



CHEMICAL MANUFACTURERS ASSOCIATION

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October 28, 1997

VIA FEDERAL EXPRESS

Dr. Larry G. Hart
Executive Secretary
National Toxicology Program
Report on Carcinogens (MD WC-05)
111 Alexander Drive, Bldg. 101
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Review of 1,3-Butadiene Classification for
the Report on Carcinogens, Ninth Edition

Dear Dr. Hart:

The Chemical Manufacturers Association Olefins Panel (Panel) is submitting these comments in response to the National Toxicology Program (NTP) request for input to its review of 1,3-butadiene for listing in the 9th Report on Carcinogens. 62 Fed. Reg. 51674 (October 2, 1997). NTP has prepared a Draft Background Document for 1, 3-Butadiene ("Draft Background Document") which contains a tentative recommendation that butadiene be classified as "known to be a human carcinogen." These comments address the discussion of the underlying data in the Draft Background Document as well as the tentative cancer classification recommendation. Members of the Olefins Panel include the major domestic producers and importers as well as some users of butadiene.¹

¹ Members of the Panel include: Asahi Chemical Industries, America; Amoco Chemical Company; BP Chemicals, Inc.; Chevron Chemical Company; The Dow Chemical Company; DuPont; Eastman Chemical Company; Exxon Chemical Company; Huntsman Corporation; Lyondell Petrochemical Company; Occidental Chemical Corporation; Shell Oil Company; and Union Carbide Corporation.



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BACKGROUND AND INTRODUCTION

The Panel submitted a letter to NTP on August 22, 1997, in response to a previous Federal Register notice soliciting input to NTP's review of butadiene's cancer classification. The Panel included with that letter a copy of a brochure describing the Panel's ongoing butadiene toxicological research program. The Panel also urged NTP to consider information contained in two recent butadiene toxicology reviews by Himmelstein *et al.* (1997) and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1997).² Both of these documents were provided as attachments to a separate letter submitted in August, 1997 by the International Institute of Synthetic Rubber Producers (IISRP).

The Draft Background Document for butadiene is dated September 29, 1997, and was not received by the Panel until October 6, 1997. Accordingly, this letter provides only preliminary comments on the Draft Background Document. The Panel anticipates submitting additional comments and information at later stages in the NTP review process. Also, the Panel will provide additional data to NTP as the results from various portions of its research program become available over the next several months.

The Panel's general comments at this time are presented in this letter, and additional technical comments are included as Attachment 1. Additionally, a statement prepared by Dr. Richard Irons of the University of Colorado is included as an attachment to the technical comments. See Appendix A to Attachment 1. Dr. Irons' statement presents emerging evidence that the excess leukemia finding reported by Delzell *et al.* (1996)³ may be confounded by the presence of other biologically active compounds, such as dimethyldithiocarbamate (DMDTC), which was used as the primary reaction stopper in styrene-butadiene rubber (SBR) production from approximately 1950 to 1965.

Detailed comments on the discussion of human data in the Draft Background Document are presented in a statement prepared by Dr. John F. Acquavella. Dr. Acquavella's statement is included as an attachment to separate comments submitted by IISRP. The CMA Olefins Panel supports and incorporates by reference Dr. Acquavella's comments and recommendations.

² M.W. Himmelstein, *et al.* (1997). Toxicology and Epidemiology of 1,3-Butadiene. *Critical Reviews in Toxicology* 27:1-108; ECETOC (1997). *1,3-Butadiene OEL Criteria Document (Second Edition)*, CAS No. 106-99-0. Special Report No. 12 (Brussels, Belgium).

³ E. Delzell *et al.* (1996). Follow-up Study of Synthetic Rubber Workers. *Toxicology* 113:182.

GENERAL COMMENTS ON DRAFT BACKGROUND DOCUMENT FOR BUTADIENE

In general, several portions of the Draft Background Document for butadiene appear complete and well-written. Other portions, however, have significant omissions or present the available data in a way that appears neither complete nor well-balanced. Significant concerns, which are explained further in the attached technical comments, include: (1) the discussion of the human data fails to recognize significant inconsistencies in study results and overstates the strength of the available evidence; (2) the discussion of the genotoxicity data omits recent negative studies; (3) the discussion of pharmacokinetics omits significant work performed at the Chemical Industry Institute of Toxicology (CIIT); and (4) the discussion of environmental exposures creates the misleading impression that stationary sources are a significant source of butadiene emissions, when it is well-recognized that mobile sources, forest fires and prescribed burnings account for approximately 94 percent of environmental releases.

The latter three concerns can readily be addressed with information provided in the attached technical comments. The discussion of the epidemiology studies, however, needs to be substantially rewritten. Specifically, this section of the Draft Background Document should be revised and expanded to address the many significant issues and concerns presented in the statement prepared by Dr. Acquavella.

Inconsistencies in the human data need to be addressed through further research. The NTP Draft Background Document for butadiene should be written in a way that invites such further research, instead of prematurely closing the scientific dialogue on this important subject. Toward that end, the inconsistencies in the human data should be expressly recognized, the possibility of confounders in the SBR study should be acknowledged, and the Draft Background Document should specifically note that butadiene's potential to cause cancer in humans will need to be reevaluated periodically as the results of additional research become available.

COMMENTS ON PROPOSED CANCER CLASSIFICATION

The Panel believes that, under NTP's cancer classification criteria, the available animal and human data warrant classifying butadiene as "reasonably anticipated to be a human carcinogen." However, the Panel believes that the inconsistencies in the human data, as described in Dr. Acquavella's statement, raise important doubts about whether it is appropriate to elevate the cancer classification for butadiene at this time to "known to be a human carcinogen."

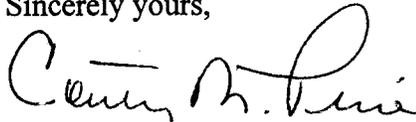
As explained in Dr. Acquavella's statement, only one human study can fairly be described as clearly positive, that study provides evidence of an excess of leukemia only in workers involved in the SBR production process, and similar excesses are not observed in monomer studies despite follow-up periods that approach half a century. Thus, arguably, only the SBR process at this point has been shown to be positive. Moreover, as demonstrated by Dr.

Irons' statement, the possibility of an alternative explanation cannot be excluded, which, under NTP's classification criteria, indicates that the proper classification for butadiene is "reasonably anticipated to be a human carcinogen."⁴

The Panel notes that classifying a compound as "reasonably anticipated to be a human carcinogen" is a significant statement, analogous to IARC or EPA classifying a compound as a "probable human carcinogen." Chemicals that receive such a classification typically are regulated as if they are human carcinogens, such that raising the classification to "known" is unlikely to have a significant impact on environmental or health regulations pertaining to a compound. On the other hand, elevating a cancer classification to "known" in the presence of important uncertainties can have negative consequences. These negative consequences include discouraging further scientific research and, to the extent the outcome is justified by an incomplete or selected review of available data, undermining the objectivity of the chemical review process. To avoid these negative consequences, and for the reasons stated above, the Panel requests that NTP consider retaining the current classification of butadiene as "reasonably anticipated" to cause cancer.

The Panel appreciates this opportunity to comment and looks forward to continuing dialogue with NTP as it reviews butadiene. If you have any questions, please call Dr. Elizabeth J. Moran, Manager of the Olefins Panel, at (703) 741-5617.

Sincerely yours,



Courtney M. Price
Vice-President, CHEMSTAR

Attachment

4

NTP's cancer classification criteria state that the "reasonably anticipated" classification is appropriate where "alternative explanations, such as chance, bias or confounding factors, could not be adequately excluded." See Draft Background Document at LC-1.

ATTACHMENT 1

TECHNICAL COMMENTS ON NTP's DRAFT BACKGROUND DOCUMENT FOR 1,3-BUTADIENE

Submitted by
The Chemical Manufacturers Association Olefins Panel

The following are additional technical comments submitted by the CMA Olefins Panel in response to NTP's request for input to its review and proposed cancer classification for 1,3-butadiene.

1. The discussion of the human data in the Draft Background Document (Section 3) should be substantially rewritten to address the issues raised in the statement prepared by John F. Acquavella, Ph.D. (included as an attachment to comments submitted by the International Institute of Synthetic Rubber Producers (IISRP)).

2. Section 3 should address the possibility that the reported excess of leukemias in the SBR study may be confounded by the presence of other biologically active chemicals used in the rubber industry, most notably dithiocarbamates. This possibility, though unproven, deserves explicit recognition because of the clear inconsistency in study results between the SBR study reported by Delzell *et al.* (1996) and the previously-reported monomer studies (where no excess leukemias were observed). The emerging evidence which points to this possibility is summarized in a statement prepared by Dr. Richard Irons of the University of Colorado (attached to these technical comments as Appendix A). Much of this information also was presented by Dr. Irons at the July, 1997, Toxicology Forum meeting. A transcript of this forum will be submitted to NTP as soon as it becomes available. Dr. Irons is conducting further research in this area, and the results of his research also will be submitted as it becomes available.

3. The discussion of the genotoxicity studies published after the last IARC and NTP reviews (Section 5.3) should be expanded to include recent negative studies. Male Sprague-Dawley rats exposed up to 1,250 ppm butadiene for 10 weeks produced no increase in

dominant lethal mutations, nor effects on pregnancy rate, or pre- and post-implantation losses when mated (BIBRA 1996).¹ Tates et al. (1996)² found no evidence for an increase in hprt gene mutations in blood sampled once a year for two years from 19 workers exposed to 1.76 ± 4.20 ppm butadiene, when adjusted for cloning efficiency, age and smoking.

4. The discussion of pharmacokinetics (Section 6.2) fails to include work done at the Chemical Industry Institute of Toxicology (CIIT). This section needs to be rewritten. Much of the missing information is summarized in the recent review document prepared by Himmelstein *et al.* (1997),³ a copy of which was submitted to NTP by IISRP in August, 1997. Primary references, however, should be reviewed, including an important paper prepared by Medinsky *et al.* (1994).⁴

5. The discussion of environmental exposures (Section 2.3) should be modified to avoid creating the incorrect impression that stationary sources are a major source of emissions. Section 2.1 states that facilities that manufacture, transport or use butadiene “are among the major anthropogenic sources of butadiene releases to the environment.” In fact, a national emission inventory recently prepared by EPA under Clean Air Act Section 112(k) shows that stationary sources represent a very small fraction of all man-made and natural releases of butadiene. Relevant excerpts from this draft emissions inventory are included in Appendix B. The emissions inventory estimates that mobile sources (on-road and non-road) account for approximately 69 percent of butadiene emissions, while forest and other wildfires and prescribed

¹ BIBRA (1996). The detection of dominant lethal mutations and fetal malformations in the offspring of male rats treated sub-chronically with 1,3-butadiene by inhalation. Report 1542/2/1/96. BIBRA Carshalton.

² Tates, A.D., van Dam, F.J., de Zwart, F.A., Darrondi, F., Natarajan, A.T., Rossner, P., Peterková, K., Peltonen, K., Demopoulos, N.A., Vlachodimitripoulos, D., and Srám, R.J. (1996). Biological effect monitoring in industrial workers from the Czech Republic that were exposed to low levels of butadiene. *Toxicology* 113:91-99.

³ Himmelstein, M.W., Acquavella, J.F., Recio, L., Medinsky, M.A., and Bond, J.A. (1997). Toxicology and Epidemiology of 1,3-Butadiene. *Critical Reviews in Toxicology* 27:1-108.

⁴ Medinsky, M.A., Leavens, T.L., Csanády, G.A., Gargas, M.L. and Bond, J.A., *In vivo* metabolism of butadiene by mice and rats: a comparison of physiological model predictions and experimental data. *Carcinogenesis*, 15:1329, 1994.

burnings account for an additional 25 percent. Industrial releases thus represent a very small percentage of national emissions, according to EPA's estimates. To correct the misimpression created at the beginning of Section 2.3.1.1, the text should begin with an explicit statement that combustion activities are the overwhelming sources of butadiene emissions, with mobile sources, forest fires and prescribed burnings accounting for approximately 94 percent.

APPENDIX A

**EMERGING EVIDENCE ON THE POSSIBLE ROLE OF DITHIOCARBAMATES AS
POTENTIAL CONFOUNDERS IN BUTADIENE EPIDEMIOLOGY**

STATEMENT PREPARED BY
RICHARD D. IRONS, PH.D., D.A.B.T.
UNIVERSITY OF COLORADO

Submitted As An Attachment To Comments Submitted By
The Chemical Manufacturers Association Olefins Panel
On The National Toxicology Program's
Proposed Cancer Classification For 1,3-Butadiene

October 27, 1997

STATEMENT OF RICHARD D. IRONS, Ph.D.¹

INTRODUCTION AND SUMMARY

Hematopoietic neoplasms associated with occupational exposure to 1, 3-butadiene (BD) have been the subject of controversy. In large part, this has been due to the inconsistent results of epidemiology studies that have reported alternatively no or weak associations between exposure to BD and hematopoietic neoplasms. Moreover, the specificity of association of BD exposure with individual leukemia types remains unclear. In addition, a distinct difference in the pattern of leukemia risk has been observed between workers employed in BD monomer production and those involved in styrene-butadiene rubber (SBR) production: with no increase in leukemia risk observed for exposure to BD monomer alone. These observations suggest the possibility that increases in leukemia risk in SBR may be the result of exposure to confounding factors previously not considered. Evidence is accumulating to suggest that these occupational studies may be confounded by the presence of an important class of biologically active chemicals employed in the rubber industry, dithiocarbamates (DTC).

This paper provides a brief overview of the butadiene epidemiology studies, and then presents evidence that, in the opinion of the author, provides a compelling rationale for further inquiry into the possibility that DTC are a significant confounder in butadiene epidemiology studies. Recent studies in the author's laboratory (unpublished) show that dimethyldithiocarbamate (DMDTC) is several thousand-fold more potent in inhibiting human T lymphocyte activation than the most potent BD metabolite, epoxybutene, and is approximately 500-fold more toxic to human bone marrow cells than epoxybutene. DMDTC was used as the primary reaction stopper in the "cold" SBR production process from the early 1950's to 1965. Moreover, a strong correlation apparently exists between the opportunity for exposure to DMDTC and leukemia risk observed in the recently reported SBR study by Delzell *et al.* (1996). It is not possible at this time to draw firm conclusions concerning whether DMDTC has played a role in the development of the excess leukemias reported in the SBR industry. However, the concordance between opportunity for exposure to DMDTC and leukemia risk encountered in the industry, the demonstrated biological and clinical activity of DMDTC and other DTC, together with our emerging understanding of their potent role in the modification of gene expression in immune function and hematopoiesis, provide a compelling rationale for additional investigation. Further, the possible role of DMDTC in butadiene epidemiology studies in the SBR industry should be recognized in any butadiene hazard or risk assessment.

¹ Molecular Toxicology and Environmental Health Sciences Program, School of Pharmacy; Department of Pathology, School of Medicine; and Comprehensive Cancer Center, University of Colorado Health Sciences Center.

OVERVIEW OF EPIDEMIOLOGY STUDIES

Several epidemiology studies have examined the potential associations between occupational exposure to 1,3-butadiene (BD), a co-monomer used in the production of synthetic Styrene-Butadiene rubber (SBR), and hematopoietic or lymphoid neoplasms [Meinhardt 1982; Downs 1987; Matanoski 1987; Matanoski 1990; Matanoski 1989; Divine 1996; Delzell 1996; Cowles 1994]. These studies have reported conflicting results including: no increases in hematopoietic neoplasms, marginal increases in lymphoid neoplasms in short term but not long term workers [Divine 1996; Ward 1995], or excesses of leukemia but no consistent or discernible pattern of association between exposure to BD and a specific disease [Delzell 1996; Matanoski 1989]. In particular, a disparate pattern of leukemia risk has been observed between workers employed in BD monomer production and those involved in SBR production, with no increase in leukemia risk demonstrated for exposure to BD monomer alone. The most recent study of BD monomer and SBR production is Delzell et al. [Delzell 1996], which represents the largest and most comprehensive evaluation of BD exposed workers to date. With the exception of leukemia (SMR=131), no exposure related increases in cancer were observed over a 48 year study period. Other forms of lymphopoietic cancers were not meaningfully related to employment in the SBR industry in general or to BD monomer exposure. Moreover, no cases of leukemia were encountered in workers exposed to BD monomer alone. Increase in leukemia risk was concentrated among individuals employed in specific process groups, notably laboratory operations (SMR = 431), polymerization (SMR = 251), coagulation (SMR = 248) and certain labor maintenance activities (SMR = 131-265). The majority of leukemias occurred in workers employed in these operations during the 15-year period of 1950-1965. The obvious difference in the pattern of leukemia risk between studies of BD monomer and SBR operations, together with the concentration of leukemia risk in SBR to relatively few operations and a limited period in time, raises the serious possibility that exposure to other agents in the polymerization process might influence the outcome of these studies.

CHEMISTRY AND BIOLOGICAL ACTIVITY OF DITHIOCARBAMATES

Dithiocarbamates represent a class of thiono-sulfur containing compounds that exhibit extraordinarily complex chemical and biological properties. Representative compounds include dimethyldithiocarbamate (DMDTC) and diethyldithiocarbamate (DEDTC), as well as their respective oxidized dithiuram counterparts (e.g., tetramethylthiuram disulfide and tetraethylthiuram disulfide or disulfiram). They are used as accelerators in vulcanization of rubber, scavengers and antioxidants in polymer chemistry, as fungicides, as drugs, and also as prototype inhibitors of transcriptional activation in molecular biology. They are potent metal chelators and ionophores that are readily absorbed across biological membranes [Orrenius 1996]. Although, they have previously been regarded as antioxidants, dithiocarbamates produce both pro- and anti-oxidant effects, demonstrating the ability to inhibit hydroxyl radical formation in biological systems and to oxidize protein thiols at the same time [Orrenius 1996]. The reduced carbamates are soluble in water, while the oxidized dithiuram moieties are lipid soluble and readily penetrate the skin. In aqueous solution, dithiocarbamates exist in equilibrium between the reduced and oxidized forms.

In the middle of this century, tetraethylthiuram disulfide (disulfiram) was used as a disinfectant, as a fungicide and as a drug in the treatment of parasitical skin diseases [Fredga, 1950]. The well-known use of disulfiram (Antabuse) in the behavioral treatment of alcoholism became established after recognition of the potency of disulfiram as an inhibitor of aldehyde dehydrogenase in the late 1940's [Hald 1948; Fredga, 1950; Asmussen 1948; Martensen-Larsen, 1948; Hald 1948]. It was common knowledge that occupational exposure of rubber workers to dithiocarbamates resulted in very disagreeable effects if alcohol was ingested [Solmann, 1957]. DTC's are also potent inhibitors of a variety of other metabolizing enzymes including: cytochrome p450 2E1 [Guengerich 1991], cholesterol 7 α -hydroxylase [Ogishima 1987], CYP 3A [Zhang 1996], superoxide dismutase [Heikkila 1978] and prostaglandin synthase [Marnett 1977], among others. While concomitant exposure to DTC could reasonably be expected to protect against the primary oxidation of 1,3-BD by CYP 2E1, other putative interactions are likely to be more complex. For example, disulfiram has been demonstrated to potentiate the carcinogenicity of 1,2-dibromomethane in rats, presumably due to the inhibition of CYP2E1 [Wong 1982; Kim 1990].

Claims also have been made for the clinical efficacy of DEDTC as an "immunorestorative", as a treatment for tuberculosis, rheumatoid arthritis, chronic bronchitis, and as an adjuvant in post-surgical healing [Brewton 1989]. Marginal antiviral activity against HIV was initially reported in 1985, which led to investigation of its use as a possible therapeutic adjunct in the treatment of AIDS [Pompidou, 1985]. After a number of clinical trials, the results are controversial, with DTC reported to have some modest efficacy in delaying the progression of AIDS [Hersh 1991; Reisinger 1990; Kaplan 1989; Lang 1988], or alternatively to have no significant effect [Hording 1990; The HIV 87 Study Group, 1993]. For the most part, the recognized adverse side effects of DTC have generally reflected their well-known effect on alcohol tolerance, although cases of myelotoxicity have been observed. Bone marrow toxicity has been frequently reported as a side effect of thiono-sulfur-containing compounds [Neal 1982]. Thrombocytopenia has been reported in a small number of patients receiving Antabuse therapy [Thompson 1982], suppression of neutrophil, monocyte, and platelet counts has been observed as an unwanted side effect in HIV-infected subjects treated with DEDTC [Shenep 1994], and functional changes in granulocytes also have been reported in workers occupationally exposed to DTC fungicides [Tsvetkova, 1992]. Immunotoxicity has been observed in mice following percutaneous absorption of methylthiocarbamate [Pruett 1992].

Dithiocarbamates are potent prototype inhibitors of activation of the transcription factor, nuclear factor kB (NF-kB) [Schreck 1992]. NF-kB is representative of a large family of transcriptional regulatory proteins that are critically involved in the regulation of gene expression in mammalian cells. For example, NF-kB plays a central role in T lymphocyte signaling and activation, with NF-kB nuclear translocation and DNA binding demonstrated to be a requirement for expression of a number of genes that are important in T lymphocyte function, including Interleukin-2 (IL-2). Activation of NF-kB is a requirement for the transcription of HIV-1 genes. It has been hypothesized that oxygen radicals play an important role in the activation of NF-kB [Schreck 1992]; however, the molecular basis for inhibition of NF-kB by DTC remains unclear. Inhibition of NF-kB activation apparently does not involve direct redox modification of the protein itself, nor does it appear to directly interfere with NF-kB-DNA binding [Orrenius 1996;

this laboratory unpublished results]. Inhibition of NF- κ B can result in cell transformation in vitro, presumably as a result of the deregulation of a set of genes whose expression prevents uncontrolled growth [Narayanan 1992]. Recent studies in our laboratory have revealed that dithiocarbamates, including DMDTC, inhibit NF- κ B activation in human T lymphocytes with an IC_{50} of 1×10^{-7} M. In contrast, the major metabolites of BD, epoxybutene and diepoxybutene, produced no significant inhibition of NF- κ B. Consequently, DMDTC is several thousand times more potent in inhibiting human T lymphocyte activation than the most potent BD metabolite, epoxybutene, and several thousand times more toxic to human bone marrow cells than epoxybutene (unpublished data).

USE OF DIMETHYLDITHIOCARBAMATE IN SBR PRODUCTION

In the mid-1930's government and industry in the United States embarked on an ambitious project to develop independence from natural rubber by developing a domestic source for synthetic styrene-butadiene rubber or SBR. A total of 16 Rubber Reserve plants were constructed and brought on line between 1938 and 1940. Patterned on the same design, all 16 plants employed essentially the same chemistry and had the same suppliers, utilizing a hot emulsion free radical polymerization process to produce SBR. This process essentially used heat (50°C) and persulfates to generate free radicals which catalyzed the polymerization of styrene and butadiene. Initially, the reaction was stopped by the addition of dinitrochlorobenzene and then hydroquinone. Increasing demand for SBR rubber in the immediate post war period led to the adoption of cold redox polymerization chemistry originally developed in Germany. In this process, co-monomers are polymerized at 5°C by free radicals generated using organic hydroperoxides and ferris iron as oxidizers and reducer, respectively. By 1952, all original Rubber Reserve plants had converted to the cold process for approximately 75% of their SBR production, although some limited use of the hot process for the production of specialty rubber formulations continues to this day. From the early 1950's to 1965, the primary reaction stopper used in the cold process was DMDTC. The stopping agent was added in excess to the reactor latex in order to inhibit the polymerization reaction. A major product of the decomposition of DMDTC is carbon disulfide. Increasing appreciation in the U.S. industry that breakdown of DMDTC resulted in carbon disulfide emission problems led to widespread replacement of DMDTC by diethylhydroxylamine in 1965. In the United States diethylhydroxylamine is the primary agent used today, although DTC's appear to be still in limited use. However, dithiocarbamates apparently are extensively used in Australia, China and Southeast Asia.

OPPORTUNITY FOR EXPOSURE TO DMDTC IN SBR PRODUCTION

Information is not currently available to evaluate exposure to DMDTC on a quantitative basis. However, circumstantial evidence suggests that the greatest opportunity for exposure to DMDTC correlates with leukemia risk. The process groups with significant opportunity for exposure to DMDTC during the period 1950-1965 are identical to those demonstrating the highest risk of leukemia. Those groups are: polymerization, coagulation, some maintenance activities, and, especially, laboratory operations. Absorption of DMDTC can occur by either inhalation or dermal routes with exposure likely to occur from contact with coagulating latex, open lines and filters, and aerosol from open vats. Laboratory activities likely

to result in significant exposure to DMDTC typically included: batch sampling, pouring, evaporation, extraction and refluxing of latex polymer and emulsion. These procedures were usually performed on the bench top without the use of gloves or protective equipment. In the initial years of the cold redox process many laboratories also maintained responsibility for compounding the shortstop solutions on a regular basis. Taken together with historical reports of alcohol sensitivity among rubber workers and changes in granulocytes in workers occupationally exposed to DTC fungicides, these observations suggest that absorption of a biologically relevant dose of DTC has occurred in occupational settings. A striking correlation exists between the opportunity for exposure to DMDTC and leukemia risk observed in the Delzell study: 87% of polymerization, coagulation or laboratory workers that developed leukemia were employed during the 1950-1965 period when DMDTC was used extensively. The average duration of exposure for these workers was 9.2 ± 5 years.

CONCLUSIONS

For many years, the epidemiology in the rubber and tire industry has been plagued by controversy. Increases in leukemia incidence have been reported for employment during certain time periods and for individual job descriptions. However, attempts to interpret data relating leukemia causation to exposure to specific solvents or monomers have proven to be less than satisfactory. When one considers the complexity of the process environment historically encountered in the SBR industry, two possible explanations that have received remarkably little attention are: 1) that the etiology of leukemia may not track with the chemicals or behaviors that to date have been evaluated in retrospective exposure analyses, or 2) that increased leukemia risk does not result from exposure to a single chemical.

The likelihood that any given study design might overlook a critical exposure scenario is enhanced in evaluation of complex processes where the chemical of hypothetical concern is a relatively minor component of the overall exposure environment. Moreover, when viewed in the context of the growing scientific consensus that carcinogenesis is a multifactorial process requiring involvement of multiple genes and arising from multiple independent genetic pathways, it is overly simplistic to assume a priori that occupational carcinogenesis is necessarily the result of chronic exposure to a single agent. At present, there is no scientific basis to definitely conclude whether DTC do or do not play a critical role in the development of leukemias observed in the SBR industry. However, the concordance between opportunity for exposure to DTC and leukemia risk encountered in the industry, and the demonstrated biological and clinical activity of DTC, together with our emerging understanding of their potent role in the modification of gene expression in immune function and hematopoiesis, provide a compelling rationale for further investigation.

Future studies of SBR workers should include efforts to develop exposure estimates for stopping agents, such as DMDTC, in addition to monomers and solvents. In retrospective analyses, carbon disulfide may prove useful as surrogate for estimating potential exposure to DTC. Basic toxicology and metabolism studies aimed at addressing the absorption, metabolism and distribution of DTC's would also be useful in interpreting exposure analyses. Finally, additional studies on the molecular and cellular mechanisms of toxicity should be

conducted in order to more fully understand and predict the biologic significance of exposure to this complex class of compounds and their potential role in occupational carcinogenesis.

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