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Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens (MD WC-05)
111 Alexander Drive
Research Triangle Park, NC 27709

**Re: Review of 1,3-Butadiene for NTP's
Biennial Report on Carcinogens**

Dear Dr. Jameson:

The International Institute of Synthetic Rubber Producers (IISRP) has been conducting important toxicologic and epidemiologic research on 1,3-butadiene for more than a decade. We anticipate that our updated study of styrene-butadiene rubber (SBR) manufacturing workers by Dr. Delzell, *et al.*, will be one of the primary reports the National Toxicology Program will review in preparing its Ninth Report on Carcinogens (62 Fed. Reg. 37272, July 11, 1997).

We urge NTP to consider the interpretative comment now available and the follow-up research now underway to elucidate the results of the Delzell study. We believe there are significant issues regarding butadiene and human carcinogenicity that this active research program can reasonably be expected to address. Accordingly, to assist NTP's review, we are transmitting the following:

Himmelstein, et al., "Toxicology and Epidemiology of 1,3-Butadiene" (published in *Critical Reviews in Toxicology*, 27(1): 1-108, 1997) and 1-3 Butadiene OEL Criteria Document (2nd Ed.) (Special Report No. 12 of the European Centre for Ecotoxicology and Toxicology of Chemicals).

These two recent reviews of butadiene health effects contain in-depth discussions of the epidemiologic cancer mortality and incidence database, including the Delzell study and the other recent studies by Divine & Hartman, Cowles, and Ward. Both reviews call attention to various uncertainties concerning the observed leukemia excess in the Delzell study that require further study. These include the absence of such an association among butadiene monomer workers, the absence of specificity in the association with respect to leukemia cell type, and the possibility that short-term, high level exposures may be

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responsible for the excess. Each of these uncertainties is the subject of ongoing research as detailed below.

The Possibility of a Confounding Factor in the SBR Industry.

The absence of a leukemia association among BD monomer workers has stimulated inquiry into differences between that industry and the SBR industry to see if there are possible confounding exposures in the latter facilities that might be responsible for the association in the Delzell study. One possibility being researched is dimethyldithiocarbamate (DMDTC), a compound used as a polymerization stopper in the SBR process between 1948 and 1965, which is biologically active. This issue was addressed by Dr. Richard Irons of the University of Colorado at the July 9, 1997, Toxicology Forum meeting. A transcript of this meeting will be available later this year and will be provided to NTP. Dr. Irons is conducting further research in this area.

Leukemia Cell Type Analysis and Exposure Re-Assessment

A number of follow-up assessments of the Delzell study are being pursued by IISRP. First, work is underway to identify the cell types of all leukemia cases in the study to determine whether the observed excess was limited to any of the four types (acute and chronic lymphocytic and acute and chronic nonlymphocytic). Second, various questions have been raised about the exposure estimates and the exposure modeling methodology employed in the Delzell report. These questions are relevant to dose-response analysis (one criterion for causality) and risk characterization and are being examined through a rigorous review of all exposure estimating methods. Initially, this review was conducted with respect to exposure in one plant; a second phase encompassing the other plants is now underway.

* * * *

We look forward to a continuing dialogue with NTP and its Board of Scientific Counselors as they review butadiene. As noted above, the on-going research is directly relevant to assessment of whether butadiene is a human carcinogen. As further information becomes available on our research programs, we will forward it; in the meantime, if you have any questions, please contact us.

Sincerely yours,



Richard Killian
IISRP Managing Director

12.4 FINAL EVALUATION AND RECOMMENDATION

12.4.1 Hazard Identification

Based on considerable evidence from both animal and epidemiological studies it is clear that the critical health effect related to exposure to 1,3-BD is carcinogenicity. It follows that protection against carcinogenic hazard will protect for all other possible health effects of 1,3-BD.

Since 1,3-BD is a gas at room temperature, skin absorption is not a concern and a skin notation is not warranted (ECETOC, 1993b).

12.4.2 Risk Assessment

12.4.2.1 Animal Data

1,3-BD is transformed in the body by both activation and deactivation processes. Oxidation by cytochrome P₄₅₀ to the mono and diepoxides may be followed by hydrolysis to the diols or conjugation with GSH. Studies in rodents show that the balance between activation and deactivation in the mouse favours the formation of free epoxides in tissues and blood. The levels of these metabolites are much lower in rats than in mice as this balance is markedly different.

Genotoxic activity has been demonstrated clearly in the mouse and equivocally in the hamster, but not in other non-human species. Consequently it is clear that the potency of 1,3-BD to induce genotoxic effects in mice is higher than in other species. Nevertheless, the metabolites of 1,3-BD thought to be responsible for the genotoxic action in mice are formed in other mammals, although the rates of formation and detoxification differ considerably.

1,3-BD is a multi-organ carcinogen in both the rat and the mouse. In a two-year bioassay 1,3-BD produced lung tumours in female mice at concentrations as low as 6.25 ppm, the lowest concentration tested. Rats are very much less susceptible to the effects of 1,3-BD with significant increases of treatment-related tumours observed only following exposures to 8,000 ppm. As the tumour types, incidences and concentrations eliciting tumour responses in rats and mice are so different it is probable that the mechanisms of action of 1,3-BD are different in the two species. 1,3-BD is a genotoxic carcinogen in mice, whereas in rats, tumours are seen only in endocrine-sensitive organs suggesting a non-genotoxic process. To further complicate the analysis, T-cell lymphomas in mice are also known to be derived from non-genotoxic mechanisms resulting from a cytotoxic effect of the monoepoxide on a sub-population of haematopoietic stem cells in the mouse. This effect is unique to the mouse.

exposure and the relationship between chronic lymphocytic leukaemia and 1,3-BD exposure was much weaker than that observed between all leukaemias and 1,3-BD exposure (Delzell *et al*, 1995).

Taken at face value, the SBR workers' findings indicate a lowest effect level in the 20-99 ppm-years category and no increased risk for the 1-19 ppm-years category. However, Delzell *et al* (1995) present a series of Poisson regression analyses based on different cut-off points and a variety of structural forms for relative risk including linear, multiplicative, power and polynomial, which indicate that the trend is not uniform or well defined. Some of these analyses do not show a steadily increasing relative risk with 1,3-BD exposure as observed in Table XXIX. One analysis based on cut-off points of 25, 50 and 150 ppm-years shows barely increased relative risks for 0.1-24 ppm-years (RR = 1.2, 19 leukaemias) and 50-149 ppm-years (RR = 1.3, 10 leukaemias). The highest relative risk was in the 150+ ppm-years (RR = 3.8, 11 leukaemias) and the relative risk was also elevated in the 25-49 ppm-years category. Analyses which incorporate nine exposure categories show a random, but increased, pattern of relative risk in the six exposure categories between 5 and 200 ppm years. These analyses suggest that some caution is required when attempting to derive a working lifetime safe level.

The dose response relationship between leukaemia and cumulative exposure in the SBR study is poorly defined. Cumulative exposure to 1,3-BD was only just significant at a 5% level in analyses using a range of models which incorporated a single term for 1,3-BD exposure. One explanation for this poor relationship is that the cumulative exposure metric is an inappropriate starting point for calculating a numerical value for a working lifetime safe level. The groups exhibiting elevated leukaemia rates in the SBR workers study are those that experienced intermittent high exposures. This suggests that high level intermittent exposures may be more important for the critical effect than long periods of low exposure. Support for this concept is also provided by the data from stop exposure studies in the mouse.

Analyses of the SBR workers data that also take into account exposure to peaks of greater than 100 ppm, indicated that the highest relative risks were observed for workers with exposure to peaks and cumulative exposures of over 200 ppm years, but that there was no increased relative risk in workers exposed to less than 100 ppm years who never experienced exposure to peaks of 100 ppm or more (Delzell *et al*, 1996a). The median exposure of workers in the 20-99 ppm-years exposure category was 42.7 ppm-years which would suggest that a cumulative exposure of 40 ppm-years is a conservative working lifetime safe level.

A number of other considerations suggest that the working lifetime safe level is at least as high as 40 ppm-years. The quantitative exposure assessment for SBR workers, while remarkable in methods and scope, had a number of conventions that might underestimate exposure. In addition, exposures characteristic of the monomer industry from 1943-1994 were not related to excess leukaemia risk.

12.4.3 Derivation of Occupational Exposure Limit Value

The following factors provide the basis for deriving an OEL for 1,3-BD.

- Leukaemia is the critical health effect from epidemiological studies.
- The dose-response relationship between leukaemia and cumulative exposure in the SBR study is poorly defined at cumulative exposure levels below 150 ppm-years. Consequently it is difficult to define a working lifetime safe level using only information about cumulative exposure.
- A recent analysis of the SBR study data incorporating information about peak exposure has demonstrated the significance of peak exposures in man. The data from stop-exposure studies in the mouse suggest that the cumulative exposure metric alone is an imperfect starting point for calculating a numerical value for an OEL because short periods of high exposure may be more important than long periods of low exposure.
- Analyses of the SBR workers data that also take into account exposure to peaks of greater than 100 ppm, indicated that the highest relative risks were observed for workers with exposure to peaks and cumulative exposures of over 200 ppm-years. There was no increased relative risk in workers assigned to the 20-99 ppm-years exposure group who never experienced exposure to peaks of 100 ppm or more. Consequently this concentration (100 ppm) can be used to define a working lifetime safe level.
- A conservative approach would be to take the median exposure of workers in this group, i.e. 42.7 ppm-years as an effective working lifetime safe level.
- Additional margins of safety are built into the above argument as there is little evidence that there was increased risk in workers exposed to 1,3-BD below 200 ppm-years and that exposures may have been underestimated in the SBR workers study.
- The above arguments indicate that an OEL of 1 ppm would protect workers against non-neoplastic and neoplastic effects.
- Exposures characteristic of the monomer industry from 1943-1994 were not related to excess leukaemia risk although it is likely that exposures to 1,3-BD would have been well in excess of 1 ppm.

12.4.4 Recommendation

An OEL of 1 ppm (8-h TWA) is recommended for 1,3-BD.

Peak exposures are central to the epidemiological data and consequently a STEL is required to protect against potential effects. However, it is not possible to define a STEL on a scientific basis. Thus, a STEL of 10 ppm (15-min TWA) is recommended on a pragmatic basis, being 10 times the recommended OEL.

No skin notation is warranted.

At present no method for biological monitoring can be recommended.

A number of suitable methods are available for short-term, long-term and continuous sampling measurements of 1,3-BD at the recommended OEL of 1 ppm.

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ABSTRACT: 1,3-Butadiene is a colorless, volatile gas that has high-volume usage in the synthesis of polybutadiene, styrene-butadiene, and other polymers. Due to its volatile nature, uptake of butadiene occurs almost exclusively by inhalation and absorption through the respiratory system. Sources of exposure include production, transport, and end-use processes in industrial settings or environmental exposures through automotive fuel, fossil fuel combustion, and cigarette smoke. Chronic inhalation studies established that butadiene is carcinogenic in B6C3F1 mice and Sprague-Dawley rats, and that mice are considerably more sensitive than rats. For the most part, epidemiologic studies for butadiene have been equivocal, although a recent retrospective follow-up study of styrene-butadiene rubber workers provides the first internally consistent evidence of a relationship between butadiene exposure and leukemia. The mechanism(s) of butadiene-induced carcinogenicity are not entirely understood but are thought to involve covalent interactions of the butadiene epoxide metabolites, epoxybutene and diepoxybutane, with DNA. Species differences in butadiene metabolism are evident. *In vitro* and *in vivo* studies clearly reveal that mice have a higher capacity to form reactive epoxides than rats or humans. This is reflected by the very high levels of epoxides in blood and tissues of mice compared with rats exposed to butadiene. These differences in metabolism may explain the greater sensitivity of mice to the carcinogenicity of butadiene. *In vitro* metabolism data for humans show interindividual variation, but when compared with other species, the data for humans closely parallel metabolism in the rat, suggesting that the use of mice for quantitative risk assessments overestimates the potency of butadiene in humans. The metabolism findings are corroborated by genotoxicity studies in laboratory animals and humans occupationally exposed to butadiene. The use of physiologically based pharmacokinetic modeling approaches to estimate butadiene epoxide burdens has made notable progress and thus promises to be an integrating factor in understanding interspecies differences in metabolism, disposition, and high-to-low dose extrapolation. This review summarizes the available data on the epidemiology, toxicity (cancer and noncancer), genotoxicity, metabolism, toxicokinetics, biomonitoring, and risk assessment of butadiene. The goal is to enumerate key research issues that, when interpreted as a whole, will aid in producing realistic estimates of risk for humans exposed to butadiene.

KEY WORDS: toxicology, epidemiology, 1,3-butadiene, volatile gas, polybutadiene, styrene-butadiene.

I. INTRODUCTION

During the last two decades, a considerable amount of literature has been published on various aspects of butadiene toxicology. However, it was not until after the literature summarizing the carcinogenicity of butadiene in laboratory animals was published (mid-to-late 1980s) that a significant effort was expended to explore the mechanisms of action for this compound. A significant body of data has been published on butadiene epidemiology and biochemical and molecular studies with butadiene. Several risk assessments have been conducted by both the government and the private sector.

Existing reviews of the butadiene toxicologic and epidemiologic literature include those published by Choudary (1994), Birnbaum (1993), European Centre for Ecotoxicology and Toxicol-

ogy of Chemicals (ECETOC) (1993), Agency for Toxic Substances and Disease Registry (ATSDR) (1992), Health Effects Institute (HEI) (1993), International Agency for Research on Cancer (IARC) (1992), Melnick et al. (1990a), and de Meester (1988). The purpose of this review is to consolidate and critically assess research findings on various aspects of butadiene epidemiology (exposure assessment, case-control studies, and cohort studies), toxicity (acute, cancer, and noncancer effects), genotoxicity, metabolism and toxicokinetics, biomarkers of exposure, and the risk assessment of butadiene.

II. GENERAL CONSIDERATIONS

1,3-Butadiene* is a colorless gas (Merck Index, 1989) that is produced commercially as a by-product of ethylene production during the steam

* CAS #106-99-0: synonyms: α,γ -butadiene, bivinyl, divinyl, erythrene, biethylene, pyrrolylene, and vinyl ethylene.