproductive status. Uteri were examined for number, position and status of implantation. Females mated to the BD-exposed males during the first 2 weeks post-exposure were described as more likely than control animals to have increased numbers of dead implantations per pregnancy.

For week one, the percentage of dead implantations in litters sired by males exposed to 1,000 ppm was significantly higher than controls. There were smaller increases at 200 ppm and 1000 ppm that were not statistically significant. The percentage of females with two or more dead implantations was significantly higher than the control value for all three exposure groups. For week two, the numbers of dead implantations per

pregnancy in litters sired by males exposed to 200 ppm and 1000 ppm were also significantly increased, but not for those exposed to 5000 ppm. No significant increases in the end points evaluated were observed in weeks three to eight. These results suggested to the authors that the more mature cells (spermatozoa and spermatids) may be adversely altered by exposure to BD. (Ex. 23–74)

The State of California Department of Health Services concluded that the above mentioned study showed no adverse effect from exposure to BD, with the possible exception of the increase in intrauterine death seen as a result of male exposures to 1000 ppm BD at the end of one week post exposure. (Ex. 32–16) Since values for the 5000 ppm exposure group were not significantly elevated for this same period of follow up, the California Department of Health thought the biological significance of the results of the 1000 ppm exposure was questionable. (Ex. 32–16) On the other hand, Dr. Marvin Legator stressed the low sensitivity of the dominant lethal assay which, he felt was due to the endpoint-lethality. He expressed the opinion that the studies were ''consistent with an effect on mature germ cells.'' (Ex. 72) He felt that since an effect was observable in this relatively insensitive assay that only the ''tip of the iceberg'' was observed, and that ''[t]ransmissible genetic damage, displaying a spectrum of abnormal outcomes can be anticipated at concentrations (of BD) below those identified in the dominant lethal assay procedure.'' (Ex. 72, p. 17)

The dominant lethal effect of BD exposure was more recently confirmed by Anderson et al. in 1993. (Ex. 117–1, p. 171) They studied CD–1 mice using a somewhat modified study design. Two exposure regimens were used. In the first, ''acute study,'' male mice were exposed to 0 (n=25), 1250 (n=25), or 6250 (n=50) ppm BD for 6 hours only. Five days later they were caged with 2 untreated females. One female was allowed to deliver her litter and the other was killed on day 17 of gestation and examined for the number of live fetuses, number of early and late post-implantation deaths and the number and type of any gross malformation. The authors stated that sacrifice on day 17 (rather than the standard days 12 through 15) allowed examination of near-term embryos for survival and abnormalities. The mean number of implants per female was reduced compared with controls at both concentrations of BD, but was statistically significant only at 1250 ppm. Neither post-implantation loss nor fetal abnormalities were significantly increased at either concentration. The authors concluded that ''a single 6-hour acute exposure to butadiene was insufficient to elicit a dominant lethal effect.'' (Ex. 117–1, p. 171)

In the second phase of the study, the ''subchronic study,'' CD–1 mice were exposed to 0 (n=25), 12.5 (n=25), or 1250 (n=50) ppm BD for 6 hours per day, 5 days per week, for 10 weeks. They were then mated. The higher 1250 ppm BD exposure resulted in significantly reduced numbers of implantations and in significantly increased numbers of dominant lethal mutations expressed as both early and late deaths. See Table V–6. Non-lethal mutations expressed as birth abnormalities were also observed in live fetuses (3/312; 1 hydrocephaly and 2 runts).

The lower exposure (12.5 ppm) did not result in decreases in the total number of implants, nor in early deaths; however, the frequencies of late deaths and fetal abnormalities (7/282; 3 exencephalies in 1 litter and one in another, two runts and one with blood in the amniotic sac) were significantly increased.

The authors felt that their finding of increased late deaths and fetal abnormalities at a subchronic, low exposure of 12.5 ppm was the main new finding of the study. They noted that these adverse health effects were increased 2–3 fold over historical controls. In evaluating these latter two studies OSHA notes that while there was no demonstrable effect on dominant lethality as a result of a single exposure to 1250 ppm BD, subchronic exposure to 12.5 ppm, the lowest dose tested, resulted in the induction of dominant lethal mutations and perhaps non-lethal mutations. (Ex 117–1, p 171) OSHA has some reservations about whether or not the fetal abnormalities observed in the Anderson et al. ''subchronic'' study were actually caused by non-lethal mutations or by some other mechanism because they were observed in only a few of the litters produced by the mice. (Ex. 117–1, p. 171)

TABLE V–6.—EFFECT OF BD ON REPRODUCTIVE OUTCOMES IN CD–1 MICE

	Implantations		Early deaths		Late deaths		Late deaths including dead fetuses		Abnormal fetuses	
	No.	Mean	No.	Mean [a]	No.	Mean [a]	No.	Mean [a]	No.	Mean [a]
Control	278	12.09±1.276	13	0.050±0.0597	0		2	0.007±0.0222	0	
12.5	306	12.75±2.507	16	0.053±0.0581	7	0.23**±0.038	8	0.026±0.0424	[b]7	0.024*±0.062
1250 ppm ...	406	10.68**±3.103	87	0.204***±0161	6	0.014***±0.0324	7	0.016±0.339	[c]3	0.011**±0.043≤

* Significantly different from control at: *p≤0.05; **p≤0.01; ***p≤0.001 (by analysis of variance and least significance test on arc-sine transform data).

[a] Per implantation.

[b] Four exencephalies (three in one litter), two runts (≤70% and 60% of mean body weight of others in litter; total litter sizes 7 and 9, respectively one fetus with blood in amniotic sac but no obvious gross malformation (significance of difference not altered if this fetus is excluded).

[c] One hydrocephaly, two runts (71% and 75% of mean body weight of others in litter; total litter sizes; 2 and 11, respectively).

A dominant lethal test was also performed by Adler et al. (Ex. 126) Male(102/E1XC3H/E1)F_1 male mice were exposed to 0 and 1300 ppm BD. They were mated 4 hours after the end of exposure with untreated virgin females. Females were inspected for the presence of a vaginal plug every morning. Plugged females were replaced by new females. The mating continued for four consecutive weeks. At pregnancy day 14–16 the females were killed and uterus contents were evaluated for live and dead implants. Exposure of male mice to 1300 ppm BD caused an increase of dead implants during the first to the third mating week after 5 days of exposure. The dead implantation rate was significantly different from the concurrent controls only during the second mating week. Adler et al. concluded that dominant lethal mutations were induced by BD in spermatozoa and late stage spermatids and that these findings confirmed the results of the Battelle/NTP study which showed effects on the same stages of

sperm development. (Ex. 23–74) The authors were of the opinion that BD may induce heritable translocations in these germ cell stages.

The earliest reproductive study reported on BD was conducted by Carpenter et al. in 1944. (Ex. 23–64) In this study, male and female rats were exposed by inhalation to 600, 2,300 or 6,700 ppm BD, 7.5 hours per day, six days per week for an 8-month period. Although this study was not specifically designed as a reproductive study, the fertility and the number of progeny were recorded. No significant effects due to BD exposure were noted for either the number of litters per female animal or for the number of pups per litter.

In the Hazelton study, Sprague-Dawley (SD) rats were exposed by inhalation to 0, 200, 1,000 or 8,000 ppm BD on days 6 though 15 of gestation. (Ex. 2–32) There were dose-related effects on maternal body weight gain, fetal mean weight and crown-to-rump length. Post-implantation loss was slightly higher in all BD-exposed groups. In addition, there were significant increases in hematoma in pups in the 200 and 1,000 ppm exposure groups. In the 8,000 ppm exposure group, a significantly increased number of pups had lens opacities and there was an increased number of opacities per animal. According to the authors, the highest exposure groups also had a significantly increased number of fetuses with skeletal variants, a higher incidence of bipartite thoracic centra, elevated incidence of incomplete ossification of the sternum, higher incidence of irregular ossification of the ribs, and ''other abnormalities of the skull, spine, long bones, and ribs.'' The authors concluded that the fetal response was not indicative of a teratogenic effect, but was the result of maternal toxicity.

In the Battelle/NTP study, pregnant Sprague-Dawley (SD) rats and pregnant Swiss mice were exposed to 0, 40, 200, or 1,000 ppm BD for 6 hours per day from day 6 through day 15 of gestation. (Ex. 23–72) Animals were sacrificed and examined one day before expected delivery. In the rat, very little effect was noted; in the 1,000 ppm exposure group only there was evidence of maternal toxicity, i.e., depressed body weight gains during the first 5 days of exposure. No evidence of developmental toxicity was observed in the SD rats evaluated in the study, e.g., the number of live fetuses per litter and the number of intrauterine deaths were within normal limits.

In the mouse, exposure to the above mentioned concentrations did not result in significant maternal toxicity, with the exception of a reduction in extra-gestational weight gain for the 200 ppm and 1000 ppm BD exposed dams. In the female mice, there was a significant depression of fetal body weight only at the 200 and 1,000 ppm exposure levels. Fetal body weight for male pups was reduced at all exposure concentrations, including the 40 ppm exposure level, even though evidence of maternal toxicity was not observed at this exposure concentration. No significant differences were noted in incidence of malformations among the groups. However, the incidence of supernumerary ribs and reduced ossification of sternebrae was significantly increased in litters of mice exposed to 200 and 1,000 ppm BD.

In reviewing these data, Drs. Melnick and Huff noted that since maternal body weight gain was reduced at the 200 and 1000 ppm exposure levels and body weights of male fetuses were reduced at the 40, 200, and 1000 exposure levels ''[t]he male fetus is more susceptible than the dam to inhaled 1,3-butadiene.'' (Ex. 114, p. 116) They further stated that ''the results of the study in mice reveal that a toxic effect of 1,3-butadiene was manifested in the developing organism in the absence of maternal toxicity.'' On the basis of this study, the authors concluded that ''1,3-butadiene does not appear to be teratogenic in either the rat or the mouse, but there is some indication of fetotoxicity in the mouse.'' (Ex. 23–72)

On the other hand, Dr. Mildred Christian was of the opinion that the significant decrease in male mouse fetal weight gain in the 40 ppm exposure group was not a selective effect of BD on the conceptus, but rather was a result of the statistical analysis used which she considered inappropriate. (Ex. 118–13, Att. 3, p. 6) She was also of the opinion that the larger litter sizes in the 40 ppm exposure group as compared with the control group contributed to the statistical finding. Dr. Christian, however, did not present any specific information on the type of analysis used for statistical testing that she thought made the results inappropriate. In general, one would expect that the evaluation of data from larger litter sizes would give one more confidence in the statistical findings.

In reviewing the same study, the State of California, Department of Health Services was more cautious. It stated that ''The increased incidence of reduced ossifications and the fetal weight reductions in the absence of apparent maternal toxicity in the 40- and 200-ppm groups is evidence of fetotoxicity * * * in the Swiss (CD–1) mouse.'' After reviewing the study results and arguments about the study, OSHA concluded that the NTP study provides evidence of fetotoxicity in the mouse. (Ex. 23–72)

Mouse spot test

Adler et al. (1994) conducted a spot test in mice. (Ex. 126) The spot test is an *in vivo* method for detecting somatic cell mutations. A mutation in a melanoblast is detected as a coat color spot on the otherwise black fur of the offspring. Pregnant females were exposed to 0 or 500 ppm BD for 6 hours per day on pregnancy days 8, 9, 10, 11 and 12. They were allowed to come to term and to wean their litters. Offspring were inspected for coat color spots at ages 2 and 3 weeks. Gross abnormalities were also recorded. Exposure to a concentration of 500 ppm did not cause any embryotoxicity, nor were gross abnormalities observed. The BD exposure, however, significantly increased the frequency of coat color spots in the offspring. This study demonstrates that BD exposure is capable of causing transplacentally induced somatic cell mutations that can result in a teratogenic effect in mice.

Summary of Reproductive and Developmental Effect

OSHA has limited its discussion on reproductive and developmental hazards to a qualitative evaluation of the data. This approach was chosen because no generally accepted mathematical model for estimating reproductive/developmental risk on a quantitative basis was presented during the rulemaking. For example, the CMA Butadiene panel disagreed with OSHA's findings in the proposal regarding the potential reproductive and developmental risks presented by BD exposure using an uncertainty factor approach. (See Ex. 112) They cited Dr. Christian's conclusion that the mouse possessed a ''special sensitivity'' to BD and should not be used as a model on which to base risk estimates.

The agency has determined, however, that animal studies, taken as a whole, offer persuasive qualitative evidence that BD exposure can adversely effect reproduction in both male and female rodents. The Agency also notes that BD is mutagenic in both somatic and germ cells. (Ex. 23–71; Ex. 114; Ex. 126)

Some evidence of maternal and developmental toxicity was seen in rats exposed to BD, but the concentrations used were much higher than those that elicited a response in mice. (Ex. 118–13, Att. 3, p. 2) In mice, evidence of fetotoxicity was observed in either the presence or absence of maternal toxicity, the latter evidence being

provided by decreased fetal body weight in male mice whose dams were exposed to 40 ppm BD, the lowest dose tested in the study. In addition, a teratogenic effect was observed in mice (coat color spot test) as a result of transplacentally induced somatic cell mutation.

OSHA is also concerned about the observation of a significant excess of sperm head abnormalities as a result of BD exposure, even though this expression of toxicity is not necessarily correlated with the development of abnormal fetuses or of reduced fertility. The Anderson study, which did evaluate reduced fertility and fetal abnormality, demonstrated a significant excess of both early and late fetal mortality and perhaps fetal abnormality as a result of male mice exposure to BD. (Ex. 117–1, P. 171) This observation could only occur as a result of an adverse effect on the sperm. Two additional studies also provide evidence of dominant lethality as a result of male exposure to BD. (Ex. 23–74; Ex. 126) The observation of germ cell effects is supported by additional evidence of genotoxicity in somatic cells, as demonstrated by positive results in the micronucleus test and in the mouse spot test. (Ex. 126)

Some of the adverse effects related to reproductive and developmental toxicity in the mouse, e.g., ovarian atrophy, testicular atrophy, reduced testicular weight, abnormal sperm heads, dominant lethal effects, were acknowledged by Dr. Christian, but she urged the Agency not to rely on these findings because of negative study results in other species, or because positive findings in other species required much higher exposure levels. (Ex. 118–13, Att. 3, p. 1)

For example, a CMA witness has argued that the diepoxide is responsible for the ovarian atrophy observed in relation to low level BD exposure (6.25 ppm). (Ex. 118–13, Att. 3) However, the monoepoxide could also play a role in the ovarian atrophy and evidence indicates that humans can form the monoepoxide of BD and that humans have the enzymes present that could cause conversion to the diepoxide. Therefore on a qualitative basis, the observation of ovarian atrophy in the mouse is meaningful in OSHA's view. In addition, the metabolic factors related to testicular atrophy, malformed sperm and dominant lethal mutations in the mouse are not known. (See section on *in vitro* metabolic studies.) These observations further support the findings in mice as being meaningful for humans on a qualitative basis. The mouse spot test which demonstrates a somatic cell mutation leading to a teratogenic effect inconsistent with data showing the ability of BD to cause adverse effects on chromosomes and *hprt* mutations in humans exposed to BD.

OSHA also notes that studies of workers exposed to low concentrations of BD demonstrated a significant excess of chromosomal breakage and an inability to repair DNA damage. Thus, BD exposure seems capable of inducing genetic damage in humans as a result of low level exposure. Therefore, the mouse studies which demonstrate genetic damage (mutations) in both somatic and germinal cells seem to be a better model on a qualitative basis than the rat for predicting these adverse effects in humans.

D. Other Relevant Studies

1. Acute Hazards

At very high concentrations, BD produces narcosis with central nervous system depression and respiratory paralysis. (Ex. 2–11) LC_{50} values (the concentration that produces death in 50 percent of the animals exposed) were reported to be 122,170 ppm (12.2% v/v) in mice exposed for 2 hours and 129,000 ppm (12.9% v/v) in rats exposed for 4 hours. (Ex. 2–11, 23–91) These concentrations would present an explosion hazard, thus limiting the likelihood that humans would risk any such exposure except in extreme emergency situations. Oral LD_{50} values (oral dose that results in death of 50 percent of the animals) of 5.5 g/kg body weight for rats and 3.2 g/kg body weight for mice have been reported. (Ex. 23–31) These lethal effects occur at such high doses that BD would not be considered ''toxic'' for purposes of Appendix A of OSHA's Hazard Communication Standard (29 CFR 1910.1200), which describes a classification scheme for acute toxicity based on lethality data.

At concentrations somewhat above the previous permissible exposure level of 1,000 ppm, BD is a sensory irritant. Concentrations of several thousand ppm were reported to cause irritation to the skin, eyes, nose, and throat. (Ex. 23–64, 23–94) Two human subjects exposed to BD for 8 hours at 8000 ppm reported eye irritation, blurred vision, coughing, and drowsiness. (Ex. 23–64)

2. Systemic Effects

In the preamble to the proposal, OSHA reviewed the literature to discern the systemic effects of BD exposure. (55 FR 32736 at 32755) OSHA discussed an IARC review which briefly examined several studies from the former Soviet Union. In these, various adverse effects, such as hematologic disorders, liver enlargement and liver and bile-duct diseases, kidney malfunctions, laryngotracheitis, upper respiratory tract irritation, conjunctivitis, gastritis, various skin disorders and a variety of neurasthenic symptoms, were ascribed to occupational exposure to BD. (Ex. 23–31) OSHA and IARC have found these studies to be of limited use primarily due to their lack of exposure information. Except for sensory irritant effects and hematologic changes, evidence from studies of other exposed groups have failed to confirm these observations.

Melnick and Huff summarized the observed non-neoplastic effects of BD exposure in the NTP I and NTP II mouse bioassays. They listed the following effects associated with exposure of B6C3F [1] mice to BD for 6 hours per day 5 days per week for up to 65 weeks:

* * * epithelial hyperplasia of the forestomach, endothelial hyperplasia of the heart, alveolar epithelial hyperplasia, hepatocellular necrosis, testicular atrophy, ovarian atrophy and toxic lesions in nasal tissues (chronic inflammation, fibrosis, osseous and cartilaginous metaplasia, and atrophy of the olfactory epithelium.) (Ex. 114, p. 114)

They noted that the nasal lesions were seen only in the group of male mice exposed to 1250 ppm BD and that no tumors were observed at this site. Further, Melnick and Huff suggested that some of the proliferative lesions observed in the bioassay might represent pre-neoplastic changes.

The findings of testicular and ovarian atrophy are discussed more fully in the Reproductive Effects section of this preamble,.

Nephropathy, or degeneration of the kidneys, was the most common non-carcinogenic effect reported for male rats in the Hazelton Laboratory Europe (HLE) study in which rats were exposed to 1000 or 8000 ppm BD for 6 hours per day, 5 days per week for up to 2 years. Nephropathy was one of the main causes of death for the high dose males. (Ex. 2–31, 23–84) The combined incidence of marked or severe nephropathy was significantly elevated in the high dose group over incidence in the low dose group and over incidence in the controls ($p<.001$). HLE's analysis of ''certainly fatal'' nephropathy shows a significant dose-related trend ($p<.05$), but when ''uncertainly fatal'' cases were included, the trend disappeared.

The HLE study authors concluded that the interpretation of the nephropathy incidence data was equivocal. They stated that ''an increase in the prevalence of the more severe grades of nephropathy, a common age-

related change in the kidney, was considered more likely to be a secondary effect associated with other unknown factors and not to represent a direct cytotoxic effect of the test article on the kidney.''

Upon reviewing the HLE rat study for the proposed rule, OSHA expressed concern that only 75% of the low-dose male rats in the HLE study exhibited nephropathy, while 87% of the control rats had some degree of nephropathy, suggesting low-dose male rats were less susceptible to kidney degeneration than control rats, thereby decreasing the comparability between rats in the low-dose and control groups. (55 FR 32736 at 32744) Dr. Robert K. Hinderer, in testifying for the CMA BD Panel, countered that the NTP I mouse study also had ''selected instances where the response in the test group (was) lower than that in the controls'' and that ''* * * (o)ne cannot look at single or a few individual site responses to evaluate the health status or overall effect of the chemical.'' (Ex. 51) OSHA agrees that there may be some variability in background response rates for specific outcomes. However, the Agency believes that it is important to assess the impact of the variability in background response rates when drawing conclusions about dose-related trends in the data. This was not done in the HLE study nephropathy analysis.

Other non-carcinogenic effects observed in the HLE rat study were elevated incidence of metaplasia in the lung of high dose male rats at terminal sacrifice as compared with incidence in male controls at terminal sacrifice, and a significant increase in high dose male rat kidney, heart, lung, and spleen weights over the organ weights in control male rats.

3. Bone Marrow Effects

There was a single study of BD-exposed humans discussed in the proposal—a study by Checkoway and Williams that examined 163 hourly production workers who were employed at the SBR facility studied by McMichael et al.. (described more fully in the Epidemiology Section of this Preamble.) (Ex. 23–4, 2–28).

Exposure to BD, styrene, benzene, and toluene was measured in all areas of the plant. BD and styrene concentrations, 20 (0.5–65) ppm and 13.7 (0.14–53) ppm, respectively, were considerably higher in the Tank Farm than in other departments. In contrast, benzene exposures, averaging 0.03 ppm, and toluene concentrations, averaging 0.53 ppm, were low in the Tank Farm. The authors compared the hematologic profiles of Tank Farm workers (n=8) with those of the other workers examined.

The investigation focused on two potential effects, bone marrow depression and cellular immaturity. Bone marrow depression was suspected if there were lower levels of erythrocytes, hemoglobin, neutrophils, and platelets. Cellular immaturity was suggested by increases in reticulocyte and neutrophil band form values.

Although the differences were small, adjusted for age and medical status, hematologic parameters in the Tank Farm workers differed from those of the other workers. Except for total leukocyte count, the hematologic profiles of the Tank Farm workers were consistent with an indication of bone marrow depression. The Tank Farm workers also had increases in band neutrophils, a possible sign of cellular immaturity, but no evidence that increased destruction of reticulocytes was the cause.

While acknowledging the limitations of the cross-sectional design of the study, the authors felt, nevertheless, that their results were ''suggestive of possible biological effects, the ultimate clinical consequences of which are not readily apparent.'' OSHA finds any evidence of hematological changes in workers exposed at BD levels well below the existing permissible limit (1000 ppm) to be of concern since such information suggests the inadequacy of the present exposure limit. However, this cross-sectional study involved only 8 workers with relatively high levels of exposure to BD and low levels of exposure to benzene, so it is quite insensitive to minor changes in hematologic parameters.

In a review of BD-related studies, published in 1986, an IARC Working Group felt the study of Checkoway and Williams could not be considered indicative of an effect of BD on the bone marrow (Ex. 2–28). In 1992, IARC concluded that the ''changes cannot be interpreted as an effect of 1,3-butadiene on the bone marrow particularly as alcohol intake was not evaluated.'' (Ex. 125, p. 262)

In light of the more recent animal studies that were not available to IARC, however, OSHA believes that the bone marrow is a target of BD toxicity. Furthermore, the fact that changes in hematologic parameters could be distinguished in workers exposed to BD at 20 ppm indicates that such measurements may prove a sensitive indicator of excessive exposure to BD.

In testimony for the CMA BD Panel, Dr. Michael Bird stated his conclusion that the hematological differences between the 8 tank farm workers and the lesser exposed group of workers was not ''statistically significant by the usual conventional statistics.'' (Tr. 1/18/1991, p. 1078) He believed that although the raw data were not available, the reported means were within the historical and expected range for these parameters. (Tr. 1/18/1991, p., 1078) In contrast, OSHA concludes from this study that the hematologic differences observed in BD-exposed workers, although small, are suggestive of an effect of BD on human bone marrow under occupational exposure conditions.

Thus OSHA considers the Checkoway and Williams study to be suggestive of hematologic effects in humans, but does not regard it as definitive. No other potential systemic effects of BD exposure on this population were addressed in the Checkoway and Williams study.

In 1992, Melnick and Huff reviewed the toxicologic studies of BD exposure in laboratory animals. (Ex. 114) Only slight to no systemic effects were observed in an early study of rats, guinea pigs, rabbits and a dog exposed to BD up to 6,700 ppm daily for 8 months. (Ex. 23–64) The study of Sprague Dawley rats exposed to doses of BD up to 8,000 ppm daily for 13 weeks also did not result in hematologic, biochemical, neuromuscular, nor urinary effects. However, there were marked effects seen in exposed mice.

Epidemiologic studies of the styrene-butadiene rubber (SBR) industry suggest that workers exposed to BD are at increased risk of developing leukemia or lymphoma, two forms of hematologic malignancy (see preamble section on epidemiology). Consequently, investigators have looked for evidence of hematopoietic toxicity resulting from BD exposure in animals and in workers. For example, Irons and co-workers at CIIT found that exposure of male $B6C3F_1$ mice to 1,250 ppm of BD for 6–24 weeks resulted in macrocytic-megaloblastic anemia, an increase in erythrocyte micronuclei and leukopenia, principally due to neutropenia. Bone marrow cell types overall were not altered, but there was an increase in the number of cells in the bone marrow of exposed mice due to an increase in DNA synthesis. (Ex. 23–12)

Melnick and Huff also reviewed the available information on bone marrow toxicity. (Ex. 114, p. 114) Table V–7 represents the reported findings of a study of 10 $B6C3F_1$ mice sacrificed after 6.25–625 ppm exposure to BD for 40 weeks. The authors concluded that these data demonstrated a concentration-dependent decrease in red blood cell number, hemoglobin concentration, and packed red cell

volume at BD exposure levels from 62.5 to 625 ppm. The effects were not observed at 6.25 and 20 ppm exposure levels. Melnick and Kohn also noted the increase in mean corpuscular volume in mice exposed at 625 ppm, and suggested that this and other observations (such as those of Tice (Ex. 32–38D)) who observed a decrease in the number of dividing cells in mice and decreased rate of their division), suggested that BD exposure led to a suppression of hematopoiesis in bone marrow. Melnick and Huff concluded that this, in turn, led to release of large immature cells from sites such as the spleen, which was considered indicative of macrocytic megaloblastic anemia by Irons. They concluded that these findings ''(establish) the bone marrow as a target of 1,3-butadiene toxicity in mice.'' (Ex. 114, p. 115)

TABLE I.—HEMATOLOGIC CHANGES IN MALE B6C3F$_1$ MICE EXPOSED FOR 6 HOURS/DAY, 5 DAYS/WEEK FOR 40 WEEKS

BD exposure (ppm)	Red blood cell count (×10^6/ul)	Hemoglobin conc. (g/dl)	Volume packed RBC (ml/dl)	Mean corpuscular vol
0	10.4±0.3	16.5±0.4	48.1±1.5	46.3±0.8
6.25	10.3±0.3	16.4±0.5	47.8±1.7	46.4±1.0
20	10.4±0.4	16.7±0.7	48.2±2.2	46.3±0.8
62.5	[a] 9.9±0.4	[a] 15.9±0.6	[a] 45.9±2.1	46.7±1.2
200	[a] 9.6±0.5	[a] 15.6±0.9	[a] 45.4±2.7	47.2±1.0
625	[a] 7.6±1.2	[a] 13.5±1.8	[a] 39.9±5.3	[a] 53.2±2.9

Adapted from Melnick and Huff, Exhibit 114.
[a] Different from chamber control (0 ppm), P<0.05. Results of treated groups were compared to those of control groups using Dunnett's t-test.

4. Mutagenicity and Other Genotoxic Effects

OSHA discussed the genotoxic effects of BD exposure in some detail in the proposal. (55 FR 32736 at 32760) Briefly, BD is mutagenic to *Salmonella typhimurium* strains TA 1530 and TA 1535 when activated with S9 liver fraction of Wistar rats treated with phenobarbital or Arochlor 1254. These bacterial strains are sensitive to base-pair substitution mutagens. Since the liver fraction is required to elicit the positive mutagenic response, BD is not a direct-acting mutagen and likely must be metabolized to an active form before becoming mutagenic in this test system. IARC published an extensive list of ''genetic and related effects of 1,3-butadiene.'' (Ex. 125) They noted in summarizing the data that BD was negative in tests for somatic mutation and recombination in *Drosophila*, and that neither mouse nor rat liver from animals exposed to 10,000 ppm BD showed evidence of unscheduled DNA synthesis.

As OSHA described in the proposed rule, and Tice et al. reported in 1987, BD is a potent *in vivo* genotoxic agent in mouse bone marrow cells that induced chromosomal aberrations and sister chromatid exchange in marrow cells and micronuclei in peripheral red blood cells. (55 FR 52736 at 52760) Some of these effects were evident at exposures as low as 6.25 ppm (6 hours/day, 10 days). However, similar effects were not observed in rat cells exposed to higher levels of BD (10,000 ppm for 2 days).

Sister chromatid exchange is a recombinational event in which nucleic acid is exchanged between the two sister chromatids in each chromosome. It is thought to result from breaks or nicks in the DNA. Irons et al. described micronuclei as ''* * * chromosome fragments or chromosomes remaining as the result of non-dysjunctional event. Their presence in the circulation is frequently associated with megaloblastic anemia.'' (Ex. 23–12).

In a subsequent study, Filser and Bolt exposed B6C3F$_1$ mice to the same 3 concentrations of BD, 6.25, 62.5 or 625 for 6 hours/day, 5 days/week, for 13 weeks. (Ex. 23–10) Peripheral blood samples were taken from 10 animals per group and scored for polychromatic erythrocytes (PCE) and micronucleated normochromatic erythrocytes (MN–NCE). The MN–NCE response, which reflects an accumulated response, was significantly increased in both sexes at all concentrations of BD, including 6.25 ppm.

Certain metabolites of BD also produce genotoxic effects. These are detailed in a number of reviews (see for example, Ex. 114, 125). Briefly, epoxybutene (the monoepoxide) is mutagenic in bacterial systems in the absence of exogenous metabolic activation. Epoxybutene also reacts with DNA, producing two structurally identical adducts and has been shown to induce sister chromatid exchanges in Chinese hamster ovary cells and in mouse bone marrow *in vivo*.

IARC in its review concluded that the diepoxide, 1,2,:3,4-diepoxybutane, induced DNA crosslinks in mouse hepatocytes and, like epoxybutene, is mutagenic without metabolic activation. As discussed below, BD diepoxide also induced SCE and chromosomal aberrations in cultured cells.

A human cross-sectional study involving a limited number of workers in a Texas BD plant indicated genotoxic effects. (Ex. 118–2D) Peripheral lymphocytes were cultured from 10 non-smoking workers and from age- and gender-matched controls who worked in an area of very low BD exposure (0.03 ppm). Production areas in the plant had a mean exposure of 3.5 ppm BD, with most exposed workers in this sample experiencing exposure of approximately 1 ppm BD.

Standard assays for chromosomal aberrations and a gamma irradiation challenge assay that was designed to detect DNA repair deficiencies were performed. The results of the standard assay indicated that the exposed group had a higher frequency of cells with chromosome aberrations and higher chromatid breaks compared with the control group. This difference was not statistically significant. In the challenge assay, the exposed group had a statistically significant increased frequency of aberrant cells, chromatid breaks, dicentrics (chromosomes having 2 centromeres) and a marginally significant higher frequency of chromosomal deletions than controls. Au and co-workers concluded that cells exposed to BD are likely to have more difficulty in repairing radiation induced damage. (Ex. 118–2D)

To determine the mutagenic potential of both BD and its three metabolite epoxides, Cochrane and Skopek studied effects in human lymphoblastoid cells (TK6) and in splenic T cells from exposed B6C3F$_1$ mice. (Ex. 117–2, p. 195) TK6 cells were exposed for 24 hours to epoxybutene (0–400 uM), 3,4-epoxy-1,2-butanediol (0–800 uM), or diepoxybutane (0–6 uM). All

metabolites were mutagenic at both the *hprt* (hypoxanthine-guanine phosphoribosyl transferase) and tk (thymidine kinase) loci, with diepoxybutane being active at concentrations 100 times lower than epoxybutane or epoxybutanediol.

They also studied mice exposed to 625 ppm BD for 2 weeks and found a 3-fold increase in *hprt* mutation frequency in splenic T cells compared with controls. They also intended to give daily IP doses of epoxybutene (60, 80 or 100 mg/kg) or diepoxybutane (7, 14, or 21 mg/kg) every other day for three days. However, only animals given the lowest dose of the diepoxide received three doses because of lethality. After two weeks of expression time, cells were isolated for determination of mutation frequency. Both exposure regimens resulted in increased mutation frequency. For example, at the highest exposure to epoxybutene, the average mutation frequency was 8.6×10^{6}, while the diepoxide exposed group had a frequency of 13×10^{6}, compared to a control mutation frequency of 1.2×10^{6}.

Cochrane and Skopek used denaturing gradient gel electrophoresis to study the nature of the splenic T cell *hprt* mutants in the DNA. They found about half were frameshift mutations. A potential ''hotspot'' was also described in which a plus one (+1) frameshift mutation in a run of six guanine bases was observed in four BD-exposed mice, in four expoxybutene-exposed mice and in two mice exposed to the diepoxide. They observed both G:C and A:T base pair substitutions in the epoxide treated group; however, similar to the findings of Recio, et al. (described below), A:T substitutions were observed only in the BD-treated group. The authors offered no hypothesis for this observation. These researchers also noted a significant correlation of dicentrics with the presence of a BD metabolite, (1,2-dihydroxy-4-(N-acetyl-cysteinyl-S)butane) in the urine of exposed workers. They further concluded that:

> This study indicates that the workers had exposure-induced mutagenic effects. Together with the observation of gene mutation in a subset of the population, this study indicates that the current occupational exposure to butadiene may not be safe to workers. (Ex. 118–2D)

An abstract by Hallberg submitted to the Environmental Mutagenesis Society describes a host-cell reaction assay in which lymphocytes transfected with a plasmid with an inactive chloramphenicol acetyl transferase (CAT) reporter gene were challenged to repair the damaged plasmid and reactivate the CAT gene. No effect was noted among cells of workers exposed to 0.3 ppm benzene; however, BD-exposed workers (mean exposure 3 ppm) had significantly reduced DNA repair capacity ($p=0.001$). The authors believed that this finding confirmed the DNA repair defect due to BD exposure observed in the Au et al. study's challenge assay. (Ex. 118–2D)

Ward and co-workers reported the results of a preliminary study to determine whether a biomarker for BD exposure and a biomarker for the genetic effect of BD exposure could be detected in BD-exposed workers. (Ex. 118–12A) The biomarker for exposure was excretion of a urinary metabolite of BD, (1,2-dihydroxy-4-(n-acetylcysteinyl-S)butane. The genetic biomarker was the frequency of lymphocytes containing mutations at the hypoxanthine-guanine phosphoribosyl transferase (*hprt*) locus. Study subjects included 20 subjects from a BD production plant and 9 from the authors' university; all were verified non-smokers. Seven workers were in areas or at jobs that were ''considered likely to expose them to higher levels of butadiene than in other parts of the plant.'' Ten worked in areas where the likelihood of BD exposure was low. Three ''variable'' employees worked in both types of jobs or areas. *hprt* assays of 6 of the 7 high exposure group and 5 of the 6 non-exposed groups were completed at the time of the report. Air sampling was used to estimate exposure. In the production area, the mean was approximately 3.5 ppm, with most samples below 1 ppm. In the central control area (lower exposure) the mean was 0.03 ppm. The frequency of mutant lymphocytes in the high-exposure group compared with either the low- or no-exposure group was significantly increased. The low- and non-exposed groups were not significantly different from each other in mutant frequencies.

Similarly, the concentration of the BD metabolite in urine was significantly greater in the high exposure group than in the lower- or non-exposed groups. There was a strong correlation among exposed subjects between the level of metabolite in urine and the frequency of the *hprt* mutants ($r=0.85$). (Ex. 118–2A)

Another study of humans for potential cytogenetic effects of BD exposure was reported recently by Sorsa et al. in which peripheral blood was drawn from 40 BD production facility workers and from 30 controls chosen from other departments of the same plants, roughly matched for age and smoking habits. (Ex. 124) Chromosome aberrations, micronuclei and sister-chromatid exchanges were analyzed. No exposure related effects were seen in any of the cytogenetic endpoints. The typical exposure was reported as less than 3 ppm. (Ex. 124)

Among the limited number of human studies involving BD exposed workers is that of Osterman-Golker who evaluated post-exposure adduct formation in the hemoglobin of mice, rats, and a small number of workers. (Ex. 117–2, p. 127) Mice and rats were exposed at 0, 2, 10, or 100 ppm for 6 hours per day, 5 days per week for 4 weeks and their blood tested for the presence and quantity of the BD metabolite, 1,2-epoxybutene, forming an adduct with the N-terminal valine of hemoglobin. The result was a linear response for mice at 2, 10 and 100 ppm; and, for rats at 2 and 10 ppm, with the 100 ppm dose group deviating from linearity. In addition, while the adduct level per gram of globin in the 100 ppm rats was about 4 times lower than the level observed in mice exposed to 100 ppm BD, at lower exposures, the adduct levels were similar.

In the portion of the study dealing with effects on humans, blood was taken from four workers in two areas of a chemical production plant with known BD exposure, and five workers from two non-production areas where BD concentrations were low. In the higher exposure area, the mean BD exposure was about 3.5 ppm, as determined by environmental sampling. The lower exposure areas had a mean BD level of about 0.03 ppm. On a mole of adduct per gram of hemoglobin level, the adduct levels in the higher BD exposed workers were 70 to 100 times lower than those of either the rat or mice exposed at the 2 ppm level discussed above. Production workers had adduct levels ranging from 1.1 to 2.6 pmol/g globin. Most controls in the study were below the level of detection of the assay (0.5 pmol adduct/ g globin). (Two heavy smokers reported from a previous study had higher adduct levels than non-smokers; their levels approached those observed in BD exposed workers and were consistent with the amount of BD in mainstream smoke.)

Similar results for mice and rats exposed to BD were reported by Albrecht et al. (Ex. 117–2, p. 135) In this study which exposed the rodents to 0, 50, 200, 500 or 1300 ppm for 6 hours/ day, for 5 consecutive days, BD monoepoxide adduct levels in the hemoglobin of mice were about five times that of the rat at most BD exposure concentrations. Humans were not studied in this report.

Another observation pertaining to human cytogenetics with potentially important implications for BD-induced

human disease is contained in a report by Wiencke and Kelsey. (Ex. 117–2, p. 265) These researchers studied the impact of the BD metabolite, diepoxybutane, exposure on sister chromatid exchange (SCE) frequencies in several groups of human blood cell cultures (n=173 healthy workers). They discovered that the study populations were bimodally distributed according to their sensitivity to induction of SCEs when cell cultures were exposed to 6 uM diepoxybutane. Wiencke and Kelsey reported that they had observed in earlier studies that ''genetic deficiency of glutathione S-transferase type u leads to bimodal induction of SCEs by epoxide substrates of the isozyme'' and that cells from individuals with the deficiency had SCE induction scores that were significantly higher than those observed in the general population. (Ex. 117–2, p. 271) Approximately 20% of the tested groups were sensitive to induction of SCE and the remaining 80% were relatively insensitive.[1] Subsequent testing indicated that the sensitive population was also sensitive to induction of chromosomal aberrations by diepoxybutane with significant increases in the frequencies of chromatid deletions, isochromatid deletions, chromatid exchanges and total aberrations. The relevance of these findings in not yet clear; however, they may indicate that certain subsets of the population are more highly susceptible to the effects of this mutagenic metabolite of BD.

Recio et al. used transgenic mice containing a shuttle vector with a recoverable lac 1 gene to study *in vivo* mutagenicity of BD and the spectrum of mutations produced in various tissues. (Ex. 118–7D) Mice were exposed to 62.5, 625 or 1250 ppm BD for 4 weeks (5 days/week, 6 hours/day). The investigators extracted DNA from bone marrow and determined mutagenicity at the lac 1 transgene.

The mutant DNA was sequenced. Dose-dependent mutagenicity—up to a 3-fold increase over air controls—was observed among mice exposed at 625 or 1250 ppm. Although a number of differences in patterns were noted, the most striking was that sequence analysis indicated an increased frequency of *in vivo* point mutations induced by BD exposure at adenine and thymine (A:T) base pairs following inhalation.

In further studies of BD-exposed transgenic mice, Sisk and co-workers exposed male $B6C3F_1$ mice to 0, 62.5, 625, or 1250 ppm, BD for 4 weeks (6 hour/day, 6 days/week). (Ex. 118–7Q) Bone marrow cells were isolated and mutation frequency and spectrum evaluated. Lac 1 mutation frequencies were significantly increased at all 3 exposure levels and were dose-responsive in the 62.5 and 625 ppm BD-exposed mice, compared to controls. A plateau in mutation frequencies was observed at 1250 ppm BD-exposed mice, perhaps indicating saturation or mutant loss due to the effects of high level exposure.

When the mutants were sequenced, several from the same animal were found to have identical mutations. Although they might have arisen independently, Sisk et al. felt that this was likely due to clonal expansion of a bone marrow cell with a mutated lac 1 gene.

As had Recio et al., Sisk et al. observed a higher frequency of mutations at A:T sites in the exposed mice DNA, compared with controls. A:T to G:C transitions comprised only 2% of the background mutations, but made up 15% of those in the exposed mice.

Sisk et al. concluded that their observation coupled with *in vitro* studies ''* * * suggest that BD may mutate hematopoietic stem cells.'' (Ex. 118–7Q, p. 476)

As discussed in the animal carcinogenicity section in this preamble, BD-induced mouse tumors have been found to have activated proto-oncogenes. Specifically, the K-ras oncogene is activated and is the most commonly detected oncogene in humans. (Ex. 129)

OSHA concludes that BD is mutagenic in a host of tests which show point and frameshift mutations, *hprt* mutations, chromosome breakage, and SCEs in both animals and humans. The data suggest that mice are more susceptible than rats to these alterations. In addition, certain subsets of the human population may be more susceptible to the effects of BD exposure than others (based on the Wiencke and Kelsey study of human blood cell cultures, Ex. 117–2, p. 265). OSHA further notes with concern the fact that the data suggest that BD exposure at relatively low levels adversely affects DNA repair mechanisms in humans and is associated with mutational effects.

5. Metabolism

In vitro genotoxicity studies have shown that BD is mutagenic only after it is metabolically activated. Biotransformation is probably also important to the carcinogenicity of this gas. It is thought that the formation of epoxides, specifically epoxybutene, also termed the ''monoepoxide'' and 1,2:3,4-diepoxybutane, termed the ''diepoxide,'' is required for activity and that the reaction is cytochrome P450 mediated[2]. Both the mono- and diepoxide are mutagenic in the Salmonella assay, with the diepoxide being more active. The reactive epoxides can bind to DNA, and formation of DNA adducts is hypothesized to initiate a series of events leading to malignancy.

As described earlier, for most cancer sites, mice are more sensitive than rats to the carcinogenic effects of BD exposure. Studies of the metabolism of BD have been undertaken in an attempt to elucidate the contributions of dose-metric factors for the observed differences in carcinogenicity between the species.

Much of the research in this area has been performed at the Chemical Industry Institute of Toxicology and in German laboratories. Work on metabolism of BD was described by OSHA in the 1990 proposal. (55 FR 32736 at 32756) OSHA reviewed the current literature in the record and concluded:

1. The rate of metabolism of BD in mice is approximately twice that in rats;

2. Mice accumulate more radiolabelled BD equivalents in a 6 hour exposure than do rats at the same concentration;

3. Mice have about twice the concentration of the metabolite (1,2-epoxy-3-butene) (BMO) in blood as rats exposed at similar concentrations;

4. Over a wide range of exposures, mice received a larger amount of inhaled BD per unit body weight than rats, and had a higher concentration of BMO in the blood than rats (As expected, because of body size differences and breathing rates, and some enzymology);

5. BD is readily absorbed and widely distributed in tissues of both mice and rats, with tissue concentrations per umole BD inhaled higher in mice than in rats, by factors of 15-fold or more;

6. While there are species differences in the amount of BD metabolism at various sites, both mice and rats metabolize BD to the same reactive metabolites suspected of being ultimate carcinogens.

In comments on OSHA's proposal, Dr. Michael Bird of Exxon testified on behalf of the CMA BD Task Group that the mouse ''will attain a significantly higher amount of the epoxides over a longer period of time than the rat. . . or primate when exposed to butadiene.''

[1] For example, in the 58 newspaper workers tested, 24% had greater than 95 SCE/cell, while the remaining 76% had fewer than 80 SCE/cell.

[2] Cytochrome is defined as any of a class of hemoproteins whose principal biologic function is electron transport by virtue of a reversible valency change of its heme iron. Cytochromes are widely distributed in animal and plant tissues.

(Ex. 52, p. 27) Dr. Bird concluded that the differences in metabolism of BD in the species help ''explain the greater sensitivity of the mouse to BD carcinogenic activity.'' He further concluded that the differences in rates of enzyme mediated processes indicate non-human primates have lower internal concentrations of BD or BMO, and ''man is more similar to the primate with respect to 1,2-epoxy-3-butene formation than the rat or mouse.'' (Ex. 52, p. 22) He argued that the mouse may be ''uniquely sensitive '' to BD carcinogenicity due to its greater uptake, faster BD metabolism and ''elimination of the epoxide 1,2-epoxy-3-butene is saturable in mice but not in rats.'' (Ex. 52, p. 21) He felt this observation correlated well with the observed cytogenetic and bone marrow response (seen in mouse, but not rats.)

Others hold an opposing view, e.g., Melnick and Kohn argued that ''[b]ecause the rat appears to be exceptionally insensitive to leukemia/lymphoma induction, the mouse must be considered as the more appropriate model for assessing human risk for lymphatic and hematopoietic cancers.'' (Ex. 130, p. 160)

Dr. Bird urged OSHA to use the monkey data of Dahl, et al. which indicated that the retention rate for BD in primates is over 6 times lower than that for the mouse, in ''drawing any firm conclusions about the cancer risk to humans.'' (Ex. 52, p. 36) During the public hearing, the work of Dahl was presented as a preliminary report. (Ex. 44) Dahl exposed 3 cynomolgus monkeys to BD and measured uptake and metabolism. Each animal was exposed to three concentrations of C^{14}-labeled BD, progressing from 10,300 to 8000 ppm with at least 3 months separating the re-exposure of each monkey. Post-exposure blood was taken. Each animal's breathing frequency and tidal volume was measured.

Dahl and co-workers found BD uptake to be lower in monkeys than in rats. The reported blood levels of the epoxides were also lower in the monkey than the levels reported by Bond et al. in rats and mice.

Dahl et al. attempted to quantitate total BD metabolites through collection of feces, urine and exhaled material though use of cryogenic traps. Measurement of residual labeled material retained in the animals at the end of the 96 hour post exposure period was not determined. HPLC (high-performance liquid chromatography) identification of the trapped material (at 95 C) indicated that only 5 to 15% of the radioactivity was present as monoepoxide.

Melnick and Huff, in reviewing this study, found its significance ''clouded'' because only three animals of unknown age were studied and there was uncertainty about the ability of vacuum line cryogenic distillation alone to identify and quantitate BD metabolites. (Ex. 114, p. 133) In testimony at the public hearing, Dr. James Bond of CIIT acknowledged the limitations of the use of vacuum-line cryogenic distillation as follows:

> * * * there will be some material no matter what kind of vacuum you apply to it * * * simply will not move into the traps. That's referred to as non-volatile material.
>
> We don't know what that material is and I think that's an important component of this study, because, in fact, in many cases it can represent 70 to 80 percent of the material that actually distills out. (Tr. 1/22/91, p. 1553)

Melnick and Huff were also concerned that only the monkeys, not the mice or rats, were anesthetized during exposure and question what impact that might have had on respiratory rates and cardiac output and what the influence might be on inhalation pharmacokinetics of BD. (Ex. 114, p. 133) In their 1992 review, Melnick and Huff concluded that studies to date have not revealed species pharmacokinetic differences of sufficient magnitude ''to account for the reported different toxic or carcinogenic responses in one strain of rats compared to two strains of mice.'' (Ex. 114, p. 134) In post hearing comments Dr. David A. Dankovic of NIOSH reviewed this topic and concluded ''* * * the most prudent course is to base 1,3-butadiene risk assessments on the external exposure concentration, unless substantial improvements are made in the methodology used for obtaining 'internal' dose estimates.'' (Ex. 101, Att. 2, p. 5)

Recent Studies

Recent studies have focused on the metabolism of BD to the epoxides, epoxybutene and diepoxybutane, and their detoxification by epoxide hydrolase and glutathione. Bond et al. recently reviewed BD toxicologic data. (Ex. 118–7G) Epoxybutene and diepoxybutane were reported to be carcinogenic to mice and rats via skin application and/or subcutaneous injection, with the diepoxide having more carcinogenic potency. Bond et al. also concluded that the diepoxide is more mutagenic than the monoepoxide by a factor of nearly 100 on a molar basis. The diepoxide also induces genetic damage *in vitro* mammalian cells (Chinese hamster ovary cells and human peripheral blood lymphocytes). These studies are summarized in this preamble discussion of reproductive effects.

In vitro metabolic studies

In 1992 Csanady et al. reported use of microsomal and cytosolic preparations from livers and lungs of Sprague-Dawley rats, $B6C3F_1$ mice and humans to examine cytochrome P450-dependent metabolism of BD. (Ex. 118–7AA) The preparations were placed in sealed vials and BD was injected by use of a gas-tight syringe. Air samples were taken from the head space at 5 minute intervals and analyzed by gas chromatography for epoxybutene.

Cytochrome P450-dependent metabolism of the monoepoxide to the diepoxide was examined. Enzyme mediated hydrolysis of BMO by epoxide hydrolase was measured. (Non-enzyme mediated hydrolysis was determined using heat-inactivated tissue and none was observed.) Second order rate constants were determined using 100 mM monoepoxide and 10 mM GSH. The human samples were quite variable, with rates ranging from 14 to 98 nmol/min/mg protein.

The maximum rates for BD oxidation to monoepoxide (Vmax) were determined to be highest for mouse liver microsomes[3] (2.6 nmol/mg protein/min); the Vmax values for humans were intermediate, at 1.2 nmol/mg protein/min; the Vmax values for rats was 0.6 nmol/mg protein/min. For lung microsomes, the Vmax in the mouse was found to be similar to the mouse liver rate, but over 10-fold greater than that of either humans or rats.

From these data Csanady et al. calculated a ratio of activation to detoxification for each species tested. These values, expressed as mg cytosolic protein/gm liver [glutathione-S-transferase is a cytosolic enzyme], resulted in the determination of an overall activation:detoxification ratio of 12.3 for the mouse, 1.3 for the rat, and 4.4 for the human samples.

If these *in vitro* liver microsomal studies can be extrapolated to the whole animal *in vivo,* then this implies, as pointed out by Kohn and Melnick, that the mouse produces 2.8 times as much BMO per mol of BD as the human and that the human activation:detoxification ratio is 3.4 times that of the rat. However, the Csanady et al. study demonstrated a wide variability in BD metabolic activity among the 3 human liver microsomes, and a 60-fold variation was found in 10 human liver

[3] A microsome is defined as one of the finely granular elements of protoplasm, resulting from fragmentation (homogenization) of the endoplasmic reticulum.

samples by Seaton et al. (Ex. 118–7N) Kohn and Melnick noted that this human variability in CYP2E1, the P450 enzyme primarily responsible for the activity, suggests that a ''* * * fraction of the human population may be as sensitive to butadiene as mice are.'' (Ex. 131, p. 620).

A study similar to that of Csanady et al., reported by Duescher and Elfarra in 1994, determined that the Vmax/Km ratios for BD metabolism in human and mouse liver microsome were similar and were nearly 3 to 3.5 fold higher than the ratio obtained with rat liver microsomes. (Ex. 128) Duescher and Elfarra suggest that differences between their results and those of Csanady et al. may have been due in part to experimental methodology differences, such as incubation and assay methods. Duescher and Elfarra found that two P450 isozymes, 2A6 and 2EI, were most active in forming BMO of the 7 isozymes tested. They concluded that since human liver microsomes oxidized BD at least as efficiently as mouse liver microsomes (and much more so than rat liver microsomes), this ''suggests that if [BMO] formation rate is the primary factor which leads to toxicity, humans may be at higher risk of expressing BD toxicity than mice or rats, and that the mouse may be the more appropriate animal model for assessing toxicity.'' Duescher and Elfarra felt that since P450/2A6 appears to play a major role in BD oxidation in human liver microsomes, and that it is more similar to that of mouse P450/2A5 than to rat P450/2A1, the mouse may be a better model to use in assessing human risk.

In 1994 Himmelstein et al. hypothesized that ''[S]pecies differences in metabolic activation and detoxification most likely contribute to the difference in carcinogenic potency of BD by modulating the circulating blood levels of the epoxides.'' (Ex. 118–13, Att 3) To address this, Himmelstein and colleagues looked at the levels of BD, BMO, and BDE in blood of rats and mice exposed at 62.5, 625, or 1250 ppm BD. Samples were collected at 2, 3, 4, and 6 hours of exposure for BD and BMO and at 3 and 6 h for the BDE. Blood was collected from mice by cardiac puncture and from rats through an in-dwelling jugular cannula. Melnick and Huff criticized earlier studies which failed to use in-dwelling cannulae.

> Because steady state levels of [monoepoxide] are lower in rats than in mice and because the metabolic elimination rate for this compound is 5 times faster in rats than in mice, any delay in obtaining immediate blood samples would have a much greater effect on analyses in blood samples obtained from rats than those obtained from mice. (Ex. 114, p. 133)

Himmelstein et al. found that the concentration of BD in blood was not directly proportional to the inhaled concentration of BD, suggesting that the uptake of BD was saturable at the highest inhaled concentration. In both rats and mice BD and the BMO blood levels were at steady state at 2, 3, 4 and 6 hours of exposure and declined rapidly when exposure ceased. This is consistent with exhalation being the primary route of elimination of BD. (Ex. 118–7B)

Genter and Recio used Western blot and immunohistochemical analyses to detect P450/2E1 in bone marrow of $B6C3F_1$ mice. (Ex. 118–7T) Although both methods detected the presence of the protein in livers of both male and female mice, non was seen in the bone marrow. The limits of detection were not stated in the report. The author hypothesized the BD might be converted to the monoepoxide in the liver prior to uptake by the bone marrow or that another pathway (e.g., myeloperoxidase) is responsible for BD oxidation in the marrow. Recio and Genter suggest that the greater sensitivity of mice to BD-induced carcinogenicity can be explained in part by the higher levels of both epoxides in the blood of mice compared with that of rats.

Himmelstein et al. furthered this work in 1995 in a report in which they determined levels of the epoxides in livers and lungs of mice and rats exposed to BD. (Ex. 118–7/O) Animals were exposed at 625 or 1250 ppm of BD for 3 or 6 hours. Himmelstein et al. found that in mice exposed to this regimen, the monoepoxide levels were higher in lungs than in livers. Rats at 625 and 1250 ppm had lower concentrations of BMO in lungs and livers than mice. When rats were exposed to 8000 ppm BD, the maximum concentration of BMO in the lung and liver was nearly the same. The diepoxide levels in lungs of mice exposed at 625 and 1250 ppm were 0.71 and 1.5 nmol/g respectively. The diepoxide was not detected in livers or lungs of rats exposed at any tested level.

Himmelstein et al. also observed depletion of glutathione in liver and lung samples from both rodent species. Following 6 hours of exposure, the lungs of mice exhibited greater depletion of GSH than mouse liver, rat liver or rat lung at all concentrations of BD tested. The conclusion reached by the study authors was that their data indicate that GSH depletion is associated with tissue burden of the epoxides and that this target organ dosimetry might help explain some of the non-concordance of cancer sites observed between the species. OSHA notes, however, that while % GSH depletion was highest in the mouse lung, the major increase in depletion was at 1250 ppm BD, while lung tumor incidence was increased in the female mice at 6.25 ppm and in male mice at 62.5 ppm. Depletion of glutathione was dependent on concentration and duration of BD exposure.

Himmelstein et al. stressed the importance of the fact that the diepoxide was detected in the mouse lung but was not quantifiable in the mouse liver, and stated that if the diepoxide was formed in the liver, it is rapidly detoxified or otherwise moved out of the liver. They also found that depletion of glutathione was greater in mouse than rat tissues for similar inhaled concentrations of BD and concluded that conjugation of the monoepoxide with glutathione by glutathione S-transferase is an important detoxification step.

In contrast to rats and mice, lungs and livers from humans had much faster rates of microsomal monoepoxide hydrolysis by epoxide hydrolase compared to cytosolic conjugation with glutathione by the transferase. (Ex. 118–7AA)

Thornton-Manning et al. in 1995 examined the production and disposition of monoepoxide and diepoxide in tissues of rats and mice exposed at 62.5 ppm BD. (Ex. 118–13, Att. 3) They found monoepoxide was above background in blood, bone marrow, heart, lung, fat, spleen and thymus tissues of mice after 2 or 4 hours of exposures to BD. In rats, levels of monoepoxide were increased in blood, fat, spleen and thymus tissues. No increase in monoepoxide in rat lung was observed. The more mutagenic diepoxide was detected in all tissues of the mice examined immediately following 4 hours of exposure. It was detected in heart, lung, fat, spleen and thymus of rats, but at levels 40- to 160-fold lower than those seen in mice.

In mice, the level of diepoxide exceeded the monoepoxide levels immediately after exposure in such target organs as the heart and lungs. Thornton-Manning et al. concluded that the high concentrations of diepoxide in heart and lungs they observed suggested to them that this compound may be particularly important in BD-induced carcinogenesis.

The study authors noted that neither epoxide was detected in rats' liver and was present only in quite low concentrations in the livers of mice. Thornton-Manning et al. found this

surprising since epoxides present in blood in the liver should have yielded values greater than those observed in the liver samples. They hypothesized that it might be due to prior metabolism of the epoxides before reaching the liver or it might be an artifact due to post-exposure metabolism of the epoxides in the liver.

Thornton-Manning et al. did not detect the monoepoxide in rat lungs, and found the diepoxide level to be quite low. In contrast, in the mice they found both epoxides present in lung tissue, with the monoepoxide level present at a concentration less than expected using blood volume values, and the diepoxide level agreeing with that expected as a function of blood volume. Thornton-Manning et al. concluded that these results ''* * * suggest that the lung is capable of metabolizing BDO, but perhaps is less active in metabolizing BDO_2. (Ex. 118–13, Att. 3) Moreover, Thornton-Manning et al. believed that although BD is oxidatively metabolized by similar metabolic pathways in the rats and mice, the quantitative differences in tissue levels between species may be responsible for the increased carcinogenicity of BD in mice.

TABLE V–8.—TISSUE LEVELS [PMOL/GM TISSUE, MEAN±S.E.] OF EPOXYBUTENE AND DIEPOXYBUTANE IN RATS AND MICE FOLLOWING A 4-HOUR EXPOSURE TO 62.5 PPM BD BY INHALATION

Tissue	Epoxybutene		Diepoxybutane	
	Rats	Mice	Rats	Mice
Blood	36±7	295±27	5±1	204±15
Heart	40±16	120±15	3±0.4	144±16
Lung	ND	33±9	0.7±0.2	114±37
Liver	ND	8±4	ND	20±4
Fat	267±14	1302±213	2.6±0.4	98±15
Spleen	7±6	40±19	1.7±0.5	95±12
Thymus	12.5±3.2	104±55	2.7±0.7	109±19
Bone marrow [1]	0.2±0.1	2.3±1.5	ND	1.4±0.3

ND=Not Detected.
[1] Bone marrow data are presented as mean pmol/mg protein ±; n=3 or 4 for each determination. Adapted from Ex. 118–13, Att. 3.

These data are shown in Table V–8.

Seaton et al. examined the activities of cDNA-expressed human cytochrome P450 (CYP) isozymes for their ability to oxidize epoxybutene to diepoxybutane. (Ex. 118–7N) They also determined the rate of formation of the diepoxide by samples of human liver microsomes (n=10) and in mice and rat liver microsomes. Seaton et al. found that two of the cytochrome P450 isozymes, CYP2E1 and CYP3A4, catalyzed oxidation of 80 uM of monoepoxide to detectable levels of diepoxide, and that CYP2E1 catalyzed the reaction at higher levels of monoepoxide (5mM), suggesting the predominance of 2E1 activity at low substrate concentrations. Hepatic microsomes from all 3 species formed the diepoxide when incubated with the monoepoxide. Seaton et al. hypothesized that the difference between these results and those of Csanady et al. (who did not detect the diepoxide when the monoepoxide was substrate in a similar microsomal assay) was due to differences in experimental methodology.

Seaton et al. noted a 25-fold variability in Vmax/Km among the 4 human livers. They reported that Vmax/Km for oxidation of the monoepoxide to the diepoxide for the 4 human samples was 3.8, 1.2, 1.3 and 0.15, while that of the pooled rat samples was 2.8, and the mouse ratio was 9.2.

The authors, using available data, calculated an overall activation/detoxification ratio (Vmax/Km for oxidation of BD to the monoepoxide) taking into account hydrolysis of the monoepoxide by epoxide hydrolase and conjugation with glutathione. The activation/detoxification ratio was estimated at 1295 for the mouse, 157 for rats and 230 for humans. However, Melnick and Kohn point out that ''when yields of microsomal and cytosolic protein content and liver size were considered, the activation to detoxification ratio was only 2.8 times greater in mice than in humans and 3.4 times greater in humans than in rats. These ratios do not take into account inter-individual variability in the activities of the enzymes involved.'' (Ex. 131)

Recently, Seaton et al. studied production of the monoepoxide in whole airways isolated from mouse and rat lung. (Ex. 118–7C) They explained the impetus to use fresh intact tissue by stating that lung subcellular fractions, as employed in experiments by Csanady et al., described above, contained mixtures of cell type ''so that the metabolizing capacities of certain cell populations may have been masked.'' They anticipated that use of airway tissue would allow more precise quantitation of differences in lung metabolism of BD.

Whole airways or bronchioles isolated from both male $B6C3F_1$ mice and male Sprague-Dawley rats were incubated for 60 min with 34 um BD. Levels of 10.4±5.6 nmol epoxybutene/mg protein were detected in mouse lungs, while 2–3 nmol/mg protein was observed in rat lung airway regions. Seaton et al. noted that while the species differences ''are not dramatic,'' they may in part contribute to the differences in carcinogenicity observed in mice and rats.

To characterize conjugation of BD metabolites with glutathione (GSH), Boogard et al. prepared cytosol from lungs and livers of rats and mice and from 6 human donor livers and incubated them with 0.1 to 100 mM diepoxide and labeled glutathione (GSH). (Ex. 118–7J) NMR (nuclear mass resonance) and HPLC techniques were used to characterize and quantitate conjugate formation.

Non-enzymatic reaction was concluded to be negligible. The conjugation rates (Vmax) in mouse and rat livers were similar and 10-fold greater than those observed in the human samples. The initial rate of conjugation (Vmax) was much higher in mouse than rat lung. Both rodent species exhibited higher initial rates of conjugation than human. This led Boogard et al. to conclude that the higher diepoxide levels observed in BD-exposed mice compared with rats ''are not due to differences in hepatic or pulmonary GSH conjugation of BDE (the diepoxide),'' and further that since humans oxidize BD to the epoxides at a low rate, the low activity of GSH conjugation of the diepoxide in human liver cytosol demonstrated in this study ''will not necessarily lead to increased BDE (diepoxide) levels in humans

potentially exposed to BD.'' They also pointed out the need to determine the rate of BDE detoxification by other means, specifically by epoxide hydrolase in all three species.

Studies of Urinary Metabolites of BD

Two metabolites of BD have been identified in urine of exposed animals by Sabourin et al. (Ex. 118–13 Att. 3) These are 1,2-dihydroxy-4-N-acetylcysteinyl-S-)-butane, designated MI, and MII, which is 1-hydroxy-2-N-acetylcysteinyl-S-)-3-butene. (Ex. 118–13–Att. 3)

These mercapturic acids are formed by addition of glutathione (GSH) at either the double bond (MI) or the epoxide (MII). MI is thought to form by conjugation of GSH with butenediol, the hydrolysis product of the monoepoxide, while MII is thought to form from conjugation of the monoepoxide with GSH.

Sabourin et al. measured MI and MII in urine from rats, mice, hamster and monkeys. Mice were observed to excrete 3 to 4 times as much MII as MI, while the hamsters and rats produced about 1.5 times as much MII as MI. The monkeys produced primarily MI.

The ratio of formation of metabolite I to the total formation of the two mercapturic acids, MI and MII, correlated well with the known hepatic epoxide hydrolase activity in the different species, suggesting that the monoepoxide undergoes more rapid conjugation with glutathione in the mouse than in the hamster or rats, and that the least rapid conjugation occurs in the monkey. The epoxide availability is inversely related to the hepatic activity of epoxide hydrolase, which removed the epoxide by hydrolysis.

In 1994, Bechtold et al. published a paper describing a comparison of these metabolites between mice, rats, and humans.[4] In workers exposed to historical atmospheric concentrations of 3 to 4 ppm BD, Bechtold measured urine levels of MI and MII by use of isotope-dilution gas chromatography, and found MI, but not MII, to be readily detectable. Bechtold et al. found that employees who worked in production areas (having 3–4 ppm BD exposure) could be distinguished by this assay from outside controls and that low level human exposure to BD resulted in formation of epoxide.

Bechtold et al. stated in their abstract that since monkeys displayed a higher ratio of MI to MI + MII than mice did, and ''because humans are known to have epoxide hydrolase activities more similar to those of monkeys than mice, we postulated that after inhalation of butadiene, humans would excrete predominantly MI and little MII.'' (Ex. 118–13 Att. 3) Their observations suggested that the predominant pathway for clearance of the monoepoxide in humans is by hydrolysis rather than conjugation with glutathione.

Bechtold et al. found when mice and rats were exposed to 11.7 ppm BD for 4 hours and the ratio of the two metabolites was then measured, for mice, the ratio of MI to MI ± MII (or the % of total which is MI) was 20%, that of rats was 52%, while humans exhibited more than 97% MI. These data also indicate the predominance of clearance by hydrolysis pathways rather than GSH conjugation in the human.

Nauhaus et al. used NMR techniques to study urinary metabolites of rats and mice exposed to ([(1,2,3,4)-^{13}C]-butadiene). (Ex. 118–7I) They characterized metabolites in mouse and rat urine following exposure by inhalation to approximately 800 ppm BD for 5 hours. Urine was collected over 20 hours from exposed and control animals, centrifuged and frozen.

The findings of this study are quite extensive and are briefly summarized as follows. Nine metabolites were detected and chemically identified in mouse urine and 5 in that of rats. Five were similar in the 2 species, though differing markedly in concentration. One was unique to the rat and four to the mouse. Nauhaus et al. observed that ''when normalized to body weight (umol/kg body weight), the amount of diepoxide-derived metabolites was four times greater in mouse urine than in rat urine.'' They further hypothesized that ''the greater body burden of (diepoxide) in the mouse and the ability of rats to detoxify [it] though hydrolysis may be related to the greater toxicity of BD in the mouse.'' Nauhaus et al. found that both mice and rats conjugated the monoepoxide with glutathione, but the rat preferentially conjugated at the two carbon, while the mouse preferentially conjugated at the one carbon. Additionally, the finding of a metabolite of 3-butenal, a proposed intermediate in the oxidation of BD to crotonaldehyde, an animal carcinogen, is suggestive of an alternative carcinogenic pathway for BD. In general, this study supports the *in vitro* findings of Csanady et al. who reported similar rates for BMO conjugation with glutathione between rats and mice. (Ex. 118–7AA)

Interaction of Butadiene With Other Chemicals

Bond et al. described use of available data to simulate the potential interaction of BD with other workplace chemicals. (Ex. 118–7V) Specifically they modeled potential interaction assuming competitive inhibition of BD metabolism by styrene, benzene and ethanol. The model predicted that co-exposure to styrene would reduce the amount of BD metabolized, but that because of its relative insolubility, BD would not effectively inhibit styrene metabolism. Benzene, which, like BD, is metabolized by P450/2E1, was also predicted to be a highly effective inhibitor of BD metabolism because of its solubility in tissues. The models predicted that ethanol would have only a marginal effect on BD metabolism at concentrations of BD ''relevant to human exposure.''

BD and styrene co-exposures often occur in the SBR industry and both are metabolized by oxidation to active metabolites, in major part, by cytochrome P450/2E1. To determine the metabolic effect of joint exposure to BD and styrene, Levans and Bond developed and compared two PBPK models, one with one oxidative pathway and competition between BD and styrene and the other with two oxidation pathways for both BD and styrene. (Ex. 118–7E) For model validation, Levans and Bond exposed male mice to mixtures of BD and styrene of 100 or 1000 ppm BD and 50, 100 or 250 ppm styrene for 8 hours. They used chamber inlet and outlet concentrations to calculate uptake and, when steady-state was reached, calculated the rate of metabolism. They analyzed blood for styrene, styrene oxide, epoxybutene and diepoxybutane by GC–MS.

Leavens and Bond found BD metabolism was inhibited when mice were co-exposed to styrene. The inhibition approached maximum value at co-exposure concentrations of styrene above 100 ppm.

The report also described the preliminary development of pharmacokinetic models to simulate the observed rate of BD metabolism in co-exposed mice. Their results supported the hypothesis that ''more than one isozyme of P450 metabolized BD and styrene and competition does not occur between BD and styrene for all isozymes.'' They were unable to accurately predict blood concentrations of styrene following exposure, and felt that '' perhaps the diepoxide may inhibit metabolism of styrene by competing for the same P450 enzyme.''

[4] A preliminary study on the human population of this study is described in the section of this preamble dealing with the genetic toxicology of BD exposure.

Although preliminary in nature and reflecting effects of relatively high exposures, these observations of interactions between styrene and BD exposure may have implications for the observed pattern of BD-induced effects in human populations jointly exposed. Specifically, the cancer effects seen in SBR production workers may underestimate the effects of BD with no styrene or benzene exposure.

Pharmacokinetic Modeling of BD Metabolism

In a recent publication, Bond et al. reviewed the results of application of a number of physiologically-based pharmacokinetic (PBPK) dosimetry models. (Ex. 118–7M) They noted that three of the models which included monoepoxide disposition (Kohn and Melnick, Johanson and Filser, Medinsky) predicted that, for any BD exposure concentration, steady-state monoepoxide levels will be higher for mice than for rats. Bond et al. further observed that ''while the three models accurately predict BD uptake in rats and mice, they overestimate the circulating blood concentrations of (monoepoxide) in these species compared to those experimentally measured by Himmelstein.'' Their results also led Bond et al. to conclude that the disagreement between model predictions for the monoepoxide and experimental data suggests that the structure and/or parameter values employed in these models are not accurate for predicting blood levels of BD epoxides, and conclusions based on model predictions of BD epoxide levels in blood or tissue may be wrong.'' (Ex. 118–7M, p. 168) OSHA agrees with these authors that BD epoxide levels should not be used in assessing risk. In the discussion, the authors pointed to the need for inclusion of diepoxide toxicokinetics (as well as that of the monoepoxide) in future modeling exercises, since they believe the diepoxide to be the ultimate carcinogenic metabolite of BD.

Kohn and Melnick, in a recent publication, used available data and attempted to apply a PBPK model to see whether it was consistent with observed *in vivo* uptake and metabolism. (Ex. 131) The model included compartments for rapidly and for slowly perfused tissues. Rate equations for monoepoxide formation, its hydrolysis, and for conjugation with glutathione were included.

Kohn and Melnick acknowledged numerous sources of uncertainty in applying the model to the data (in which there are many gaps), necessitating various assumptions. Their calculations led them to conclude that the ''model reproduces whole-body observations for the mouse and rat'' and that it predicts that ''inhalation uptake of butadiene and formation and retention of epoxybutene are controlled to a much greater extent by physiological parameters than by biochemical parameters. . . '' (Ex. 131)

When Kohn and Melnick interchanged the biochemical parameters in the mouse and human models to see if ''the differences in calculated net uptake of butadiene among the three species were due to differences in metabolic activity,'' they found that use of human parameters in the mouse model decreased the level of absorption of BD, but not to a level as low as that of the human. Kohn and Melnick noted that the model predictions of epoxybutene levels in the heart and lung of mice and rats failed to account for the observation that mice, but not rats, develop tumors at these sites. Kohn and Melnick suggested that factors other than epoxybutene levels, not accounted for in the model, are probably crucial to induction of carcinogenesis.

Conclusions

Many metabolism studies have been conducted both *in vitro* and *in vivo*, mostly in mice and rats, to determine the BD metabolic, distribution, and elimination processes, and these studies have been extended in attempts to explain, at least in part, the greater carcinogenic potency of BD in the mouse, whether the mouse or the rat is a better surrogate for human cancer and reproductive risk assessment, and what is the proper dose-metric to use in dose-response assessments. The question of whether the mouse or the rat is a better model for the human on the basis of tumor response is partly addressed in the risk assessment section of this preamble. This section more specifically considers whether these metabolic studies in total can explain the different cancer responses and potencies observed in the mouse, rat, and human. What is clear throughout the record is that most scientists who study the topic consider not BD itself, but the major epoxide metabolites of BD, BMO and BDE and 1, 2-epoxybutane-3,4-diol, to be the putative carcinogenic agents. Most of this research has focused on the relative species production of BMO and BDE. Both BMO and BDO have been reported in early studies to be carcinogenic to mice and rats via skin application and/or subcutaneous injection, with BDO being somewhat more potent. (Ex. 23–88, Ex. 125).

Metabolism of BD to BMO in both the liver and lung of mice, rats and humans is by the P450 oxidation pathway, with CYP2E1 and CYP1A6 being the major enzymes. Based on the studies reviewed by OSHA, overall the mouse metabolizes BD to the monoepoxide and the diepoxide in these organs at a faster rate than do the rat and human. This is supported by the following evidence: (1) The mouse has higher BMO and BDE levels in blood, lung, and liver (i.e., see Ex. 118–7S, Ex. 118–7D, and Ex. 118–13), which are the target organs for cancer in the mouse but not the rat; (2) the mouse has higher *in vitro* lung and liver microsome Vmax/Km ratios for both BD and BMO metabolism than do rats or humans (Ex. 118–7AA); and (3) the mouse has higher hemoglobin-BMO adduct levels than rats and much higher levels than humans. (Ex. 118–7Y) A major exception to the findings of these studies is the study by Duescher and Elfarra, who found the *in vitro* BD Vmax/km ratios to be the same in mice and human liver microsomes and 3–4 times higher than they were in rats, suggesting that mice and humans have similar BD metabolic potential, at least in the liver. (Ex. 128) Large variations, about 60 fold, were found among 10 human liver microsome BD metabolic activities. (Ex. 118–7N) A recent BD *in vitro* metabolism study by Seaton et al. on whole rat and mouse lung airway isolates found that the mouse produced about twice the amount of BMO as the rat (this difference could not explain the difference between mouse and rat tumor incidence). (Ex. 118–7C)

BMO and BDE were also measured in heart, spleen, thymus, and bone marrow (target sites for mouse but not rat tumors) following 4 hour BD inhalation exposure (62.5 ppm) to mice and rats. (Ex. 118–13) In these tissues, mouse BMO and BDE levels were 3 to 55 fold higher than rat levels for the same metabolites, although the mice organ levels of these metabolites correlated poorly with the mouse target organ cancer response at this exposure level. Only high BDE levels in the mouse lung were consistent with the mortality adjusted cancer incidence (see hazard identification—animal studies section, Ex. 114). This suggests that BD metabolite tissue levels can, at best, only partly explain differences in carcinogenic response. Differences in both species and tissue sensitivity must also be accounted for.

The Thornton-Manning and other studies also provided information about BD elimination. (Ex. 118–7I) With higher experimental exposure levels, the major route of elimination of BD is via expiration. Elimination of BMO occurs

by different pathways in different species and different organs. At higher BD exposure concentrations, some BMO is expired. The mouse liver and lung appear to eliminate BMO predominantly by direct conjugation with GSH[5]. For the rat there is approximately equal elimination by the GSH and EH mediated pathways, while for the human and monkey hydrolysis to butanediol is the major pathway for excretion. (Ex. 118–13 Att. 3) This species elimination pathway difference is a partial explanation for the higher levels of both BMO and BDE seen in the mouse, assuming that most of the BD metabolism takes place in the liver. With respect to the bone marrow BD distribution and metabolism, mouse levels of the BD metabolites in the bone marrow were lower than at any of the other target organs studied. (Ex. 118–13) *In vitro* studies by Gentler and Recio have found no detectable P4502E1 in the bone marrow of $B6C3F_1$ mice. (Ex. 118–7T) These authors conclude that this ''suggests that BD is converted to BMO outside of bone marrow and is subsequently concentrated in bone marrow, or that the conversion of BD to BMO occurs by an alternate enzymatic pathway within the bone marrow.'' The latter appears to be the more likely since Maniglier-Poulet and co-workers showed that *in vitro* BD metabolism to BMO in both $B6C3F_1$ mouse and human bone marrow occur by a peroxidase-mediated process and not via the P450 cytochrome system. (Ex. L–133) Since in their system both human and mouse bone marrow generated about the same amount of BMO/cell, this suggests that both BD distribution to bone marrow and local metabolic reactions should be considered in species-to-species extrapolations and in PBPK modeling.

Inclusion of bone marrow local reactions becomes even more important when considering the animal species to use for modeling human cancer. BD is genotoxic in the bone marrow of mice, but not in rats. (Tice et al. 1987; Cunningham et al. 1986, reported in Ex. 131) BD and BMO have been implicated as affecting primitive hematopoietic bone marrow stem and progenitor cells related to both T-cell leukemia and anemia in the mouse. (Irons et al., 1993, in Ex. 117–2) BD causes lymphoma in mice, but no lymphoma or leukemia in rats even at 8,000 ppm. Furthermore, the body of epidemiologic evidence strongly indicates that BD exposure poses an increased risk of human leukemia (see the epidemiologic section and especially Ex. 117–1).

Fat storage of BD during exposure, and release following cessation of exposure, is also a major concern, both in estimating target organ levels and in determining species differences. There is little in the record on the effect of fat storage and release. In the Thornton-Manning study discussed above, both mouse and rat fat levels of both BMO and BDE declined rapidly following cessation of exposure, suggesting little lingering effect. However, Kohn and Melnick present a model in which post-exposure release of BD from the fat would result in extended epoxide production in humans in contrast with the mouse. (Ex. 131)

Bond et al. suggest that the more rapid metabolism of BD to BMO in the mouse, and the more rapid EH BMO elimination pathways in the rat and human may be an explanation for lower, if any, BDE levels seen in rat and human liver microsomes and why BD will not be carcinogenic to humans at exposure levels seen in the environment or the workplace. (Ex. 130) They also conclude that ''Since significant tumor induction in male rats occurs only at 8000 ppm BD, BMO levels are probably not predictive of a carcinogenic response.'' Thornton-Manning et al. characterize the peak levels of BDE in the mouse lung and heart as being either greater than or equivalent to peak levels of BMO, and suggest ''that the formation of BDE may be more important than the formation of BMO in the ultimate carcinogenicity of BD.'' (Ex. 118–13) However, BMO levels in these organs were also quite high, and were higher than BDE levels in blood and bone marrow, target organs for hematopoietic system cancers. OSHA believes that the evidence is not sufficient to dismiss the potential contribution of BMO to mouse, rat or human carcinogenicity; to conclude that BDE should be considered more actively carcinogenic than BMO; or to find that BDE levels are sufficiently characterized in either mouse or human tissue to be used as the dose metric for BD human risk assessment.

Thus, OSHA concludes, based on the body of metabolic and other evidence presented, and the above discussion, that the mouse is a suitable animal model for the human for BD cancer risk assessment purposes, and that metabolism of BD to active metabolites is probably necessary for carcinogenicity. However, while the uptake, distribution, and metabolism of BD to active carcinogenic agents are important, local BD metabolic reactions and specific species sensitivities appear to have at least as large an impact on BD potency in the various species. This is likely to be especially true in the human, whose metabolic processes appear to be much more variable with respect to BD. Thus, although the metabolism studies provide insight into BD's metabolic processes in various species and organs (with the possible exception of mouse lung tumorigenicity related to lung BDE levels and protein cross linking), OSHA finds that too many questions remain unanswered, both with PBPK modeling efforts and with actual *in vivo* measurements (and the lack of such measurements in humans) to base a quantitative risk assessment on BD metabolite level equivalence between mice and humans. (Ex. L–132)

VI. Quantitative Risk Assessment

A. Introduction

In 1980, the United States Supreme Court ruled on the necessity of a risk assessment in the case of *Industrial Union Department, AFL–CIO* v. *American Petroleum Institute,* 448 U.S. (607), the ''Benzene Decision.'' The United States Supreme Court concluded that the Occupational Safety and Health (OSH) Act requires, prior to issuance of a standard, that the new standard be based on substantial evidence in the record considered as a whole, that there is a significant risk of health impairment at existing permissible exposure limits (PELs) and that issuance of the standard will significantly reduce or eliminate that risk. The Court stated that, before the Secretary of Labor can promulgate any permanent health or safety standard, he is required to make a threshold finding that a place of employment is unsafe in the sense that significant risks are present and can be eliminated or lessened by a change in practices. (448 U.S. 642)

In 1981, the Court's ruling on the OSHA's Cotton Dust Standard (*American Textile Manufacturers Institute* v. *Donovan, 452 U.S. 490 (1981)*) reaffirmed its previous position in the Benzene Decision, that a risk assessment is not only appropriate, but that OSHA is required to identify significant health risk to workers and to determine if a proposed standard will achieve a reduction in that risk, and OSHA as a matter of policy agrees that assessments should be put into quantitative terms to the extent possible.

For this rulemaking, OSHA has conducted a quantitative risk assessment to estimate the excess risk for cancer and consequently for premature deaths associated with

[5] One exception: Seaton et al. found evidence ''that in mouse airways hydrolysis of BMO by epoxide hydrolase (EH) contributes to BMO detoxification to a greater extent than does glutathione conjugation.'' (Ex. 118–7C)

exposure to an 8-hour time-weighted-average (TWA), 5 days/week, 50 weeks/year, 45-year exposure to BD at concentrations ranging from 0.1 to 5 ppm, the range of permissible exposure limits (PELs) considered by OSHA in this rulemaking. The data used in the quantitative risk assessment were from a National Toxicology Program (NTP) chronic inhalation study in which $B_6C_3F_1$ mice of both sexes were exposed to either ambient air or BD exposure concentrations ranging from 6.25 to 200 ppm, known as NTP II. (Ex. 90) For seven gender-tumor site combinations, multistage Weibull time-to-tumor models were fit to these NTP II data. The best fitting models were chosen via a log-likelihood ratio test.

OSHA's maximum likelihood estimate (MLE) of the excess risk of developing cancer and subsequent premature death as a result of an 8-hour TWA occupational lifetime exposure to 2 ppm BD, the PEL proposed by OSHA in 1990, was 16.2 per 1,000 workers, based on the most sensitive gender-tumor site combination, female mouse lung tumors. If the occupational lifetime 8-hour time-weighted-average (TWA) exposure level is lowered to 1 ppm BD, based on female mouse lung tumors, the estimate of excess cancer and premature death drops to 8.1 per 1,000 workers. In other words, an 8-hour TWA lifetime occupational exposure reduction from 2 ppm to 1 ppm BD would be expected to prevent, on average, 8 additional cases of cancer and probable premature deaths per 1,000 exposed workers. Based on the individual tumor site dose-response data, which were best characterized by a 1-stage Weibull time-to-tumor model, (male-lymphoma, male-lung, female-lymphoma and ovarian), on average, one would expect there to be between 1 and 6 fewer excess cases of cancer per 1,000 workers based on a 8-hour TWA occupational lifetime exposure to BD at 1 ppm versus BD at 2 ppm. Estimates of leukemia deaths at the former 8-hour TWA PEL of 1,000 ppm of BD, for an occupational lifetime, are not presented because contemporary BD exposures are generally far lower than this level.

B. Assessment of Carcinogenic Risk

1. Choice of Data Base for Quantitative Risk Assessment

The choice of data provides the platform for a quantitative risk assessment (QRA). Either animal studies which evaluate the dose-response relationship between BD exposure and tumorigenesis or epidemiological dose-response data may be suitable sources of data.

Estimates of the quantitative risks to humans can be based on the experience of animals from a chronic lifetime exposure study. Chronic lifetime inhalation bioassays with rats and mice generally last 2 years or two-thirds of the lifespan of the animal. (Ex. 114) These types of studies provide insight into the nature of the relationship between exposure concentration, duration and resulting carcinogenic response under a controlled environment. Furthermore, some researchers have estimated a variety of measures of dose of BD, including inhaled and absorbed dose as well as BD metabolites, to estimate human risks based on the observed dose-response relationship of animals in a bioassay; the form of the dose used in a dose-response analyses is called the dose-metric.

The carcinogenicity of lifetime inhalation of BD was studied in Sprague-Dawley rats by the International Institute of Synthetic Rubber Producers (IISRP) and in $B_6C_3F_1$ mice by the National Toxicology Program. The IISRP sponsored a two-year inhalation bioassay of Sprague-Dawley rats performed at Hazelton Laboratories Europe (HLE). (Ex. 2–31) Groups of 110 male and female Sprague-Dawley rats were exposed for 6-hours per day, 5 days per week to 0, 1,000, or 8,000 parts per million (ppm) of BD. The males were exposed for 111 weeks and the females for 105 weeks. Statistically significant increased rates of tumors were found in both male and female rats. Among exposed male rats, there were increased occurrences of pancreatic and testicular tumors and among the exposed female rats there were higher incidence rates of uterine, zymbal gland, mammary and thyroid tumors than in the control groups.

The National Toxicology Program (NTP) has performed two chronic inhalation bioassays using $B_6C_3F_1$ mice. (Ex. 23–1; 90; 96) The first study, NTP I, was intended to be a two-year bioassay, exposing groups of 50 male and female mice to 0, 625, or 1,250 ppm of BD for a 6-hour day, 5 days/week. The study was prematurely curtailed at 60 weeks for the males 61 weeks for the females caused by an unusually high cancer mortality rate due to malignant neoplasms in multiple organs. Despite some weaknesses in the way the study was conducted, the results of this study show that BD is clearly carcinogenic in these mice, with statistically significant increases in malignant lymphomas, heart hemangiosarcomas, lung tumors, and forestomach tumors in comparison to the controls for exposed male and female mice. (Ex. 90)

The second NTP BD chronic inhalation bioassay, NTP II, had groups of 70 (except for the group exposed to the highest concentration, which contained 90) male and female mice exposed to concentrations of 0, 6.25, 20, 62.5, 200 and 625 ppm for 6 hours/day, 5 days/week for up to 104 weeks. The NTP II bioassay provided lower exposures, closer to prevailing occupational exposure levels, than the NTP I and HLE chronic inhalation studies. The NTP II supported the pattern of carcinogenic response found in NTP I. Both male and female mice exposed to BD developed tumors at multiple sites including: lymphomas, heart hemangiosarcomas, and tumors of the lung, liver, forestomach, and Harderian gland (an accessory lacrimal gland at the inner corner of the eye in animals; they are rudimentary in man). Reproductive tissues were also adversely affected. Among the exposed males there were significant increases in tumors of the preputial gland; among females there were significant increases in the incidence of ovarian and mammary tumors.

In 1996, a retrospective cohort study by Delzell and co-workers of about 18,000 men who worked in North American synthetic rubber plants was submitted to OSHA. (Ex. 117–1) In this study researchers derived estimates of occupational exposure to BD using a variety of resources, such as work histories, engineering data, production notes, and employees' institutional memories. In their October 2, 1995 report Dr. Delzell et al., characterized their effort as follows:

> Retrospective quantitative exposure estimation was done to increase the power of the study to detect associations and to assist with the assessment of the impact of specific exposure levels on mortality from leukemia and other lymphopoietic cancers. (Ex. 117–1)

In April 1996, Dr. Delzell expressed concern with possible discrepancies between estimated cumulative exposures and actual measurements. (Ex. 118–2) OSHA believes that in a well-conducted study, retrospective exposure estimates can be reasonable surrogates for true exposures; misclassifications or uncertainty can decrease the precision of the risk estimates derived from such a study, but the problem must be severe and widespread to invalidate the basic findings.

At the time of publication of the proposed standard on occupational exposure to BD (August 1990), only the NTP I mouse and HLE rat bioassays were available for quantitative risk assessments (QRA). Presented in Table

V–9 is an overview of authorship and data sets used in the various QRAs submitted to the OSHA docket. With one exception, the rest of the QRA's in the BD Docket have relied on animal chronic exposure lifetime bioassays. Each of the five risk assessments discussed in the proposal based its quantitative risk assessment on one or both of the higher-exposure chronic bioassays (exposure groups exposed to BD concentrations ranging between 625–8,000 ppm). (Exs. 17–5; 17–21; 23–19; 28–14; 29–3; 32–27) The three QRAs conducted using bioassay data subsequent to the publication of the NTP II study used NTP II data with exposures of 6.25–625 ppm BD, closer to actual occupational exposures, for calculating their best estimates of risk. (Exs. 90; 118–1b; 32–16)

A summary of each of the ten QRA's follows:

TABLE V–9.—SUMMARY TABLE OF QUANTITATIVE RISK ASSESSMENTS (QRAS) IN ORDER OF THEIR REVIEW IN THE OSHA BD STANDARD

Exhibit	Author	Data-set
90	National Institute for Occupational Safety and Health (NIOSH) (Preliminary).	NTP II[a] bioassay (preliminary).
118–1b	NIOSH	NTP II bioassay.
118–1	NIOSH	Delzell et al. epidemiological study.
17–21	United States EPA Carcinogen Assessment Group (CAG)	NTP I[b] and HLE[c] bioassays; Epidemiological based on Fajen Exposure Data.
32–27	California Occupational Health Program (COHP) of the California Department of Health services (CDHS).	NTP I; HLE bioassays Epidemiological based on Fajen Exposure Data
32–16	Shell Oil Corporation	NTP I, NTP II and HLE bioassays.
17–5	United States EPA Office of Toxic Substances (OTS)	NTP I bioassay.
23–19	ICF/Clement Inc	NTP I bioassay.
29–3	Center for Technology, Policy, and Industrial Development at the Massachusetts Institute of Technology.	NTP I and HLE bioassays.
28–14	Environ Inc	HLE bioassay.

[a] NTP II, The National Toxicology Program, Technical Report 434, 2-year bioassay of $B_6C_3F_1$ mice to 5 exposure groups receiving between 6.25 and 625 parts per million (ppm) of BD

[b] NTP I, The National Toxicology Program, prematurely terminated longtime bioassay of $B_6C_3F_1$ mice to 2 exposure groups receiving either 625 or 1,200 ppm of BD

[c] HLE, Hazelton Laboratories Europe's, lifetime bioassay of Sprague Dawley rats, exposed groups received 1,000 ppm of BD or 8,000 ppm of BD

NIOSH-Quantitative Risk Assessments based on NTP II

In the early 1990's, two QRAs were conducted sequentially by the National Institutes for Occupational Safety and Health (NIOSH). One was a preliminary and the other a final, with the latter using final pathology data for histiocytic sarcomas and one particular type of lymphoma from NTP II. In 1991, NIOSH submitted a preliminary QRA using the then preliminary NTP II tumor pathology data for various individual organ sites (8 from the female mice and 6 from the male mice) to estimate excess cancer risk at different BD exposures over an occupational lifetime. (Ex. 90) For all gender-tumor site analyses, NIOSH excluded the 625 ppm exposure group in its best estimate of risk since the plethora of competing tumors[6] in this high exposure group provide less information for a dose-response analysis of individual tumor sites than do data from some of the lower exposure groups. Another reason for the exclusion was that the dose-time-response relationship in mice is saturated for exposures above 500 ppm and the data would thus provide very little additional information for low dose extrapolation. NIOSH's QRA relied on an allometric conversion of body weight to the three-quarters power, $(mg/kg)^{3/4}$, and equated a 900-day-old mouse to a 74-year old human. To avoid duplication of risks, NIOSH presented only maximum likelihood estimates based on the aggregate of all types of lymphomas even though dose-response data were also available for the lymphocytic lymphoma subset.

Of the fourteen gender-tumor site data sets NIOSH modeled to extrapolate animal data to humans, 12 (86%) yielded excess risks greater than 2 cancer deaths per 1,000 workers, given an 8-hour TWA lifetime occupational exposure of 1 ppm BD. Estimates of excess risks to workers based on the best fitting models for each of the six dose-time-response relationships for male tumor sites were between 0.4 and 15.0 per 1,000 workers assuming an 8-hour TWA, 45 year occupational exposure to 1 ppm BD. Among estimates based on male mice's dose-response data, the lowest and highest excess risk estimates were from the heart hemangiosarcoma and Harderian gland dose-response relationships, respectively. For estimates of excess risk based on either gender's set of individual tumor dose-response relationships, only the heart hemangiosarcoma data predicted a risk of less than 1 per 1,000 workers with an occupational lifetime exposure of 1 ppm: these data predicted 0.4 and 3×10^{-3} excess cancer cases per 1,000 workers based on the best fitting models for male and female mice, respectively.

Based on tissue sites in females, the excess risk estimates for 8-hour TWA occupational lifetime exposure to 1 ppm BD range between 4 and 31 per 1,000 workers.

NIOSH presented its findings for lifetime exposure to 2 ppm as follows:

> Based on tumors at the most sensitive site, the female mouse lung [assuming $(mg/kg)^{3/4}$ conversion], our maximum likelihood estimates of the projected human increased risk of cancer due to a lifetime occupational exposure to BD at a TWA PEL of 2 ppm is approximately 60 in 1,000 (workers). (Ex. 90)

For the linear models, if scaling were on a (mg/kg) basis rather than the $(mg/kg)^{3/4}$ used by NIOSH for allometric conversion, the revised estimate of excess cancer risk for an 8-hour TWA occupational lifetime exposure to 2 ppm BD would decrease approximately 6 fold to 9.2 per 1,000 workers based on the same female mouse lung tumor data.

In 1993, NIOSH finalized its estimates of excess risk caused by occupational exposure based on the tumorigenesis

[6] Competing tumors refers to the lack of opportunity of a later developing tumor to express itself due to the occurrence of early developing lethal tumor; Among the 625 ppm exposure group lymphocytic lymphomas were mortal early developing tumors which prevented later developing disease such as heart hemangiosarcomas from possibly developing.

experience of mice in the NTP II study. (Ex. 118–1B) The rounded maximum likelihood estimates (MLE) from the final QRA are presented in Table V–10. NIOSH expanded the gender-tumor sites to include histiocytic sarcoma for both male and female mice. NIOSH chose to present only its risk estimate based on lymphocytic lymphoma, rather than an assessment based on the aggregate of lymphomas. In the preliminary and final NIOSH QRAs, 1-stage time-to-tumor models'' rounded estimates of risk associated with lifetime exposure to 1 ppm BD ranged from 1 to 30 excess cancer cases per 1,000 workers, with estimates based on the male-lymphocytic lymphoma and the female-lung dose-response data providing the lower and upper ends of the range of risk, respectively.

As part of its sensitivity analyses, NIOSH derived the estimates of risk based on (1) equating a human lifespan to a mouse equivalent age of 784 days, a figure OSHA has used, and (2) equating a human lifespan to a mouse lifespan of 900 days (a figure more often used by NIOSH.) The best estimates of risk equating human lifespan to a mouse lifespan of 784 days were lower, by about one-third, than those assuming a human lifespan equivalency to 900 days for the mouse, all else held constant.

TABLE V–10.—NIOSH'S [a] FINAL QUANTITATIVE RISK ASSESSMENT'S (QRA) MAXIMUM LIKELIHOOD ESTIMATES (M.L.E.S) [b] PER 1,000 WORKERS OF LIFETIME EXCESS RISK DUE TO AN OCCUPATIONAL [c] EXPOSURE TO 1 PPM OF BD USING BEST FITTING MODELS, AS DESIGNATED BY NUMBER OF STAGES OF THE WEIBULL TIME-TO-TUMOR MODEL

Gender-tumor site	MLE, Final QRA (Stages)
Male mouse:	.....
Forestomach	0.03 (2)
Harderian gland	10 (1)
Heart hemangiosarcoma	0.5 (2)
Histiocytic sarcoma	8 (1)
Liver	4 (1)
All Lymphoma	NA
Lymphocytic lymphoma	0.9 (1)
Lung	10 (1)
Female mouse:	.....
Forestomach	5 (1)
Harderian Gland	7 (1)
Heart hemangiosarcoma	3×10^{-3} (3)
Histiocytic sarcoma	10 (1)
Liver	7 (1)
All lymphoma	NA
Lymphocytic lymphoma	9 (1)
Lung	30 (1)
Mammary	4 (1)
Ovarian	9 (1)

[a] Based on NTP II, excluding the 625 ppm exposure category, equating a 900-day-old mouse to a 74-year old human and assuming an allometric conversion of $(mg/kg)^{3/4}$.
[b] Rounded to one significant figure.
[c] Occupational lifetime is an 8-hour time-weighted-average, 40-hours per week, 50-weeks per year, time-weighted-average (TWA) for 45-years.

The Carcinogen Assessment Group QRA

The Carcinogen Assessment Group (CAG) and the Reproductive Effects Assessment Group of the Office of Health and Environmental Assessment at the United States Environmental Protection Agency (EPA) also conducted an assessment of the mutagenicity and carcinogenicity of BD. (Ex. 17–21) In its quantitative risk assessment, CAG used both male and female response data from the two chronic bioassays available at the time, NTP I with $B_6C_3F_1$ mice and the HLE Sprague Dawley rat study. The CAG analysis is based on EPA's established procedures for quantitative risk analyses, which fit the total number of animals with significantly increased or highly unusual tumors with the linearized multistage model and use the upper 95% confidence interval. Mice dying before week 20 and rats dying during the first year of the study (before the observation of the first tumor) were eliminated from the analysis to adjust for non-tumor differential mortality.

The dose-metric was based on a preliminary report by the Lovelace Inhalation Toxicology Research Institute of its six-hour exposure study in $B_6C_3F_1$ mice and Sprague Dawley rats at different concentrations of BD, roughly corresponding to the concentrations used in NTP I and HLE, with total internal BD equivalent dose expressed as a function of inhalation exposure concentration. Then CAG estimated the amount and percent of BD retained for various exposure concentrations in these bioassays. These internal dose-estimates were then extrapolated to humans based on animal-to-human ppm air concentration equivalence.

CAG adjusted risk estimates from the mouse study by a factor of $(\text{study duration/lifetime})^3$ to account for less-than-lifetime observations, since the NTP I study was prematurely terminated at 60 weeks for males and 61 weeks for females due to predominating cancer mortality. CAG extrapolated the short lifespan mouse data to an expected mouse lifetime, 104 weeks, in order to estimate lifetime risk to humans.

CAG estimated all risks based on continuous exposure to BD, 24 hours per day, 365 days per year, for a 70-year lifetime. The incremental unit risk estimates for the female mouse were about eight times as high as those for the female rat; for the males, the incremental unit risk estimate for mice was about 200 times as high as for rats. The CAG final incremental unit risk estimate of $0.64\ (ppm)^{-1}$ is based on the geometric mean of the upper-limit slope estimates for male and female mice and would predict an upper limit of 640 excess cancers per 1,000 people exposed to 1 ppm continuously throughout their lifetime, 70 years. Extrapolating this same estimate to an equivalent 45-year working lifetime of 240 work days per

year at an 8-hour TWA exposure to 1 ppm BD would yield an upper-limit risk estimate of 90 excess cancers per 1,000 workers. If the working day is assumed to require one-half ($10 m^3$) the daily tidal volume, the total amount of air inhale, the excess would be 135 cancers per 1,000 workers.

California Occupational Health Program (COHP) QRA

In 1990, five years after the CAG conducted its quantitative risk assessment, the California Occupational Health Program (COHP) produced its estimates of risk with a similar assessment of the carcinogenicity of BD, using the same available bioassays, with more recent information on BD risk in humans, pharmacokinetic (PK) modeling, and animal low exposure absorption efficiency. (Ex. 32–16) Using three separate dose-metrics for each bioassay and multistage models to characterize the basic dose-response relationship, CAG presented several quantitative estimates of incremental lifetime unit risks. Quantal lifetime response multistage models were fit to the data. COHP, like NIOSH, used the individual data with a multistage Weibull time-to-tumor model to characterize the dose response relationship. COHP stated that it also fit Mantel-Bryan and log-normal models to the data, and that the multistage models gave a better fit; the results obtained with these other models were not reported.

COHP performed calculations on each primary tumor site separately, and also did calculations on the pool of primary tumors that showed significantly increased tumor incidences. For their main dose-metric, COHP refined the CAG approach, using a revised estimate of low-exposure absorption via inhalation. COHP also included an estimate of the PK model derived BD monoepoxide metabolites, but de-emphasized their use by stating that these were ''presented for comparative purposes only.'' The third dose-metric was straight ppm for animal-to-human species conversion (adjusting for duration of exposure). COHP stated:

> (COHP) followed standard EPA practice and assumed that a certain exposure concentration in ppm or mg/m^3 in experimental animals was equivalent to the same exposure concentration in humans. (Ex. 32–16)

Like CAG, COHP also adjusted for less than lifetime survival in the NTP I mouse study, by using a cubic power of time, $(\text{study duration/lifetime})^3$. COHP's potency estimate adjustment for the male mouse study with 60-week survival was 5.21; for the 61-week female mouse survival the adjustment was 4.96.

With all the combinations of sites, species, sexes, models, and dose-metrics, COHP presented over 60 potency estimates for the rat and over 100 for the mouse. As with the CAG and other analyses, the estimates based on NTP I were typically one to two orders of magnitude greater than those based on the rat for similar dose-metrics, models and total tumors. COHP chose the estimates based on the male mouse as final indicators of human risk based on the ''superior quality of the mouse study.'' From these estimates, using the quantal form of the multistage model, COHP chose ''the upper bound for plausible excess cancer risk to humans.'' COHP's final cancer potency estimate of $0.32\ (ppm)^{-1}$ presented in units of continuous lifetime exposure, is based on all significant tumors in the male mouse and uses the internal BD equivalent dose conversion factor of 0.54 mg/kg-d/ppm for the mouse and animal-to-human ppm equivalency. COHP's final potency estimate was one-half the value of $0.64\ (ppm)^{-1}$ calculated by the CAG; the difference is due mainly to a low exposure absorption modification by COHP. The continuous lifetime exposure potency factor converts to a working lifetime risk of 45 to 67 excess cancers per 1,000 workers, exposed to 1 ppm of BD at an 8-hour TWA over a 45 year working lifetime.

COHP, like CAG, attempted to determine whether its animal-based risk extrapolation could predict the leukemia mortality observed in epidemiology studies. Following the approach employed by CAG in its analyses of the Meinhardt (1982) study, the COHP compared its estimates of risk from bioassays to the then most recent epidemiological studies of Downs et al. (1987) and Matanoski and Schwartz (1987). Both COHP and CAG used MLEs based on mouse lymphoma for comparing the animal-derived potency estimates with the occupational response. In addition, neither COHP nor CAG used the upward adjustment factor of approximately 5 to correct for the less-than-lifetime duration of NTP I. Because neither of these epidemiology studies (Downs et al. (1987) or Matanoski and Schwartz (1987)) had recorded exposure estimates, the COHP relied on 8-hr TWA estimates of 1 and 10 ppm taken at different but similar plants reported by Fajen et al. (1986). For lifetime unit risk estimates, COHP used the initial MLE of $0.0168\ (ppm)^{-1}$ derived from the male mouse lymphoma analysis, unadjusted for less-than-lifetime survival. This part of the analysis also assumed that a lymphocytic outcome in the animals would equate to leukemia death in humans. These assumptions yielded a range of 6 to 21 predicted lymphocytic cancer deaths (for 1 and 10 ppm exposures) versus the 8 observed by Downs et al.

Office of Toxic Substances (OTS) QRA

The Office of Toxic Substances (OTS), U.S. Environmental Protection Agency (EPA) conducted a quantitative risk assessment using only the NTP I data. (Ex. 17–5) The reasons cited for this choice include: (1) The mouse is a more sensitive test species for BD than the rat; (2) a quality control review had been done for the mouse bioassay at the time OTS wrote its risk assessment whereas none was available for the rat bioassay; (3) greater amount of histopathological data was available for the NTP I study than for the HLE rat study; and (4) the type of BD feedstock used by NTP I had a much lower dimer concentration than the BD used by HLE (increased dimer concentration results in the lowering of availability of BD for metabolism to the mono- and di-epoxides, which are thought to be the carcinogenic agents). To compensate for early termination of the NTP I study, OTS adjusted dose by a factor of (study duration/lifetime).[3] Butadiene ppm exposure concentration was used as the measure of dose and mouse-to-human species extrapolation was also on a ppm equivalence basis. OTS estimated cancer risks based on heart hemangiosarcoma and pooled tumors (grouping of sites showing statistically significant elevated incidence rates) tumors using a 1-stage quantal model. Workplace exposures to BD were converted to estimated lifetime average daily doses. Since the NTP I study was curtailed at 61 weeks, tumor incidence rates were adjusted for survival by life-table methods. Cancer risks were based on administered dose of BD and not delivered dose to various target organs. (Ex. 17–5) Estimated 95% upper confidence-limits for the excess risk of cancer from an occupational lifetime exposure to an 8-hour TWA of 1 ppm BD, for 240 days/year for 40 years, ranged between 10 and 30 per 1,000 workers, based on pooled tumor incidence for female and male animals, respectively.

ICF/Clement Estimates

In 1986, ICF/Clement (ICF) estimated the risk of cancer associated with occupational exposure to BD. (Ex. 23–19) ICF determined that only the NTP I data were suitable for a risk assessment based on animal data, (NTP II data were not available at that time) based on ICF/

Clement's concern over the discrepancies between HLE's summary statistics and individual counts. ICF chose to use individual tumor type data for some of its analyses. ICF fitted a linearized multistage quantal model to the NTP I data. Based on a preliminary study by Bond (a senior toxicologist at the Chemical Industry Institute of Toxicology), ICF adjusted the NTP I exposure concentrations for percent retention which varied inversely from 100% at 1 ppm to 5% at 1,000 ppm.

ICF assumed ppm as the proper dose-metric and ppm to ppm for the mouse-to-human species extrapolation factor. (Exs. 23–86; 23–19) The 95% upper confidence limit estimates of risk based on pooled female tumor data with a lifetime occupational exposure was 200 per 1,000 workers at 1 ppm BD, and 400 per 1,000 workers at 5 ppm BD; the non-proportionality reflects the assumption of lower percentage retentions at higher concentrations.

Massachusetts Institute of Technology (MIT) QRA

Hattis and Wasson at the Center for Technology, Policy, and Industrial Development at MIT conducted pharmacokinetic/mechanism-based analyses of the carcinogenic risk associated with BD. (Ex. 29–3) The analyses include both HLE and NTP I data. Key elements, such as partition coefficients for blood/air and tissue/blood, were not available to be measured and had to be estimated. The best estimate of excess risk of cancer given a lifetime occupational exposure of 1 ppm BD 8-hr TWA was 5 per 1,000 workers based on the NTP I female mouse data set, incorporating pharmacokinetic models which set the blood/air partition coefficient to 0.2552. Based on the HLE female rat data with a blood/air partition coefficient of 0.2552, an excess risk was estimated to be 0.4 additional cases of cancer for every 1,000 workers at an 8-hour TWA, occupational lifetime exposure to 1 ppm BD.

Environ QRA

Environ conducted a quantitative risk assessment based on the HLE rat bioassay data. (Ex. 28–14) Environ noted that the relatively high BD concentrations of the earlier bioassays (HLE with groups exposed to 8,000 and 1,000 ppm BD and NTP I with exposures of 1,250 and 625 ppm BD) made it difficult to extrapolate risks to the relevant, lower exposure levels of BD in occupational settings. Environ stated that among $B_6C_3F_1$ mice, metabolic saturation occurs with 8-hour TWA BD concentrations greater than 500 ppm; thus, the time-dose-response relationship is different at higher doses than at lower doses. Environ stated that the methodological problems and the high early mortality shown in the NTP I data contributed to the uncertainty of its relevance to human risks and therefore chose to use the HLE rat bioassay data instead. Environ believes that human metabolism of BD is more similar to that in the Sprague-Dawley rat than in the $B_6C_3F_1$ mouse. Extrapolated risks were based on estimates of absorbed dose, expressed in mg/kg, as defined in the Bond et al. (1986) absorption study. (Ex. 23–86)

Environ used the HLE female rats to estimate the extra lifetime risk of developing cancer given an occupational lifetime 8-hr TWA exposure to 1 ppm BD. Using MLEs from multistage, Weibull, and Mantel-Bryan models, based on the total number of female rats with significantly increased tumors, Environ's predicted occupational lifetime risks were 0.575 (Multistage), 0.576 (Weibull), and 0.277 (Mantel-Bryan) per 1,000 workers.

Shell Oil Company QRA

Shell Oil Company estimated excess cancer risks by the multistage quantal and the Weibull time-to-tumor models based on female heart hemangiosarcomas and pooled malignant tumors from the NTP II study. Shell estimated human risks based on various assumptions, correcting for BD retention and/or relative human epoxide dose. Shell stated that the Weibull time-to-tumor model better characterized risks since it was able to fully utilize available dose-response data, including time until onset of tumors and latency (time from initiation until detection of tumor). (Ex. 32–27) Shell used

> * * * crude time-to-tumor data consisting of early deaths to 40- weeks, 40-week interim sacrifices, deaths to 65- weeks, 65-week interim sacrifices, death to 104- weeks and terminal sacrifices * * * in-lieu of individual animal data [for NTP II data]. (Ex. 32–27)

OSHA believes that the true dose-response relationship is obscured by Shell's use of crude time-to-tumor data and its grouping of early deaths to 40 weeks, deaths to 65 weeks and deaths to 104 weeks; instead, dose-time-tumor response data for each individual mouse should have been used.

Shell did not explain why it chose one model over the other. For example, without explanation, Shell dropped the highest exposure group, 625 ppm, when estimating lifetime occupational risk for all of its Weibull time-to-tumor models and dropped additional dose groups when using some multistage quantal models. Moreover, estimates of excess risk were presented only for 5-stage Weibull time-to-tumor models, although there is no discussion of correct model specifications. For example, no reasons are given for choosing the 5-stage model rather than another. Also, Shell does not support its estimation that the latency between the induction of a tumor and its observation is for the pooled female mice malignant tumors and 40-weeks for the female mice heart hemangiosarcomas.

Based on the Shell analyses, extrapolating from pooled malignant female mice tumors, assuming 10% human BD retention efficiency at 2 ppm, and on a 5-stage Weibull time-to-tumor model, one would expect 18 excess cancers per 1,000 workers given an 8-hour TWA occupational lifetime exposure of 2 ppm BD. Based on the same data set, but assuming a mouse-to-human species conversion factor based on an epoxide ratio of 590 (mouse-to-monkey) in addition to a 10% BD retention efficiency factor, the estimate of excess risk of cancer drops to 0.3 cases per 1,000 workers with an 8-hour TWA occupational lifetime exposure of 2 ppm. Using the same pooled malignant female mice tumors, but assuming the blood epoxide estimates of the Dahl et al. study and an 8-hour TWA lifetime occupational BD exposure of 2 ppm, the estimate of excess risk of cancer is slightly lower, 0.24 per 1,000 workers. The excess risk estimates based on female hemangiosarcomas and a 5-stage Weibull time-to-tumor model and occupational lifetime exposure to 2 ppm of BD were: (a) 6.4×10^{-8} (assuming a 10% BD retention factor); (B) 6.2×10^{-15} (assuming a 10% BD retention factor and an epoxide ration of 590); and (c) 1.3×10^{-11} (assuming the blood epoxide estimates of the Dahl et al. study).

Shell also presented the Environ Inc. QRA based on the HLE Sprague-Dawley rat bioassay and made similar adjustments for BD retention and blood epoxide to those it made for the NTP II $B_6C_3F_1$ mice data. As had Environ, Shell stated that the dose- response of the rat is more relevant than that of the mice in predicting risk in humans. Shell concluded that the risk estimates derived from HLE Sprague Dawley rat data should be given greater weight than those based on the $B_6C_3F_1$ mouse data.

NIOSH's QRA Based on the Delzell et al. Study

NIOSH estimated the excess risk of workers developing leukemia based on the Delzell et al. preliminary estimates of occupational exposure categories of a retrospective cohort study. (Exs. 117–1; 118–1) NIOSH derived excess risks from

the best fitting relative risk (RR) model, the square root model, as fit by Delzell et al. who adjusted for age, years since hire, and calendar period. The preferred final model specified by Delzell et al. was:

$$\text{Relative Risk} = 1 + 0.17 \times (\text{BD ppm-years})^{0.5}$$

Under this model the age-cause specific leukemia death rates (ACSDR) are a function of cumulative occupational exposure up to that age. The occupational ACSDRs are a multiplicative function of background ACSDR times the BD-caused relative increase (0.17 * BD ppm-years) in leukemia. These total ACSDRs were then applied to an actuarial program which adjusted for competing risks to estimate lifetime excess risk of leukemia associated with 45-year 8-hour TWA occupational exposures for a number of PELs for BD. Estimates of background rates of leukemia and all causes of death were taken from the mortality rates for all males, 20 to 65 years of age, from the 1989 Vital Statistics of the United States. This model estimates the excess risk of leukemia death, given an occupational lifetime exposure of 2 ppm of BD, as 11 per 1,000 workers. Lowering the 8-hour TWA occupational lifetime BD PEL to 1 ppm, on average, one would expect there to be 8 excess leukemia deaths per 1,000 workers over a working lifetime.

In most animal bioassays, exposure to chemical carcinogens is usually associated with an elevated tumor incidence at only one or two target tissues. BD is of great concern because significantly increased incidences of tumors at multiple sites and doses were observed in both rats and mice.

OSHA's final risk assessment is based upon the NTP II bioassay. (Exs. 90; 96) In NTP II, the following tumor sites' incidence rates were elevated: Heart, lymph nodes, lung, forestomach, Harderian gland, preputial gland, liver, ovaries and mammary gland. The NTP II bioassay was preferred over the NTP I mouse and the HLE rat bioassay for several reasons. First, most of the exposure levels for NTP II (6.25, 20, 62.5 and 200 ppm) were closer to current occupational exposure levels than were those in the other bioassays (625; 1,000 and 8,000 ppm); studies with higher than typical occupational exposure concentrations may lead to difficulties in extrapolating the effects to the lower concentrations of BD which typically occur in current occupational settings. Furthermore, for doses (625 to 8,000 ppm) above the metabolic saturation level of 500 ppm, the biologically effective doses are not proportional to ppm exposure concentrations. Second, the NTP II mice were successfully randomized to exposure groups and their individual pathology reports were consistently coded. The randomization of the bioassay mouse population lends to the internal validity of the study through the similar composition of experimental and control groups. Third, Good Laboratory Practices were followed, as verified by audits. Fourth, there was a clear dose-response relationship for several cancer sites. Fifth, since the carcinogenic mechanism is still unknown, OSHA conservatively estimates excess risk to humans based on the experience of the more sensitive animal species unless there is specific evidence indicating that the choice of that species is inappropriate. Sixth, risk assessment results based on the preliminary findings from the most recent epidemiologic study suggest that the $B_6C_3F_1$ mouse is a reasonable species to use for quantitative risk assessment. (Ex. 118–1)

For its risk assessment, OSHA has focused exclusively on those tumor sites that are scientifically pertinent. From the NTP II study, the range of excess cancer risk associated with a lifetime occupational exposure to BD is estimated based on the dose-response relationships of four target tissues, three common to both genders: Heart (hemangiosarcoma), lung, and lymphoma, and one, ovarian tumors, observed in one gender only. OSHA's focus on these four individual target tissues is based not on an objection to the use of other tissue tumors and sites but rather on the judgment that the chosen animal sites are appropriate because they include both rare (e.g., heart hemangiosarcoma) and common tumors (e.g., lung) and those sites with the lowest (heart hemangiosarcoma) and highest incidence rates (lymphatic).

Three of the target organs chosen for the QRA demonstrated a significantly elevated tumor incidence in both male and female animals; ovarian tumor incidence was also significantly elevated in female animals. For both male and female mice, heart hemangiosarcomas were selected for modeling because there is virtually no background incidence of heart hemangiosarcoma among untreated mice in the NTP control population; only 0.04% of unexposed $B_6C_3F_1$ mice develop heart hemangiosarcoma, and thus any observed increase in the incidence of heart hemangiosarcoma could be attributed to BD exposure. (Ex. 114, p. 121) The earlier developing lymphocytic lymphoma caused a significant number of mice to die. Therefore, leaving mice are left at risk for the later developing tumor, heart hemangiosarcoma. (Ex. 114, p. 123) This situation is known as competing risk (the lack of opportunity for later developing tumors to express themselves because an earlier developing tumor has already caused the death of the animal. The occurrence of heart hemangiosarcomas in the NTP study is even more notable because of these competing risks.

In the absence of definitive, pharmacokinetic information, OSHA has estimated excess risks to humans based on the most sensitive species-sex-tumor site. Lung tumors are the most sensitive sites for both male and female $B_6C_3F_1$ mice and, as such, were included in OSHA's final risk assessment.

Ovarian tumors are an example of the group of reproductive tumors which also had significantly increased incidence rates among the animals in the NTP II bioassay. Other significantly increased incidence rates were seen in testicular, preputial and mammary tumors.

The increased risk of developing leukemia that has been observed in the epidemiological studies suggests that lymphomas might be the most relevant tumor site in animals for estimating the quantitative cancer risk to workers. Some have suggested that the high rate of lymphoma among $B_6C_3F_1$ mice might have been due to the presence of the murine retro virus (MuLV) and have asserted that the presence of this virus in $B_6C_3F_1$ mice may be partially responsible for the incidence of thymic lymphoma. For example, in 1990, Dr. Richard Irons reported,

> A major difference between NIH Swiss and $B_6C_3F_1$ mice is their respective exotropic retro viral background (MuLV) * * * Chronic exposure to BD (at 1250 ppm) for up to a year resulted in a fourfold difference in the incidence of thymic lymphoma between $B_6C_3F_1$ mice and NIH Swiss mice * * * The role of endogenous retro virus (MuLV) in the etiology of chemically induced murine leukemogenesis is presently not understood. (Ex. 23–104)

Dr. Melnick of the National Toxicology Program testified during his public hearing statement,

> In terms of the difference in response between the $B_6C_3F_1$ mouse or the NIH Swiss Mouse, you must be aware that the study is not a complete cancer study. It's a one-year exposure. We do not know the full response in the NIH Swiss mouse if it were conducted as a cancer study (about 2-years). (Tr. 1/16/91, p. 382)

Furthermore, NIOSH stated: ''It is not known whether the retro virus activation mechanism is operative at the lower exposure concentrations of 1,3-butadiene [below 1250 ppm].'' (Ex. 90)

There is no information in the record to show that retrovirus insertion into the $B_6C_3F_1$ mice of the NTP II study led to the induction of lymphoma. Nor is there information indicating that the murine retro virus may have led to an enhancement of butadiene-induced lymphomas in $B_6C_3F_1$ mice. The development of thymic lymphoma in BD-exposed NIH Swiss mice that do not have this endogenous virus argues against the virus alone inducing the lymphomas observed in the BD-exposed $B_6C_3F_1$ mice. (Ex. 23–104)

Tables V–11 and V–12 show the breakdown of microscopically examined tissues included in OSHA's QRA, by exposure concentration and death disposition of female and male mice. As illustrated in the tables, microscopic examination varied by tissue type, exposure group, means of death, and gender. Microscopic examinations of all tissues were made for all natural deaths, and moribund and terminal sacrifices, irrespective of exposure group.

For each gender-exposure-group, 10 animals were sacrificed at 40 and 65 weeks. Microscopic evaluations were not made for all tissue types among interim sacrifices (40 and 65 weeks). Among early sacrifices (40 weeks) for the 6.25 and 20 ppm exposure groups, there were no microscopic examinations of the relevant tissues. For the 65-week female sacrifices at the 6.25 and 20 ppm dose levels only lung and ovarian tissues were examined microscopically. No microscopic evaluations were made for male 65-week sacrifices at the 6.25 ppm exposure level, but at the 20 ppm exposure level, animals were microscopically examined for heart hemangiosarcoma and lung cancer. Male and female interim sacrifices exposed to 62.5 ppm of BD were not microscopically examined for heart hemangiosarcoma.

Only observations confirmed by microscopic examination were included in the analyses. Among natural deaths for some gender-tissue combinations, there were a few animals for which tissues were not available. Tissue unavailability was due to autolysis (cell destruction post death) and missing tissues due to the delay between accident and discovery.

TABLE V–11.—TYPES OF TISSUES MICROSCOPICALLY EXAMINED BY CONCENTRATION DOSE AND DISPOSITION GROUPS AMONG FEMALE MICE FROM NTP[a]

Concentration ppm	Natural death and moribund sacrifice	Week 40 sacrifice	Week 65 sacrifice	Terminal sacrifice
0	lymphoma, heart[b], lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.
6.25	lymphoma, heart, lung, ovaries.	none[c]	lung, ovaries	lymphoma, heart, lung, ovaries.
20	lymphoma, heart, lung, ovaries.	none	lung, ovaries	lymphoma, heart, lung, ovaries.
62.5	lymphoma, heart, lung, ovaries.	lymphoma, lung, ovaries	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.
200	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.

[a] These organs and tissue types are those contained in the OSHA risk assessment and do not reflect all of the types of tissues which were microscopically examined.
[b] Heart, specifically Heart hemangiosarcoma.
[c] None of the four tissue types used in the OSHA quantitative risk assessment were microscopically examined.

TABLE V–12.—TYPES OF TISSUES MICROSCOPICALLY EXAMINED BY CONCENTRATION DOSE AND DISPOSITION GROUPS AMONG MALE MICE FROM NTP[a]

Concentration ppm	Natural death and moribund sacrifice	Week 40 sacrifice	Week 65 sacrifice	Terminal sacrifice
0	lymphoma, heart[b], lung,	lymphoma, heart, lung	lymphoma, heart, lung	lymphoma, heart, lung.
6.25	lymphoma, heart, lung,	none[c]	none	lymphoma, heart, lung.
20	lymphoma, heart, lung,	none	heart, lung	lymphoma, heart, lung.
62.5	lymphoma, heart, lung	lymphoma, lung,	lymphoma, heart, lung	lymphoma, heart, lung.
200	lymphoma, heart, lung	lymphoma, heart, lung	lymphoma, heart, lung	lymphoma, heart, lung.

[a] These organs and tissue types are those contained in the OSHA risk assessment and do not reflect all of the types of tissues which were microscopically examined.
[b] Heart, specifically heart, hemangiosarcoma
[c] None of the four tissue types used in the OSHA quantitative risk assessment were microscopically examined.

2. Measure of Dose

The mechanism of cancer induction by BD is unknown for both rodents and humans. One or more of the metabolites of BD, epoxybutene, diolepoxybutane and diepoxybutane, are suspected as being responsible for the carcinogenic response in at least some of the cancers. However, which of the metabolites may be responsible for how much of the carcinogenic response has yet to be determined. Bond suggests that epoxybutene and diepoxybutane may be responsible for carcinogenic responses. (Ex. 32–28) Dr. Bond wrote:

> If carcinogenic response is elicited by a metabolite, as has been suggested, mice because of their higher rate of metabolism, might be expected to yield a greater (carcinogenic) response than rats. (Ex. 17–21)

Because there are different theories about which metabolites of BD are responsible for the various carcinogenic responses, some risk assessments have characterized carcinogenic risk as a result of type of dose: External, absorbed, or retained. In the BD proposal (55 FR 32736), OSHA calculated the ^{14}C–BD equivalents that were retained in mice at the conclusion of a 6-hour exposure period and incorrectly labeled the level as ''absorbed dose.'' This does not necessarily represent all the BD absorbed through inhalation exposure. (Ex. 34–1)

The metabolic and pharmacokinetic properties of BD have not been fully characterized for either humans or animals. Despite the absence of a generally accepted pharmacokinetic model, some metabolic information can still be applied to OSHA's QRA. The overall rate of BD metabolism in $B_6C_3F_1$ mice is approximately linear at external concentrations up to 200 ppm; BD metabolism increases sublinearly as concentrations increase until it is saturated at 625 ppm. (Ex. 90) Bond reported that epoxybutene is one of the putative carcinogenic metabolites for which metabolism in the $B_6C_3F_1$ mouse becomes saturated at 500 ppm; thus, the $B_6C_3F_1$ mouse is unable to eliminate epoxybutene as quickly above 500 ppm. Bond suggests that above 500 ppm direct quantitative extrapolation of risk from mouse studies may not be justified. (Ex. 23–86) Therefore, the 625 ppm exposure group was excluded from OSHA's risk assessment. Similarly, NIOSH and Shell did not include the 625 ppm exposure group in their best estimates of risks using NTP II data. However, NIOSH did include the 625 ppm dose group in its sensitivity analyses to see how the inclusion of the data would affect the specification (the form and number of dose explanatory variables e.g., d, d^2, d^3, etc.) of the model and the estimates of risk. (Ex. 90)

3. Animal-to-Human Extrapolation

A QRA based on a mouse bioassay requires setting values for some mouse and human variables, including those used in animal-to-human extrapolations. The values of these variables were chosen before conducting the analyses. In OSHA's quantitative risk assessment, a mouse's life span was assumed to be 113 weeks. Mice were 8 weeks old at the beginning of the study and were exposed for up to 105 weeks. OSHA assumes workers will have an average lifespan of 74 years and an occupational lifetime, working 5 days/week, 50 weeks/year, of 45 years. In the NTP II study, the average male mouse weighed 40.8 grams and female mouse weighed 38.8 grams. (Ex. 90) Mice were assigned breathing rates of 0.0245 l/min. Breathing rates of workers (for an 8-hour workday) were set at 10 m^3/8-hr.

OSHA has chosen to use a straight mg/kg, body weight to the first power, $(BW)^1$, intake as the animal-to-human species extrapolation factor for dose equivalence. Other BD QRAs employed various extrapolation factors such as ppm equivalence, $(mg/kg)^{3/4}$ equivalence, BD mono-epoxide blood levels between mice and monkey equivalence, and BD total body equivalence in $(mg/kg)^{2/3}$. OSHA believes that the evidence for the use of any of the alternative extrapolation factors is persuasive, although the Agency believes that body weight extrapolation is appropriate in this case because of the systemic nature of the tumors observed in both animal bioassays. This conversion of body weight, $(BW)^1$, produces estimates of risk which are lower than those derived using $(BW)^{3/4}$, everything else held constant. For example, with a linear, 1-stage model, if OSHA used the $(BW)^{3/4}$ conversion, holding all other elements constant, one would expect the estimates of excess risk to humans to be about 6.5 times higher than if the (BW) extrapolation factor had been used because of the weight of the experimental species (between 38.8 and 40.8 grams), and their breathing rate. For the quadratic (2-stage) and cubic (3-stage) models, the effect of relying on the $(BW)^{3/4}$ conversion rather than the $(BW)^1$, holding all else constant, would be to increase the predicted excess human risk more than 6.5 fold. (Ex. 90)

4. Estimation of Occupational Dose

It is necessary to estimate the development of cancer at a variety of occupational doses. This requires occupational doses to be converted into units comparable to those used to measure the animal experimental dose. As discussed earlier, OSHA first converted animal experimental exposures measured in ppm into occupational intake dose measured in (mg/kg).

An exposure of 1 ppm BD is converted into an equivalent exposure measured in mg/m^3 using the equation:

$$1\ \text{ppm BD} = \frac{\text{Molecular Weight BD}}{\text{Molecular Weight of Air}} \times \text{density of air}$$

$$1\ \text{ppm BD} = \frac{54.1\ \text{mg / mole}}{24.45\ \text{mole / m}^3} = 2.21\ \text{BD mg / m}^3$$

Given a worker weighing 70 kg, breathing 10 m^3 of air per 8-hour day, and exposed to air containing Y ppm BD, the inhaled dose of BD in mg/kg is given by:

$$\text{Y (mg / kg) BD inhaled} = \text{Y (ppm) BD} \times 2.21 \frac{\text{mg / m}^3}{\text{ppm}} \times \frac{10\ \text{m}^3}{70\ \text{kg}}$$

Using the above formula, one can calculate the estimated equivalent inhaled BD exposure among workers based on the exposure concentrations for animals (See Table V–13).

TABLE V–13.—ESTIMATE OF TOTAL HUMAN INHALED DOSE OVER A WORKDAY FOR VARIOUS EXPOSURE LEVELS OF BD

Exposure concentrations (ppm)	Estimate of total human inhaled BD over a workday (mg/kg/8-hours)
200	63.2
62.5	19.8
20	6.3
5	1.6
2	0.6
1	0.3

5. Selection of Model for Quantitative Risk Assessment

In the proposal (55 FR 32736), OSHA estimated excess risk using a quantal form of the multistage model (in a reparameterized form as calculated by GLOBAL83), which based estimates of risk to humans on the experience of the group rather than the individual. Three of the later risk assessments, Shell, NIOSH, and COHP, used a Weibull time-to-tumor form of the multistage model to fit the mouse bioassays. (Exs. 32–27; 90; 32–16) Time-to-tumor

models use more of the available information than quantal multistage models to characterize time until the development of each observable tumor, and extrapolate risks, based on an occupational dosing pattern. Since significant increases in tumor incidence occurred at multiple sites in the NTP II bioassay and a time-to-tumor model takes these competing risks into account, a time-to-tumor method is preferred over a quantal model. (Ex. 118–1B)

Therefore OSHA used a Weibull time-to-tumor form of the multistage model to characterize the risks of development of observable tumors, using the software package, TOX__RISK Version 3.5 by ICF Kaiser. The model predicts the probability, P(t,d), of tumor onset with dose pattern d by time t. It adjusts for competing causes of death prior to time t.

The Weibull time-to-tumor model is a multistage model based on the theory of carcinogenesis developed by Armitage and Doll. This theory of carcinogenesis is based on the assumption that a single line of stem cells must pass through a certain number of stages sequentially for the development of a single tumor cell. In the reparameterized form of the model used here, a k stage model is described by a polynomial of degree k, with all dose parameters greater than or equal to zero. The number of stages necessary for a model to be correctly specified varies by type of tumor, animal, and exposure agent, or any combination of the three.

Both the MLE and the 95% upper limit of the risk of developing cancer in various tissues per 1,000 workers by time t are calculated. The 95% upper bound is the largest value of excess risk that is consistent with the observed data with two-sided 95% confidence intervals. The 95% upper bound is computed based on the Weibull time-to-tumor model for which the parameters satisfy:

-2 (Log likelihood $-$ Log likelihood$_{max}$)$\leq$2.70554

Where: Log likelihood$_{max}$ is the maximum value of the log-likelihood

A 1-stage model is linear in dose; a 2-stage model is quadratic in dose; a 3-stage Weibull model is cubic in dose. Below is a mathematical representation of a 3-stage Weibull time-to-tumor model:

$$P(t,d)=1\text{-}\exp\left[-(q_0 + q_1 d + q_2 d^2 + q_3 d^3)(t - t_0^z)\right]$$

where: t_0 designates the time of onset of the tumor, t is the variable for time the tumor was observed and is assumed to follow a Weibull distribution; d is the dose-metric and is multistage; z is a parameter to be estimated, constrained between 1 and 10; the background parameter q_o and the dose parameters, q_1, q_2, q_3, are constrained to be non-negative. Constraining the dose parameters to zero or greater is biologically based, since the dose parameters are proportional to the mutation rates of the successive stages in the development of a tumor cell. The Weibull time-to-tumor model provides reasonable fits for about 75% of the tissues in the NTP historical control data base, but the precision of the fit to the dose-response data depends on the specific agent. (Ex. 90)

Four forms of the model, one less than the number of exposure groups, for each gender-outcome were fit to the data. The correct specification of the model, the number of stages, is determined by the fit of the model to the data. The likelihood ratio test identifies which model is a better fit by determining if the log-likelihood of a model is significantly greater than another model's value. The 1-, 2-, 3- and 4-stage Weibull time-to-tumor models for each gender-outcome combination were ordered according to the value of their log-likelihood. If the log-likelihood of the higher stage model is significantly greater than that of the next lower stage model's log-likelihood, one would reject the null hypothesis (the additional stage does not create a model that better characterizes the data) and conclude that the higher stage model is a significantly better predictor of the estimates of risk in the observed range than is the lower stage model.

The steps of the likelihood ratio test are as follows:

For example, assuming an alpha of 0.05, and 1 degree of freedom (the difference in the number of parameters from 1-stage and 2-stage models), the critical value would be 3.84.

Fail to Reject H_0 if:

2 (log likelihood$_{1\text{-stage}}$ $-$ log likelihood$_{2\text{-stage}}$)$<$3.84

Reject H_0 if:

2 (log likelihood$_{1\text{-stage}}$ $-$ log likelihood$_{2\text{-stage}}$)$\geq$3.84

If two times the difference of the log likelihood values of the nth stage model and the nth + 1 stage model was less than 3.84, then the additional stage would be deemed unnecessary for goodness of fit; on the grounds of parsimony, the lower stage model would be used for the risk assessment. Otherwise, the higher stage model would be judged a better fit than the lower stage one and the process would continue.

While the likelihood ratio test is suitable for testing the significance of the next higher degree dose parameter, the biologically reasonable constraint on the background incidence parameter q_0 and dose parameters that they be non-negative q_1, q_2, q_3>=0,—may impair the log-likelihood ratio test's power to determine statistical significance.

The incidences of lymphoma, heart hemangiosarcoma, lung and ovarian tumors are shown in Tables V–14 and V–15 for males and females, respectively. The TOXRISK Weibull time-to-tumor model requires that the tumor context be described for each observation. Outcomes can be put into three context categories: (1) Censored, no tumor; (2) rapidly fatal tumor; and (3) observed, tumor incidental to the animal's survival. Since OSHA was predicting the time until onset of tumor, assuming no lag time between onset and detection of tumor, t_0 was set to zero. Therefore, estimates of risk to humans based on the contribution to the likelihood of either a rapidly fatal or incidental tumor are mathematically the same.

Tables V–16 and V–17 show the Weibull time-to-tumor model estimates of log-likelihoods, the shape parameters, intercept and dose coefficients for relevant target tissues for male and female mice, respectively. The relative performance of various staged models for a specific target tissue-gender are enumerated in the log-likelihood values. It should be noted that some of the tissue-gender combination's log-likelihood values do not vary even though there is a change in the number of the stages in the model. For example, the log-likelihood values for models of all lymphoma for males and lung tumors for males and females are $-$6.986 E+1, $-$1.763 E+2, $-$1.626 E+2, respectively, regardless of the specification, number of stages, in the model. OSHA concluded that the 1-stage models were preferred.

As identified in Tables V–16 and V–17, only heart hemangiosarcoma models are non-linear. This is consistent with NIOSH's results when fitting Weibull time-to-tumor models to these gender-tumor combinations. The quadratic (2-stage) model for males and the cubic (3-stage) model for females better characterized the dose-response relationship in modeling time to detection of heart hemangiosarcoma than did the linear models. The higher stage model necessary to fit the heart hemangiosarcoma data is driven by the absence of cases in the two lower exposure groups, shown in Tables V–14 and V–15. Unlike the other tissues studied, there were no cases of heart

hemangiosarcoma in the control and lowest exposure groups for both male and female mice. Both male and female mice had similar heart hemangiosarcoma tumor rates, almost 30%, among the 200 ppm exposure groups. The intercepts, q_0, were zero for models of both male and female mice based on the dose-response of heart hemangiosarcomas. This is consistent with what one would expect, given the absence of background incidence rates of heart hemangiosarcomas.

TABLE V–14.—UNIVARIATE ANALYSIS OF HEART, LUNG, AND ALL LYMPHOMA NEOPLASMS BY EXPOSURE LEVEL OF 1,3-BUTADIENE AMONG NTP II MALE MICE ANALYZED IN THE TIME-TO-TUMOR MODELS

Neoplasm	Outcome		
	Tumor n [a] (%N [b])	Censored [c] n (%N)	Total N
All lymphoma, 0 ppm	4 (5.7)	66 (94.3)	70
All lymphoma, 6.25 ppm	3 (6.0)	47 (94.0)	50
All lymphoma, 20 ppm	8 (16.0)	42 (84.0)	50
All lymphoma, 62.5 ppm	11 (15.9)	58 (84.1)	69
All lymphoma, 200 ppm	9 (12.9)	61 (87.1)	70
Heart hemangiosarcoma, 0 ppm	0 (0)	70 (100)	70
Heart hemangiosarcoma, 6.25 ppm	0 (0)	49 (100)	49
Heart hemangiosarcoma, 20 ppm	1 (1.7)	59 (98.3)	60
Heart hemangiosarcoma, 62.5 ppm	5 (8.6)	53 (91.4)	58
Heart hemangiosarcoma, 200 ppm	20 (29.4)	48 (70.6)	68
Lung tumor, 0 ppm	22 (31.4)	48 (68.6)	70
Lung tumor, 6.25 ppm	23 (46.9)	26 (53.1)	49
Lung tumor, 20 ppm	20 (33.3)	40 (66.7)	60
Lung tumor, 62.5 ppm	33 (47.8)	36 (52.2)	69
Lung tumor, 200 ppm	42 (60.0)	28 (40.0)	70

[a] n is number of microscopically determined outcomes per tumor-context, gender, exposure-group outcome site combination.
[b] N is the total number of gender, exposure-group, outcome site combination which were microscopically examined.
[c] Tumor's context is C (censored); animals were microscopically examined and no tumor was found at this site.

TABLE V–15.—UNIVARIATE ANALYSIS OF HEART, LUNG, ALL LYMPHOMA AND OVARIAN NEOPLASMS BY EXPOSURE LEVEL OF 1,3-BUTADIENE AMONG NTP II FEMALE MICE ANALYZED IN THE TIME-TO-TUMOR MODELS

Neoplasm	Outcome		
	Tumor n[a] (%N[b])	Censored [c] n (%N)	Total N
All lymphoma, 0 ppm	10 (14.3)	60 (85.7)	70
All lymphoma, 6.25 ppm	14 (28.0)	36 (72.0)	50
All lymphoma, 20 ppm	18 (36.0)	32 (64.0)	50
All lymphoma, 62.5 ppm	10 (14.3)	60 (85.7)	70
All lymphoma, 200 ppm	19 (27.1)	51 (72.9)	70
Heart hemangiosarcoma, 0 ppm	0 (0)	70 (100)	70
Heart hemangiosarcoma, 6.25 ppm	0 (0)	50 (100)	50
Heart hemangiosarcoma, 20 ppm	0 (0)	50 (100)	50
Heart hemangiosarcoma, 62.5 ppm	1 (1.7)	58 (98.3)	59
Heart hemangiosarcoma, 200 ppm	20 (28.6)	50 (71.4)	70
Lung tumor, 0 ppm	4 (5.7)	66 (94.3)	70
Lung tumor, 6.25 ppm	15 (25.0)	45 (75.0)	60
Lung tumor, 20 ppm	19 (31.7)	41 (68.3)	60
Lung tumor, 62.5 ppm	27 (38.6)	43 (61.4)	70
Lung tumor, 200 ppm	32 (45.7)	38 (54.3)	70
Ovarian tumor, 0 ppm	1 (1.4)	68 (98.6)	69
Ovarian tumor, 6.25 ppm	0 (0)	59 (100)	59
Ovarian tumor, 20 ppm	0 (0)	59 (100)	59
Ovarian tumor, 62.5 ppm	9 (12.9)	61 (87.1)	70
Ovarian tumor, 200 ppm	11 (15.7)	59 (84.3)	70

[a] n is number of microscopically determined outcomes per tumor-context, gender, exposure-group outcome site combination.
[b] N is the total number of gender, exposure-group, outcome site combination which were microscopically examined.
[c] Tumor's context is C (censored); animals were microscopically examined and no tumor was found at this site.

TABLE V–16.—MAXIMUM LIKELIHOOD ESTIMATES OF MODEL COEFFICIENTS FROM VARIOUS STAGES OF WEIBULL TIME-TO-TUMOR MODELS USING THREE TUMOR RESPONSES OF MALE MICE IN THE NTP II STUDY, EXCLUDING 625 PPM EXPOSURE GROUP; SELECTION OF SPECIFICATION OF MODEL IS BASED ON LIKELIHOOD RATIO TEST

Neoplasm	Stage [a]	Log-likelihood	Z [b]	q_0	q_1	q_2	q_3	q_4
Heart hemangiosarcoma	W1	−7.061	9.810	0.00	8.306 E–23			
Heart hemangiosarcoma	[c] W2	−2.783 E–1	10	0.00	0.00	3.071 E–25		
Heart hemangiosarcoma	W3	−2.712 E–1	10	0.00	1.058 E–24	2.636 E–25	2.057 E–28	
Heart hemangiosarcoma	W4	−2.659 E–1	10	0.00	1.119 E–24	2.664 E–25	0.00	9.626 E–31
All lymphoma	[c] W1	−6.986 E+1	4.743	2.709 E–11	6.136 E–13			
All lymphoma	W2	−6.986 E+1	4.743	2.709 E–11	6.136 E–13	0.00		
All lymphoma	W3	−6.986 E+1	4.743	2.709 E–11	6.136 E–13	0.00	6.540 E–33	
All lymphoma	W4	−6.986 E+1	4.743	2.709 E–11	6.136 E–13	0.00	0.00	0.00
Lung tumor	[c] W1	−1.763 E+2	3.318	1.132 E–7	2.636 E–9			
Lung tumor	W2	−1.760 E+2	3.413	7.674 E–8	1.253 E–9	3.134 E–12		
Lung tumor	W3	−1.760 E+2	3.143	7.674 E–8	1.253 E–9	3.134 E–12	0.00	
Lung tumor	W4	−1.760 E+2	3.413	7.674 E–8	1.253 E–9	3.139 E–12	0.00	0.00

[a] Stage of time-to-tumor model; W1, Weibull 1-stage time-to-tumor model; W2, Weibull 2-stage time-to-tumor model; W3, Weibull 3-stage time-to-tumor model; W4, Weibull 4-stage time-to-tumor model.
[b] Z is the shape parameter; it is bounded, (1<=z<=10).
[c] Selected Model.

TABLE V–17.—MAXIMUM LIKELIHOOD ESTIMATES OF MODEL COEFFICIENTS FROM VARIOUS STAGES OF WEIBULL TIME-TO-TUMOR MODELS USING FOUR TUMOR RESPONSES OF FEMALE MICE IN THE NTP II STUDY, EXCLUDING 625 PPM EXPOSURE GROUP; SELECTION OF SPECIFICATION OF MODEL IS BASED ON LIKELIHOOD RATIO TEST

Neoplasm	Stage[a]	Log-likelihood	Z[b]	q_0	q_1	q_2	q_3	q_4
Heart hemangiosarcoma	W1	−2.097 E+1	4.957	0.00	4.356 E–13			
Heart hemangiosarcoma	W2	–8.745	6.126	0.00	0.00	2.222 E–17		
Heart hemangiosarcoma	W3[c]	−4.866	6.770	0.00	0.00	0.00	8.088 E–21	
Heart hemangiosarcoma	W4	−4.267	7.011	0.00	0.00	0.00	2.637 E–22	1.368 E–3
Ovarian tumor	W1[c]	−6.140 E+1	2.857	1.407 E–8	.031 E–9			
Ovarian tumor	W2	−6.069 E+1	4.079	5.397 E–11	7.075 E–12	1.399 E–13		
Ovarian tumor	W3	−6.069 E+1	4.079	5.397 E–11	7.075 E–12	1.399 E–13	0.00	
Ovarian tumor	W4	−6.069 E+1	4.079	5.397 E–11	7.075 E–12	1.399 E–13	0.00	0.00
All lymphoma	W1[c]	−5.724 E+1	6.857	3.453 E–15	1.338 E–16			
All lymphoma	W2	−5.501 E+1	7.143	1.18 E–15	2.577 E–18	2.453 E–19		
All lymphoma	W3	−5.426 E+1	7.230	7.758 E–16	6.847 E–18	0.00	7.809 E–22	
All lymphoma	W4	−5.401 E+1	7.258	7.360 E–18	7.359 E–18	0.00	0.00	3.387 E–24
Lung tumor	W1[c]	−1.626 E+2	3.416	2.096 E–8	2.096 E–9			
Lung tumor	W2	−1.626 E+2	3.416	2.090 E–8	2.090 E—9	0.00		
Lung tumor	W3	−1.626 E+2	3.416	2.090 E–8	2.096 E–9	0.00	0.00	
Lung tumor	W4	−1.626 E+2	3.416	2.090 E–8	2.096 E–9	0.00	0.00	0.00

[a] Stage of time-to-tumor model; W1, Weibull 1-stage time-to-tumor model; W2, Weibull 2-stage time-to-tumor model; W3, Weibull 3-stage time-to-tumor model; W4, Weibull 4-stage time-to-tumor model.
[b] Z is the shape parameter; it is bounded, (1<=z<=10).
[c] Selected Model.

OSHA's Estimates of Risk

The estimates from OSHA's quantitative risk assessment based an 8-hour TWA, occupational lifetime, working 5 days/week, 50 weeks/year, for 45 years, at various BD PELS are shown in Table V–18. The MLEs of excess risk of material impairment of health per 1,000 workers for cancer, based on tumors of various tissue sites and the 95% upper bounds, are presented. Various 8-hour TWA PELS, ranging from 0.1 to 5 ppm, are presented to provide a context in which to evaluate the OSHA final rule PEL of 1 ppm and to explore the feasibility of other PELS, including the proposed PEL of 2 ppm. Risks at the former BD 8-hour TWA PEL, 1,000 ppm, are not presented in Table V–18. Although risks could be estimated for an occupational lifetime exposure to an 8-hour TWA of 1,000 ppm of BD from the linear models, there is little relevancy to estimating the true risk at an 8-hour PEL for BD at 1,000 ppm for an occupational lifetime, since

8-hour TWA BD exposures have been generally far lower than 1,000 ppm.

Although the estimates of carcinogenic outcomes differ, excess risks derived from tumor sites common to both male and female $B_6C_3F_1$ mice had the same relative ranking from lowest to highest risk estimates by target tissues (heart hemangiosarcomas < lymphomas < lungs) within each gender group. After a lifetime occupational exposure to BD at the proposed 8-hour TWA PEL of 2 ppm based on the above model fits to these three individual tumor sites, one would expect between 2.7×10^{-4} to 16.2 excess cancer cases per 1,000 workers, depending on which gender-tumor site dose-response relationship is used as the basis for the extrapolation to human occupational excess risks. Decreasing the BD 8-hour TWA PEL from 2 to 1 ppm, results in a reduction of the range of estimates of excess risk of cancer to between 3.4×10^{-5} to 8.1 cases per 1,000 workers.

The estimate of excess cancer risk based on male mouse lymphoma is 1.3 per 1,000 workers at an 8-hour TWA for an occupational lifetime exposure to 1 ppm BD. Extrapolating from female mouse lymphoma data results in an estimate of 6.0 extra cancer deaths per 1,000 workers at a BD 8-hour TWA PEL of 1 ppm for an occupational lifetime of exposure.

Extrapolating from the most sensitive site, the female mouse lung, based on the 1-stage Weibull time-to-tumor model, with an 8-hour TWA PEL of 2 ppm of BD for an occupational lifetime, one would expect 16 excess cancer cases per 1,000 workers. Lowering the PEL to 1 ppm would cut the expected number of excess cancers in half to 8 cases, based on the same gender-tumor site. Based on male lung tumors, the estimate of excess cancer deaths for an 8-hour TWA exposure to 2 ppm BD over an occupational lifetime was 12.8 per 1,000 workers; lowering the 8-hour TWA occupational lifetime exposure level to 1 ppm BD decreases the estimate of excess cancer risk to 6.4 per 1,000 workers, a reduction of 6 cancer cases per 1,000 workers.

OSHA's estimates of premature occupational leukemia deaths based on the 1-stage Weibull time-to-tumor models for the following outcome sites: All lymphoma, lung tumors, and ovarian tumors, ranged between 1.3 and 8.1 per 1,000 workers. Similarly, NIOSH's 14 estimates of the excess risk of death due to leukemia, based on 1-stage Weibull time-to-tumor models, as a consequence of exposure to an 8-hour TWA of 1 ppm BD over an occupational lifetime, ranged between 0.9 and 30 cases per 1,000 workers. The preliminary estimate of 8 per 1,000 from the Delzell et al. study is concordant with this range of animal-based estimates. OSHA acknowledges that there is uncertainty in the Delzell et al. estimate, perhaps due to the natural sampling variability present in any epidemiologic study plus the *possibility* of extra-binomial uncertainty stemming from exposure misclassification. While this uncertainty makes it difficult to say whether quantitative risk estimates would be adjusted up or down relative to animal-based estimates, this suggestion is far less important than the basic conclusion that the Delzell et al. study *reinforces* earlier estimates. Even if refinement of exposures caused the Delzell et al. estimate to move up or down by even as much as a factor of 5 or more, it would not change this qualitative, and roughly quantitative, agreement.

TABLE V–18.—MAXIMUM LIKELIHOOD ESTIMATES (MLE) AND NINETY-FIVE PERCENT UPPER BOUNDS OF LIFETIME EXTRA RISK TO DEVELOP AN OBSERVABLE TUMOR PER 1,000 WORKERS DUE TO AN 8-HOUR TWA FOR AN OCCUPATIONAL LIFETIME[a] OF EXPOSURE TO 1,3-BUTADIENE, USING NTP II BIOASSAY[b] AND THE BEST FITTING WEIBULL TIME-TO-TUMOR MODELS

Neoplasms	Stages	8-hour time-weighted average concentration[c]											
		0.1 ppm		0.2 ppm		0.5 ppm		1 ppm		2 ppm		5 ppm	
		MLE	95% U.B.[d]	MLE	95% U.B.	MLE	95% U.B.	MLE	95% U.B.	MLE	95% MLE	MLE	95% U.B.
Male mice:													
Heart Hemangiosarcoma	2	[e]<0.1	0.2	[e]<0.1	0.4	[e]<0.1	0.9	[e]<0.1	1.8	[e]< 0.1	3.6	0.4	9.1
All lymphoma	1	0.1	0.2	0.3	0.5	0.6	1.1	1.3	2.3	2.5	4.5	6.3	11.2
Lung tumor	1	0.7	0.1	1.3	2.0	3.2	4.9	6.4	9.8	12.8	19.4	31.7	47.9
Female mice:													
Heart Hemangiosarcoma	3	[f]<0.1	[f]<0.1	[f]<0.1	< 0.1	[f]<0.1	0.2	[f]< 0.1	0.5	[f]<0.1	1.0	[f]<0.1	2.4
Ovarian tumor	1	0.1	0.3	0.3	0.5	0.7	1.3	1.4	2.6	2.8	5.2	6.9	13.0
All lymphoma	1	0.6	0.9	1.2	1.8	3.0	4.6	6.0	9.2	12.0	18.3	29.7	45.0
Lung tumor	1	0.8	1.2	1.6	2.4	4.1	6.1	8.1	12.2	16.2	24.1	40.00	59.4

[a] Occupational lifetime, working 5 days/week, 50 weeks/year, for 45 years.
[b] Using data from NTP II for the following exposure groups: 0, 6.25, 20, 62.5 and 200 ppm; the 625 ppm exposure group was excluded.
[c] Estimated lifetime excess risk for cancer assuming: mouse life-span of 113 weeks, male mouse body weight of 40.8g; female mouse body weight of 38.8 g; worker's breathing rate is 1.25 m^3/hr; mouse to human risk extrapolated in mg/kg-day equivalent units.
[d] 95% U.B., 95% Upper Bounds is the largest value of excess risk that is compatible with the animal response data at a confidence level of 95%.
[e] MLEs ranged from $1.5\mu10^{-4}$ to $6.0\mu10^{-2}$
[f] MLEs ranged from $3.4\mu10^{-8}$ to $4.3\mu10^{-3}$

VII. Significance of Risk

A. Introduction

In the 1980 ''Benzene Decision,'' the Supreme Court, in its discussion of the level of risk that Congress authorized OSHA to regulate, indicated its view of the boundaries of acceptable and unacceptable risk. The Court stated:

It is the Agency's responsibility to determine in the first instance what it considers to be a ''significant'' risk. Some risks are plainly acceptable and others are plainly unacceptable. If for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2 percent benzene will be fatal, a reasonable person might well consider the risk significant and take the appropriate steps to decrease or eliminate it. (*I.U.D.* v. *A.P.I.*, 448 U.S. 607, 655).

So a risk of 1/1000 (10^{-3}) is clearly significant. It represents the uppermost

end of the million-fold range suggested by the Court, somewhere below which the boundary of acceptable versus unacceptable risk must fall.

The Court further stated that ''while the Agency must support its findings that a certain level of risk exists with substantial evidence, we recognize that its determination that a particular level of risk is significant will be based largely on policy considerations.'' With regard to the methods used to determine the risk level present (as opposed to the policy choice of whether that level is ''significant'' or not), the Court added that assessment under the OSH Act is ''not a mathematical straitjacket,'' and that ''OSHA is not required to support its findings with anything approaching scientific certainty.'' The Court ruled that ''a reviewing court [is] to give OSHA some leeway where its findings must be made on the frontiers of scientific knowledge [and that] * * * the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of overprotection rather than underprotection'' (448 U.S. at 655, 656).

Nonetheless, OSHA has taken various steps that make it fairly confident its risk assessment methodology is not designed to be overly ''conservative'' (in the sense of erring on the side of overprotection). For example, there are several options for extrapolating human risks from animal data via interspecies scaling factors. The plausible factors range at least as widely as from body weight extrapolation at one extreme (risks equivalent at equivalent body weights, $(mg/kg)^{1}$) to $(body\ weight)^{2/3}$ (risks equivalent at equivalent surface areas) at the other. Intermediate values have also been used, and the value of $(body\ weight)^{3/4}$, which is supported by physiological theory and empirical evidence, is generally considered to be the midpoint of the plausible values. $(Body\ weight)^{2/3}$ is the most conservative value in this series, while body weight extrapolation is the least conservative. OSHA has generally used body weight extrapolation in assessing risks from animal data, an approach that tends to be significantly less risk conservative than the other methodologies and is likely to be less conservative even than the central tendency of the plausible values.

Other steps in OSHA's risk assessment methodology where the Agency does not use the most conservative approach are selection of the maximum likelihood estimate (MLE) of the parameterized dose-response function rather than selection of the upper 95% confidence limit, and the use of site-specific tumor incidence, rather than pooled tumor response, in determining the dose-response function for a chemical agent.

Other aspects of OSHA's risk assessment methodology reflect more conservative choices, including: basing the risk estimate on the more sensitive species tested (the mouse); including lung tumors in the range of risks presented in the quantitative analysis, even though excess deaths from lung cancer have not been observed in any of the human studies; and, assuming workers will be exposed to butadiene at the maximum permissible level for 45 years. As discussed below, if workers are exposed to BD for fewer years, their estimated risks from BD will be less than indicated. This caveat, of course, does not address lifetime risks taking into account occupational exposure to other substances encountered at other jobs. For reasons already explained, OSHA believes these choices are appropriate for the BD risk assessment. OSHA also recognizes that use of the most conservative approach at every step of the risk assessment analysis could produce mathematical risk estimates which, because of the additive effect of multiple conservative assumptions, may overstate the likely risk. OSHA believes its quantitative risk assessment for BD strikes an appropriate balance.

Risk assessment is only one part of the process OSHA uses to regulate toxic substances in the workplace. OSHA's overall analytic approach to regulating occupational exposure to particular substances is a four-step process consistent with judicial interpretations of the OSH Act, such as the Benzene Decision, and rational policy formulation. In the first step, OSHA quantifies the pertinent health risks, to the extent possible, performing quantitative risk assessments. The Agency considers a number of factors to determine whether the substance to be regulated currently poses a significant risk to workers. These factors include the type of risk posed, the quality of the underlying data, the plausibility and precision of the risk assessment, the statistical significance of the findings and the magnitude of risk. (48 FR 1864, January 14, 1983) In the second step, OSHA considers which, if any, of the regulatory options being considered will substantially reduce the identified risks. In the third step, OSHA looks at the best available data to set permissible exposure limits that, to the extent possible, both protect employees from significant risks and are also technologically and economically feasible. In the fourth and final step, OSHA considers the most cost-effective way to fulfill its statutory mandate by crafting regulations that allow employers to reach the feasible PEL as efficiently as possible.

B. Review of Data Quality and Statistical Significance

As discussed in the Health Effects section, OSHA has concluded that butadiene is a probable human carcinogen. This conclusion is based on a body of evidence comprised of animal bioassays, human epidemiological investigations, and other experimental studies that together are both consistent in their findings and biologically plausible. First, OSHA has reviewed four rodent inhalation bioassays, two mouse bioassays conducted under the National Toxicology Program (designated NTP I and NTP II), a mouse study by Irons et al. in 1989, and a rat study sponsored by the IISRP. (Exs. 2–32, 23–1, 32–28D, 90, 96) All three mouse studies found a consistently high tumor response in BD-exposed mice, relative to control animals. Several target organs were identified, particularly by the NTP II study; however, all three studies found dose-related increases in the incidences of lymphocytic lymphoma and heart hemangiosarcomas associated with exposure to BD. Most significantly, the NTP II study reported statistically significant increases in tumor incidence among mice exposed to BD well below OSHA's current PEL of 1,000 ppm (exposure to as low as 6.25 ppm was associated with a statistically significant increase in tumors, e.g., lung tumors in female mice). There was also evidence for a dose-rate effect, meaning that the observed tumor incidence in mice exposed to high concentrations over short periods of time was higher than that observed in mice administered an equivalent cumulative concentration over a long period of time. The study employing BD-exposed rats also found increased incidences of several types of cancer, albeit at lower response rates than were observed in the mouse studies. The two major epoxide metabolites of BD have also been shown to be carcinogenic in rats and mice.

OSHA has also reviewed a number of human epidemiological studies that have examined the mortality experience of styrene-butadiene rubber (SBR) workers. These studies have consistently reported an elevated relative risk of leukemia-or lymphoma-related death among BD-exposed workers. The most recent of these, the study by Delzell et al., updated and expanded previous SBR worker mortality studies and found a positive

and statistically significant dose-response relationship between cumulative exposure to BD and increased leukemia mortality, which remained statistically significant even after controlling for the potential confounder of concurrent styrene exposure. (Ex. 117–1) The Delzell et al. study thus provides further and more directly relevant evidence that an increased risk of leukemia-related death is associated with exposure to BD. Furthermore, other epidemiologic studies have reported finding an unusually short latency period (as little as 3 to 4 years from time of initial exposure to death) for exposure-related hematologic malignancies among workers who experienced exposures to BD in the past that were higher than exposures that prevail today. (Ex. 2–26, 3–34 Vol III H–1)

Evidence for the carcinogenicity of BD is further strengthened by a collection of studies showing that the epoxide metabolites of BD are mutagenic in a wide variety of *in vitro* and *in vivo* test systems. Examination of cultured lymphocytes from BD-exposed workers has revealed the presence of chromosome aberrations, an elevated frequency of chromatid breaks, and various mutations, thereby providing direct evidence of genotoxicity in occupationally-exposed humans. (Exs. 118–2A, 118–2D) Furthermore, the finding of activated K-*ras* oncogenes in tumors of BD-exposed mice provides additional support for a mutagenic mode of action; this finding has particular relevance to human risk in that K-*ras* is the most commonly detected oncogene in human cancer. (Ex. 129)

The findings from the animal bioassays and human epidemiologic studies identify the hematopoietic system as a primary target organ for BD-related carcinogenesis. Target organs for toxicity are not necessarily those for carcinogenicity. Other experimental findings are consistent with these observations. Studies in BD-exposed rodents have found concentration-dependent decreases in red blood cell counts, hemoglobin concentration, and other indicators of hematopoietic suppression. (Exs. 114, 32–38D, 23–12) There is also some suggestive evidence that workers exposed to BD at levels well below the current 1,000 ppm PEL exhibit hematological changes indicative of bone marrow depression. (Exs. 23–4, 2–28) Finally, many of the tumor types found in BD-exposed mice, including lymphocytic/hematopoietic cancer, lung cancer, mammary gland tumors, and possibly hemangiosarcomas, are tumors that are often found in association with exposure to other industrial chemicals known to cause lymphocytic/hematopoietic cancer in humans. Thus, OSHA finds that the body of scientific studies contained in the BD record, which includes well-conducted animal bioassays, human epidemiologic studies, and other experimental investigations, provides convincing evidence that BD is a probable human carcinogen.

This view is also held by other scientific organizations that have examined some or all of the same evidence. EPA considers BD to be a probable human carcinogen, and NIOSH regards BD as a potential occupational carcinogen and recommends controlling exposures to the lowest feasible level. In 1983, based on the findings of the first NTP bioassay alone, ACGIH classified BD as an animal carcinogen and, in the following year, recommended a new TLV of 10 ppm. In 1992, before the Delzell et al. study was released, IARC classified BD as a probable human carcinogen (Group 2A).

As discussed in the Quantitative Risk Assessment section, OSHA has selected the NTP II mouse bioassay for quantitative assessment of cancer risks for several reasons. Chief among these is that the NTP II study was conducted at BD concentrations that are representative of current exposure conditions and that the results demonstrated a strong dose-response relationship for several cancer sites. In addition, the study is of very high quality and pathology results from individual animals were available to the Agency, enabling OSHA to use a time-to-tumor model that could account for the early cancer-related deaths that occurred among the test animals (competing risks). OSHA also chose to base its risk estimates on the dose-response relationships for three cancer types: lung, ovarian, and lymphoma. The incidence of each was significantly elevated. It should be noted that pooling the total number of animals having any of these tumor types would have yielded risk estimates higher than OSHA's final values.

Because data were available on individual animals, including time of death, OSHA chose to use a Weibull time-to tumor form of the multistage model based on the biological assumption that cancer is induced by carcinogens through a series of events. This model has the advantage of accounting for competing risks.

The multistage model is most frequently used by OSHA; it is also a mechanistic model based on the biological assumption that cancer is induced by carcinogens through a series of independent stages. The model may be conservative, because it assumes no threshold for carcinogenesis and because it is approximately linear at low doses, although there are other plausible models of carcinogenesis which are more conservative. The Agency believes that the multistage model conforms most closely to what we know about the etiology of cancer, including the fact that linear-at-low-dose behavior is expected for exogenous agents, which increases the risk of cancer already posed by similar ''background'' processes. There is no evidence that the multistage model is biologically incorrect and abundant evidence supports its use, especially for genotoxic carcinogens, a category that most likely includes BD. OSHA's preference is consistent with the position of the Office of Science and Technology Policy of the Executive Office of the President, which recommends that ''when data and information are limited, and when much uncertainty exists regarding the mechanisms of carcinogenic action, models or procedures that incorporate low-dose linearity are preferred when compatible with limited information.'' (OSTP, Chemical Carcinogens: A Review of the Science and Its Associated Principles. Federal Register, March 14, 1985, p. 10379)

The BD record contained a great deal of commentary on the possible role of the principal epoxide metabolites of BD on the development of cancer in test animals, and on whether differences in BD metabolism, distribution, and excretion can explain the observed differences in cancer responses between BD-exposed mice and rats. In evaluating this information, OSHA explored the possibility of using a physiologically-based pharmacokinetic (PBPK) approach to estimate cancer risk among BD-exposed workers. In considering the use of PBPK modeling for estimating equivalent human dose in its final risk assessment for BD, OSHA considered several preselected criteria for judging whether the available data was adequate to permit OSHA to rely on a PBPK analysis in place of administered exposure levels. These are the same criteria that OSHA has recently used to rely on a PBPK-based analysis in its risk assessment of methylene chloride. The criteria included the following:

1. The predominant and all relevant minor metabolic pathways must be well described in several species, including humans.

2. The metabolism must be adequately modeled.

3. There must be strong empirical support for the putative mechanism of carcinogenesis.

4. The kinetics for the putative carcinogenic metabolic pathway must have been measured in test animals *in vivo* and *in vitro* and in corresponding human tissues at least *in vitro.*

5. The putative carcinogenic metabolic pathway must contain metabolites that are plausible proximate carcinogens.

6. The contribution to carcinogenesis via other pathways must be adequately modeled or ruled out as a factor.

7. The dose surrogate in target tissues used in PBPK modeling must correlate with tumor responses experienced by test animals.

8. All biochemical parameters specific to the compound, such as blood:air partition coefficients, must have been experimentally and reproducibly measured. This must especially be true for those parameters to which the PBPK model is sensitive.

9. The model must adequately describe experimentally measured physiological and biochemical phenomena.

10. The PBPK models must have been validated with other data (including human data) that were not used to construct the models.

11. There must be sufficient data, especially data from a broadly representative sample of humans, to assess uncertainty and variability in the PBPK modeling.

For the BD risk assessment, OSHA has chosen to use for animal-to-human dose equivalency mg/kg-day uptake based on the ppm exposure levels in the NTP II mouse study as the dose-metric.[7] While the body of data in the record leads OSHA to conclude that metabolism of BD to active metabolites is probably necessary for carcinogenicity, OSHA has chosen total body uptake rather than organ metabolic levels because the Agency was unable to determine from the record (a) which of the active metabolites are responsible for which observed tumors in the mice, (b) what the mouse and human metabolic equivalent doses were, (c) whether any of the PBPK models can successfully correlate with the tumor responses observed in mice and rats, and (d) whether local reactions in the mouse and human bone marrow were more important than total body burden.

[7] A dose metric is the way in which dose is expressed in describing a dose-response relationship. A dose metric may be expressed as an applied dose, such as ppm concentration or mg of intake per kg body weight, or as an internal dose, such as mg per gram wet weight of an organ or mg of total metabolite formed per kg body weight.

OSHA would have considered using BD metabolite body burden based on total human BD metabolites if the human chamber concentration data had been available, which would support estimating total human BD metabolism. Data of this type were available and used in OSHA's PBPK modeling for methylene chloride. In the absence of human chamber data or some better estimate of human equivalent dose, OSHA has chosen to use mg/kg-day BD uptake from the ppm inhalation exposure levels in the NTP II mouse bioassay as suitable for animal-to-human equivalency.

C. Material Impairment of Health

The 1 ppm 8-hour TWA PEL is designed to reduce cancer risks among exposed workers. As mentioned above and in the Health Effects section, some epidemiological studies indicate that the increased risk of leukemia posed by BD exposure may occur within a short period after initial exposure. (This is supported by the NTP mouse bioassays, in which there was high early mortality resulting from the development of BD-induced cancers, especially lymphomas.) Therefore, OSHA believes these hematopoietic cancers are likely to be fatal, will result in substantially shortened worker lifespans, and clearly represent ''material impairment of health'' as defined in the OSH Act and case law.

OSHA has also concluded that exposure to BD is associated with a potential risk of adverse reproductive effects in both males and females. This conclusion is based on the two NTP animal bioassays, which found testicular atrophy in male mice exposed to 625 ppm BD and ovarian atrophy in female mice exposed to BD concentrations as low as 6.25 ppm, as well as other animal studies that have reported dominant lethal effects (indicating a genotoxic effect on germ cells) and abnormal sperm morphology in BD-exposed male mice. (Exs. 23–74, 23–75, 117–1) There is also evidence that BD exposure is associated with fetotoxicity in mice, and a teratogenic effect indicative of a transplacentally induced somatic cell mutation was observed in one mouse study. (Exs. 2–32, 23–72, 126) OSHA believes that teratogenic effects and gonadal atrophy would also unambiguously constitute ''material impairment of health.'' Furthermore, although OSHA did not quantify reproductive risks that may be associated with exposure to BD, OSHA believes that reducing the 8-hour TWA PEL from 1,000 ppm to 1 ppm is likely to substantially reduce this risk.

D. Risk Estimates

OSHA's final estimate of excess cancer risks associated with exposure to 5 ppm BD (8-hour TWA) ranges from 11.2 to 59.4 per 1000, based on lymphomas, lung tumors and ovarian tumors seen in the NTP II mouse study (OSHA did not estimate the risks associated with exposure to the current PEL of 1,000 ppm, since workers are rarely, if ever, exposed to BD levels of that magnitude). Based on linear models the estimated risks at the new PEL of 1 ppm range from 1.3 to 8.1 per 1000, which represents a substantial reduction in risk from those associated with exposures to 5 ppm or greater.

OSHA's risk estimates for the 1 ppm PEL are similar in magnitude to, or lower than, most of the estimates contained in several risk assessments submitted to the BD record, which utilized a variety of models and dose metrics. Furthermore, NIOSH's quantitative assessment based on the Delzell et al. epidemiologic study of SBR workers yielded an estimate of 8 cancer deaths per 1,000 workers exposed to 1 ppm BD, a figure that is in close agreement with the upper end of the range of risks predicted by OSHA.

Risks greater than or equal to 10^{-3} (1 per 1,000) are clearly significant and the Agency deems them unacceptably high. OSHA concludes that the new BD standard substantially lowers risk but does not reduce risk below the level of insignificance. The estimated levels of risk at 1 ppm are 1.3 to 8.1 per 1000. The ancillary provisions including the exposure goal program will further reduce risk from exposure to BD.

E. ''Significant Risk'' Policy Issues

Further guidance for the Agency in evaluating significant risk and narrowing the million-fold range described in the ''Benzene Decision'' is provided by an examination of occupational risk rates, legislative intent, and the academic literature on ''acceptable risk'' issues. For example, in the high risk occupations of mining and quarrying, the average risk of death from an occupational injury or an acute occupationally-related illness over a lifetime of employment (45 years) is 15.1 per 1,000 workers. The typical occupational risk of deaths for all manufacturing industries is 1.98 per 1,000. Typical lifetime occupational risk of death in an occupation of relatively low risk, like retail trade, is 0.82 per 1,000. (These rates are averages derived from 1984–1986 Bureau of Labor Statistics data for employers with 11 or more employees, adjusted to 45 years of employment, for 50 weeks per year).

Congress passed the Occupational Safety and Health Act of 1970 because of a determination that occupational safety and health risks were too high. Congress therefore gave OSHA authority to reduce significant risks when it is feasible to do so. Within this context, OSHA's final estimate of risk from occupational exposure to BD at levels of 2 ppm (2.5 to 16.2 deaths per 1,000 workers) or higher is substantially higher than other risks that OSHA has concluded are significant, is substantially higher than the risk of fatality in some high-risk occupations, and is substantially higher than the example presented by the Supreme Court in the benzene case. Moreover, a risk in the range of 1.3 to 8.1 per 1000 at 1 ppm is also clearly significant; therefore, the PEL must be set at least as low as the level of 1 ppm documented as feasible across all industries.

Because of technologic feasibility considerations, OSHA could not support promulgating a PEL below 1 ppm. However OSHA has integrated other protective provisions into the final standard to further reduce the risk of developing cancer among employees exposed to BD.

Based on OSHA's QRA, employees exposed to BD at the 8-hour TWA PEL limit, without the benefit of the supplementary provisions, would remain at significant risk of developing adverse health effects, so that inclusion of other protective provisions, such as medical surveillance and employee training, is both necessary and appropriate. The exposure goal program and action level trigger incorporated into the standard will encourage employers to lower exposures below 0.5 ppm to further reduce significant risk if it is feasible to do so in their workplaces. Consequently, the programs triggered by the action level will further decrease the incidence of disease beyond the predicted reductions attributable merely to a lower PEL.

As OSHA has explained, numerous issues arise in quantifying estimated risk to workers from BD. Such estimates are thus inherently uncertain; and, as more information becomes available, some of that uncertainty may be addressed and may substantially alter the risk estimate. Although OSHA believes the estimates fulfill its legal obligation to provide substantial evidence of significant risk the estimates should not be interpreted as a precise quantification of the cancer risk associated with the new PEL, or as demonstrated evidence of actual worker disease caused by BD.

OSHA's determination of significant risk is predicated, consistent with empirical evidence and the legal mandates of the OSHA Act, on determining the risk to a worker exposed to BD for a working lifetime (45 years) at the PEL. To the extent that future exposures to BD are (substantially) lower than 1 ppm, the estimated risks associated with those exposures will be (substantially) lower than the range presented in OSHA's QRA.

OSHA believes the final standard will reduce the risks of BD below those estimated using the mathematical model. The estimates of risk consider only exposures at the PEL, and do not take fully into account the other protective provisions of the standard such as medical surveillance, hazard communication, training, monitoring, and the exposure goal program. The decrease in risk to be achieved by additional provisions cannot be adequately quantified beyond a determination that they will add to the protection provided by the lower PEL alone. OSHA has determined that employers who fulfill the provisions of the standard as promulgated will provide protection for their employees from the hazards presented by occupational exposure to BD well beyond those which would be indicated solely by reduction of the PEL.

Furthermore, as discussed above and in the Health Effects section, there is evidence from the NTP bioassays that exposure to periodic high concentrations of BD may be associated with a higher cancer risk compared to an equivalent cumulative exposure administered over a longer time frame. OSHA has included a 5 ppm short-term exposure limit (STEL), averaged over 15 minutes, to provide protection to employees who are exposed to elevated BD concentrations during brief periods, such as in maintenance work.

As a result, OSHA concludes that its 8-hour TWA PEL of 1 ppm and associated action level (0.5 ppm) and STEL (5 ppm) will reduce significant risk and that employers who comply with the other provisions of the standard will be taking feasible, reasonable, and necessary steps to help protect their employees from the hazards of BD.

VIII. Summary of the Final Economic Analysis

As required by Executive Order 12866 and the Regulatory Flexibility Act of 1980 (as amended 1996), OSHA has prepared a Final Economic Analysis to accompany the final standard for occupational exposure to 1,3-butadiene (BD). (The entire analysis, with supporting appendix material, has been placed in the BD rulemaking docket. See Exhibit 137.) The purpose of the final economic analysis is to:

- Describe the need for a standard governing occupational exposure to 1,3-butadiene;
- Identify the establishments and industries potentially affected by the standard;
- Evaluate the costs, benefits, economic impacts and small business impacts of the standard on affected firms;
- Assess the technological and economic feasibility of the standard for affected establishments, industries, and small businesses; and
- Evaluate the availability of effective non-regulatory approaches to the problem of occupational exposure to 1,3-butadiene.

Need for the Standard

OSHA's final BD standard covers occupational exposures to this substance, a high-volume chemical used principally as a monomer in the manufacture of a wide range of synthetic rubber and plastic polymers and copolymers. In all, about 9,700 employees are estimated to be exposed to BD. However, for 2,100 of these employees in the petroleum refining industry, BD exposures are below the action level. The largest group of exposed workers is found in the BD end-product industry. Other BD operations in which workers are exposed are crude BD production, BD monomer production, and transportation terminals handling BD monomers (stand-alone terminals).

There is strong evidence that workplace exposure to BD poses an increased risk of cancer. Animal bioassays have shown BD to be a source of significant risk for tumors at multiple sites (i.e. lung tumors, heart hemangiosarcomas, lymphomas and ovarian tumors). BD may also potentially cause both male and female reproductive effects. To protect all BD-exposed workers from these adverse health effects, the final standard lowers the airborne concentration of BD to which workers may be exposed from the current permissible exposure limit (PEL) of 1,000 ppm as an 8-hour time-weighted average (8-hour TWA) to 1 ppm, and adds a short term exposure limit (STEL) of 5 ppm, measured over 15 minutes. (For a detailed discussion of the risks posed to workers from exposure to BD, see the Quantitative Risk Assessment and Significance of Risk sections of the preamble, above.)

OSHA's final BD standard is similar in format and content to other health standards issued under Section 6 (b)(5)

of the Act. In addition to PELs, the standard requires employers to monitor the exposures of workers; establish regulated areas when exposures may exceed one of these PELs; implement engineering and work practice controls to reduce employee exposures to BD; develop an exposure goal program; provide respiratory protection to supplement engineering controls where such controls are not feasible, are insufficient to meet the PELs, are necessary for short infrequent jobs, or in emergencies; provide medical screening; train workers about the hazards of BD (also required by OSHA's Hazard Communication Standard); and keep records relating to the BD standard. Recognizing that workers exposed to BD are at significant risk, an industry-labor working group joined together to develop joint recommendations for the final standard for BD. This group's recommendations form the basis for OSHA's final rule. The contents of the standard are explained briefly in Chapter I of the final economic analysis and in detail in the Summary and Explanation (Section X of the preamble, below).

Chapter II of the economic analysis describes the uses of BD and the industries in which such use occurs. Exposure to 1,3-butadiene occurs as a result of exposure to the monomer. Once BD is in polymer form, the exposure is minimal to non-existent. In all, OSHA analyzed 5 types of processes in which BD exposure occurs: crude BD production, where the feedstock for BD monomer is produced; BD monomer production, in which BD is refined from crude BD to a 99 percent pure monomer; BD product manufacture, where BD monomer is converted to various polymer products; stand-alone terminals, which receive, store and distribute BD monomer; and petroleum refineries, where BD may occur as an unwanted byproduct in some types of refining units. Table VIII–1 shows these industry operations and the number of workers affected by the final rule. A total of 255 facilities are estimated to be potentially affected by the standard. These establishments employ 9,700 workers who are estimated to be exposed to BD in the course of their work. The industry operation with the largest number of directly exposed employees is BD product manufacture, which has 6,500 exposed employees (over two-thirds of the total).

TABLE VIII–1.—INDUSTRY OPERATIONS AND NUMBER OF WORKERS AFFECTED BY THE FINAL RULE FOR 1,3-BUTADIENE

	Number of affected workers	Number of facilities in industry [a]
Crude 1,3-Butadiene Production	540	27
1,3-Butadiene Monomer Production	552	12
1,3-Butadiene Polymer Product Manufacture	6,461	[c] 71
Standard-Alone Terminals	50	5
Subtotal	7,603	115
Petroleum Refining Sector	[b] 2,100	140
Total	9,703	255

Source: U.S. Department of Labor, OSHA, Office of Regulatory Analysis, 1996.

[a] Some facilities may fall under several industry sectors. For example, 9 monomer facilities are also crude producing facilities.

[b] Potential exposures to 1,3-butadiene are low and of extremely short duration in refining.

[c] Represents number of processes and not necessarily plants.

Chapter III of the analysis assesses the technological feasibility of the final standard's requirements, and particularly its PELs, for firms in the 5 industry operations with employee exposure identified in the Industry Profile. OSHA finds, based on an analysis of exposure data taken on workers performing the BD-related tasks identified for each operation, that compliance with the standard is technologically feasible for establishments in the industries studied. With few exceptions, employers will be able to achieve compliance with both PELs through the use of engineering controls and work practices. The few exceptions are maintenance activities, such as vessel cleaning, which have traditionally often involved the use of respiratory protection.

The exposure data relied on by OSHA in making its technological feasibility determinations were gathered by NIOSH in a series of site visits to plants in the affected industries. These data show that many facilities in the affected industries have already achieved the reductions in employee exposures required by the final rule. At least some workers in every job category work in facilities that have already achieved the PEL requirements. OSHA's analysis of technological feasibility evaluates employee exposures at the operation or task level to the extent that such data are available. In other words, the analysis identifies relevant exposure data on a job category-by-job category basis to permit the Agency to pinpoint those BD-exposed workers and job operations that are not yet under good process control and will thus need additional controls (including improved housekeeping, maintenance procedures, and employee work practices) to achieve compliance. Costs are then developed (in Chapter V of the economic analysis) for the improved controls needed to reach the new levels.

The benefits that will accrue to BD-exposed employees and their employers, and thus to society at large, are substantial and take a number of forms. Chapter IV of the analysis describes these benefits, both in quantitative and qualitative form. At the current baseline exposure levels to BD, the risk model estimates that 76 cancer deaths will be averted over a 45-year period. By reducing the total number of BD-related cancer deaths from 76 deaths to 17 deaths over 45 years, the standard is projected to save an average of 1.3 cancer deaths per year. Table VIII–2 shows these risk estimates. In addition to cancer deaths, the standard may prevent male and female reproductive effects.

TABLE VIII–2.—WORKER EXPOSURE TO BD AND LUNG CANCER RISK OVER 45 YEARS AT CURRENT EXPOSURE LEVELS AND LEVELS EXPECTED UNDER THE STANDARD

	8-hour time weighted average (ppm)							
	0–0.5	0.5–1.0	1	1.0–2.0	2.0–5.0	5.0–10.0	10+[c]	Total
Lifetime Excess Cancer Risk (per thousand workers)[a]	2.05	6.1	8.1	12.15	28.1	60	480	.....
Baseline Number of Workers Exposed	5697	354	156	598	320	440	38	7603
Estimated Excess Deaths in Baseline (Existing PEL)[b]	12	2	1	7	9	27	18	76
Predicted Number of Workers Exposed at New PEL	7177	426	0	0	0	0	0	7603