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National Institute of Environmental
Health Sciences and the National
Toxicology Program (B2-01)
P.O. Box 12233
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Re: **Review of 1,3-Butadiene for NTP's
Biennial Report on Carcinogens**

Dear Dr. Olden:

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 provided significant information to NTP for its review of the compound by letters of August 20 and October 24, 1997. For the reasons outlined in this letter, IISRP urges NTP to postpone any reclassification of butadiene in its Biennial Report on Carcinogens until the complete database can be reassessed in a deliberative manner by the Board of Scientific Counselors Subcommittee.

Since the internal NTP and Board of Scientific Counselors reviews of butadiene last summer and fall, two independent review panels (the International Agency for Research on Cancer and EPA's Science Advisory Board) have subsequently considered whether butadiene is a known human carcinogen. Each panel concluded the data were insufficient for such a classification. Although there were dissenting votes within each group, the important point is that the scientific community has not reached a consensus that butadiene is a known human carcinogen. In the absence of such consensus, it would be scientifically unjustified and legally incorrect for NTP to declare 1,3-butadiene is, in the words of the statute, "known" to be a human carcinogen.

IISRP has asked Dr. John F. Acquavella -- one of the world's leading epidemiologists following butadiene over the past decade -- to review the current database. Dr. Acquavella no longer has any business interest in butadiene, but he continues to have a strong intellectual interest in appropriate interpretation of the data. Dr. Acquavella was given only five minutes to address the NTP Board last fall, but was invited to engage in detailed discussions with both the IARC and SAB panels. Each panel was composed up of more than ten expert scientists from a variety of disciplines,

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and each deliberated for several days. The IARC and SAB reviewers were thus much more informed than was the NTP Board.

We attach Dr. Acquavella's presentation to the SAB last month. We urge you to read it carefully. It summarizes the reasons why the epidemiology results are insufficient to conclude that butadiene is known to cause human cancer -- the view reached by both IARC and the SAB.

Employing a weight of the evidence approach, Dr. Acquavella explains why it is scientifically inappropriate to conclude butadiene is a known carcinogen. As Dr. Acquavella details, the epidemiology study results are not consistent. The IISRP-sponsored styrene-butadiene rubber (SBR) worker study, conducted by Dr. Elizabeth Delzell, found a dose-related association between leukemia and estimated butadiene exposure, but no association with lymphosarcoma/non-Hodgkin's lymphoma (NHL). On the other hand, no association of butadiene with leukemia has been found in the studies of monomer workers. Although some subgroups had lymphosarcoma/NHL excesses in the monomer worker studies, there was no dose-response relationship; and there was no lymphosarcoma/NHL excess in the SBR study. Dr. Acquavella concludes (page 8):

Consistency is usually considered to be a near essential causal criterion in epidemiology...[I]n the traditional sense, consistency means that convincing positive findings are seen for a specific exposure-disease relationship in several studies conducted under different circumstances. By this definition, the evidence for butadiene workers would not be sufficient to support a known human carcinogen classification.

We also urge you to consider carefully the comments being sent by the Chemical Manufacturers Association Olefins Panel. The Panel describes their on-going research on possible confounding exposures unique to the SBR industry and outlines the data relevant to assessing the mechanism of butadiene animal carcinogenicity. These data demonstrate additional reasons why NTP should postpone any reclassification of butadiene until its Board of Scientific Counselors

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Subcommittee is given the opportunity to conduct a full, fair review of all the scientific evidence. IISRP would be glad to provide further information if it would be useful to your decision.

Sincerely yours,



Richard Killian
IISRP Managing Director

Enclosure

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COMMENTS ON
EPA HEALTH RISK ASSESSMENT
FOR 1,3-BUTADIENE
EXTERNAL REVIEW DRAFT
(EPA/600/P-98/001A, January 1998)

John F. Acquavella, PhD

April 17, 1998

**On Behalf of the International Institute
of Synthetic Rubber Producers**

COMMENTS ON
EPA HEALTH RISK ASSESSMENT
FOR 1,3-BUTADIENE
EXTERNAL REVIEW DRAFT
(EPA/600/P-98/001A, January 1998)

John F. Acquavella, PhD

I appreciate the opportunity to offer comments on EPA's draft risk assessment for 1,3-butadiene (hereafter butadiene). I followed butadiene epidemiology closely over the 10 years when I served (1986-1996) as chairman of the Epidemiology Subcommittee of the International Institute of Synthetic Rubber Producers. In that capacity, I played a coordinating role in the evolution of the industry sponsored epidemiologic studies. In addition, I participated as U.S. industry's representative in the two monograph meetings held by the International Agency for Research on Cancer (IARC) that considered butadiene, and I have offered testimony or written comments in many butadiene regulatory proceedings.

I no longer have a direct business interest in butadiene. Nonetheless, I have a strong intellectual interest in seeing the results of the available epidemiologic studies interpreted appropriately. It is from this perspective that I respectfully offer comments on EPA's draft risk assessment for butadiene. My comments focus on whether the available epidemiologic data are sufficient to classify butadiene as a known cause of human cancer and on the use of the butadiene epidemiologic data in quantitative risk assessment.

Introduction

Butadiene epidemiologic research has focused primarily on workers in two industries: the styrene-butadiene rubber (SBR) industry and the butadiene monomer industry. This literature has evolved substantially since the initial publication in 1982 which concerned SBR workers at two plants in Texas (*Meinhardt et al. 1982*). The most recent studies in the monomer (*Divine et al. 1996*) and SBR industries (*Delzell et al. 1995, 1996; Macaluso et al. 1996, Sathiakumar et al., in press*)

are characterized by carefully enumerated study populations, extremely long and high quality mortality follow-up, accurate job categorizations, detailed exposure assessments, and comprehensive statistical analyses -- which include dose response analyses. This is a marked advancement over earlier studies where exposure categorization was either vague or nonexistent, such that it was difficult to focus with certainty on findings for the highest exposed workers. This uncertainty afforded the opportunity for considerable subjectivity on the part of reviewers which would be clearly undesirable in regulatory proceedings.

In this vein, the EPA review devotes considerable attention to the early studies of butadiene exposed workers. It would greatly clarify the review, and highlight the data which are critical for causal inference, if the Agency omitted much of the detail about the earlier studies. Instead, the predominant emphasis should be on the methods and findings of the latest studies of butadiene monomer and SBR workers, specifically on the findings that have the greatest significance for causal inference -- namely findings for workers with the highest and longest exposures and the results of dose response analyses. The emphasis on the early epidemiologic studies is somewhat misleading to the extent that it gives the impression of consistency across several study populations in the SBR and butadiene monomer industries. There is really only one study population in each industry that provides appreciable information.

Herein, I will review the data which, by traditional epidemiologic standards, are most relevant for the classification of butadiene and present a weight of evidence evaluation based on these data. In offering these comments, I draw primarily on my previous writings (*Acquavella 1989, Acquavella 1990, Cole et al. 1993, Acquavella 1996, Himmelstein et al. 1997*) and on the

deliberations of the Epidemiology Work Group at the February 1998 IARC classification meeting (*IARC, in press*).

Weight of evidence

The evidence linking butadiene exposure and cancer is strongest for leukemia. This conclusion is based on one large, high quality cohort study of SBR workers which found an excess of leukemia and an exposure-response relationship with estimated butadiene exposure (*Delzell et al. 1995, Delzell et al. 1996, Macaluso et al. 1996, Sathiakumar et al. in press*). Earlier cohort studies of (practically) the same SBR workers (*Meinhardt et al. 1982, Matanoski et al. 1990*) found essentially null results for leukemia and no indication that mortality increased with duration of employment.¹ Both Meinhardt and colleagues (*1982*) and Matanoski and colleagues (*1990*) reported elevated leukemia mortality based on very small numbers for a presumably exposed subgroup(s). But other presumably exposed subgroups in these studies had null or sub-null leukemia results. Various authors interpreted these subgroup results differently (*Acquavella 1996 details the different perspectives*); the early proponents of a causal relationship (*e.g. Landrigan 1993*) made unverifiable assumptions about higher exposure potential for the subgroups with positive findings and virtually ignored null findings for other exposed subgroups.

A nested case control study, based on the larger SBR workers cohort study (*Matanoski et al. 1990*), reported a strong relationship between semi-quantitative estimates of butadiene exposure and leukemia with two separate control groups (*Matanoski et al. 1989 and 1993, Santos-Burgoa et al. 1992*). However, the magnitude of the odds ratio (OR) in both instances (approximately 8.0) was

¹ Meinhardt and colleagues (1982) studied one plant from the Delzell et al. (1995) study (actually it was two contiguous plants at the time of the Meinhardt study), and Matanoski and colleagues (1987 and 1990) studied seven plants later studied by Delzell and colleagues and one additional small plant that could not be included in the latter study.

so great as to be inconceivable given the overall null leukemia cohort results (22 observed, 22.9 expected) (*Acquavella 1989, Cole 1990, Cole et al. 1993, Himmelstein et al. 1997*). The subsequent moderate exposure response relationship reported by Delzell and colleagues (*1995, Macaluso et al. 1996*), based on quantitative estimates of butadiene exposure, and the fact that their reported leukemia excess occurred after the Matanoski et al. study period, further questions the validity of the very high ORs from the case control analyses. It has also become known that approximately 40% of the cases and controls in the case control study came from a plant where more than 2,000 non-SBR workers were inadvertently included in the SBR worker population (*see Himmelstein et al. 1997 for details*).

Arguments about the validity of the previous SBR worker studies are no longer pertinent to the carcinogen classification of butadiene. The study by Delzell and colleagues (*1995 and 1996, Macaluso et al. 1996, Sathiakumer et al. in press*) supersedes those previous studies and rectifies many of the limitations and errors of those earlier studies. The study provides internally consistent evidence of a relationship between butadiene exposure and leukemia including: the presence of an exposure response relationship, the finding of elevated leukemia mortality for process groups estimated to have had high butadiene exposure, and the finding of elevated leukemia mortality, though sometimes slight, at most plants in the study. However, this leukemia excess has not been replicated in another study population. In fact, studies of butadiene monomer workers and of other butadiene exposed workers report null results for leukemia (*Divine and Hartman 1996, Ward et al. 1995, Cowles et al. 1994, Bond et al. 1992, Downs et al. 1993*).² This may be due to lower

² With the exception of the study by Divine and Hartman (*1996*), these studies had few observed and expected leukemia deaths. Nonetheless, the fact remains that the Delzell et al. leukemia findings have not been replicated in another study population.

exposures in these industries, a cofactor in the SBR industry, or a confounder, correlated with butadiene exposure, in the SBR industry. Only the latter is inconsistent with a carcinogenic effect for butadiene. Nonetheless, the major limitation of the butadiene/leukemia epidemiologic literature from a causal perspective is the dependence on findings for one study population. This was the basis for the IARC participants deciding against a sufficient classification of the epidemiologic evidence (IARC, in press).

The available evidence is clearly insufficient for a causal relationship between butadiene and other lymphohematopoietic cancers. Lymphosarcoma has been found to be elevated for short term exposed workers in the largest study of monomer workers (*Divine and Hartman 1996*) and in one small study where 75% of the workers (277 of 366 workers) worked on one production unit of a multi-purpose chemical plant that operated only during World War II (*Ward et al. 1995*). On the other hand, there was no excess of lymphosarcoma among long term exposed workers in the largest butadiene monomer worker study nor was there any indication of an exposure response relationship for lymphosarcoma or non-Hodgkin's lymphoma (NHL) (*Divine and Hartman 1996*). Perhaps of equal or greater importance, lymphosarcoma/NHL was not elevated in the SBR cohort which had excess leukemia (*Delzell et al. 1995 and 1996*) or in the specific SBR subgroups that had excess leukemia (*Sathiakumar et al., in press*). This is strong evidence against a relationship between butadiene exposure and lymphosarcoma/NHL.

My weight of evidence evaluation for butadiene and the various lymphopoietic cancers is summarized in table 1. For lymphosarcoma (and NHL) the evidence in the SBR industry, as reviewed above, is clearly inconsistent with a relationship with butadiene exposure. For monomer workers, while there is excess mortality in short-term workers in exposed jobs in one study (*Divine*

and Hartman 1996) and excess mortality among very short term monomer workers with unspecified jobs in another study (*Ward et al. 1995*), there is no excess mortality among long term workers and no indication of an exposure response relationship in the study by Divine and Hartman (*1996*). In fact, the relative risk per unit dose in that study was 1.0. Some have argued that the findings for short term exposed workers are consistent with an effect of butadiene exposure due to high wartime exposure levels (*Landrigan 1993*). This conjecture is not borne out by the exposure response relationship presented by Divine and Hartman (*1996*). In addition, there is no indication in Divine and Hartman's exposure assessment that wartime exposures differed for short term workers and those workers who went on to become long term workers (B. Divine, personal communication 1998). Therefore, the weight of evidence for lymphosarcoma/NHL in the butadiene monomer industry is most consistent with a non-causal interpretation, as are the null findings in the SBR industry.

Mortality from Hodgkin's disease and multiple myeloma were unremarkable in the SBR and monomer workers studies. In addition, there was no exposure response relationship in either the monomer study by Divine and Hartman (*1996*) or in the SBR study by Delzell and colleagues (*1995*). These cancers seem to be unrelated to butadiene exposure.

The weight of evidence evaluation for leukemia is the most complex aspect of the butadiene literature. Results are not consistent across industries. One large study of SBR workers (*Delzell et al. 1995 and 1996, Macaluso et al. 1996, Sathiakumar et al. in press*) provides internally consistent evidence of a relationship between leukemia and butadiene exposure. The existence of a dose-response relationship in this study puts constraints on alternative explanations for the leukemia findings: namely, that another risk factor must be correlated with butadiene exposure. Such an

hypothesis is not implausible in the complex exposure milieu of the SBR industry and, in fact, Irons and Pyatt (*in press*) have hypothesized an effect of dimethyldithiocarbamate (DMDTC) -- an exposure, which based on a pilot exposure estimation study in one SBR plant (*Macaluso et al. 1997*) seems to be correlated with butadiene exposure. Nonetheless, confounding or interaction of this type is rare enough that many epidemiologists would tend to interpret the SBR-leukemia findings as indicative of an effect of butadiene exposure. Thus, the classification decision seems to depend not on the plausibility of an alternative hypothesis(es), but instead on whether it is appropriate to rely on findings for one population to establish sufficiency. An international IARC working group decided, in February 1998, that this was an insufficient basis for classifying butadiene as a known human carcinogen (*IARC, in press*). On the other hand, the National Toxicology Program (*1997*) decided that the same evidence was sufficient to classify butadiene as a known human carcinogen.³

Table 1
Weight of Evidence Evaluation for 1,3-Butadiene

	SBR workers	monomer workers	Total
lymphosarcoma/non Hodgkin's lymphoma	-	+/-	-
Hodgkin's disease	-	-	-
multiple myeloma	-	-	-
leukemia	+	-	+/-

³ As a participant in both the IARC and NTP public proceedings, it seems only fair to mention that the NTP decision was based largely on private deliberations of a limited cross-section of scientists with limited opportunity for public input and no real opportunity for debate. The IARC proceedings, on the other hand, involved a cross-section of epidemiologists from North America and Europe and ample time for public input and debate.

Consistency is usually considered to be a near essential causal criterion in epidemiology. In fact, in a review of the practice of causal inference in cancer epidemiology, Weed and Gorelic (1996) found that consistency was the causal criterion used most frequently. Causal and non-causal proponents in the butadiene literature have, at times, adopted different conventions to evaluate consistency across studies (Acquavella 1996). But, in the traditional sense, consistency means that convincing positive findings are seen for a specific exposure-disease relationship in several studies conducted under different circumstances. By this definition, the evidence for butadiene workers would not be sufficient to support a known human carcinogen classification. This is admittedly paradoxical since butadiene exposure is clearly the most straightforward explanation for the findings in the SBR industry (Himmelstein et al. 1997). Nonetheless, when intuition and scientific guidelines seem to conflict, it bears noting that scientific guidelines have an objective framework, which seems the more appropriate basis for regulatory decisions.

Implications of the epidemiologic evidence for risk assessment

Risk assessment, per se, is outside the scope of epidemiology, though epidemiologic analyses can be considered a risk assessment over an observed exposure distribution. Risk assessment calculations are frequently blind to the validity issues that concern most epidemiologists. In particular, there are characteristics of the exposure assessment in the butadiene epidemiologic studies -- and most other epidemiologic studies -- that need to be considered before such data can be used in risk assessment.

First, it must be realized that retrospective exposure estimates, no matter how sophisticated in design or description, are almost always based on idealized assumptions. This is especially true for historical exposure estimates in the SBR industry. There is simply no way to know what

individual workers actually did or were exposed to in the course of their job assignments. Thus, while individual variability may be substantial, the most specific unit of exposure estimation was the “homogeneous exposure group.” There can be substantial differences in exposure within homogeneous exposure groups that lead to exposure misclassification. If exposure really does cause disease, you would expect that workers who took less care to minimize exposures or who had higher exposures for other reasons would have the greatest risk of disease. Classifying exposures for these workers on a par with others in their homogeneous exposure group would overestimate the potency of the exposure disease relationship.

A second important issue is the potential impact of task specific peak exposures. This is especially important when the putative harmful exposure is a volatile gas like butadiene. The primary exposure metric in the SBR workers study is based on time weighted average exposure. But, SBR workers frequently get the majority of their exposures during a small fraction of the work day in the conduct of specific tasks (*McGraw 1990*). This could have biological implications for exposed workers. It would also have implications for risk assessment when the target population (viz. the general population) has a relatively low and constant level of exposure.

Delzell and colleagues assessed the influence of peak exposures on their reported leukemia excess (Delzell et al. 1996b) through analyses by cumulative butadiene exposure categories with and without control for peak exposures, defined as exceeding 100 parts per million (see table 2). Their results show an attenuation of the exposure response relationship when peak exposures are considered, such that increased risk is concentrated among those with both high cumulative exposures and frequent peak exposures. These findings, if valid, have obvious implications for extrapolations to environmental situations where peak exposures are nonexistent.

Table 2
Leukemia mortality by cumulative butadiene exposure,
with and without consideration of peak exposures

Exposure cat	<u>BD ppm years alone</u>		<u>BD ppm years & BD100 peak years</u>	
	RR	95% CI	RR	95% CI
0 ppm-yrs	1.0		1.0	
1-19 ppm-yrs	1.1	0.5-2.6	0.7	0.2-1.9
20-99 ppm-yrs	2.0	0.9-4.6	1.0	0.3-3.1
100-199 ppm-yrs	2.4	0.9-6.5	1.3	0.3-5.0
200+ ppm-yrs	4.6	1.6-13.3	2.5	0.6-10.6

Finally, the complexity of exposures in the SBR industry and the temporal pattern of the leukemia excess in the Delzell et al. (1995, 1996) study need to be considered. Delzell and colleagues did not find excess leukemia among workers who were employed in the 1940s as long as they did not work in the 1950s. The leukemia excess was concentrated among workers who began employment in the 1950s. This apparent anomaly, and the realization that there was a fundamental SBR process change in the 1950s, led to the hypothesis by Irons and Pyatt (*in press*) that DMDTC might be a factor in the leukemia excess reported by Delzell et al. This raises two possibilities that need to be considered in risk assessment: 1) that DMDTC might be leukemogenic or part of an exposure circumstance that is leukemogenic, but which does not involve butadiene; and 2) that joint exposure to DMDTC and butadiene is leukemogenic. In the former case, risk assessments based on butadiene exposure would be based on an incorrect hazard assumption. In the latter case, risk assessments based on butadiene exposure would be quantitatively unreliable. It remains to be seen whether the hypothesis of Irons and Pyatt (*in press*) will be supported by ongoing research.

Nonetheless, it is illustrative of how the complexity of exposures in the SBR industry should militate caution in extrapolating the results of epidemiologic studies of complex exposure scenarios.

Summary

Epidemiologic research on one population of SBR workers shows an excess of leukemia that appears to be related to estimates of butadiene exposure (*Delzell et al. 1995, Macaluso et al. 1996*). This finding has yet to be replicated in another population of workers who have butadiene exposure. This lack of consistency argues against a classification of the epidemiologic data as sufficient evidence that butadiene is a human carcinogen.

Lymphosarcoma mortality has been found to be elevated among short term butadiene monomer workers in two studies (*Divine & Hartman 1996; Ward et al. 1995*). However findings are null in longer term workers in the Divine and Hartman (*1996*) study and in SBR workers in jobs characterized by the highest butadiene exposures (*Delzell et al. 1995, Sathiakumar, in press*). In addition, there was no dose response for lymphosarcoma (or NHL) in the largest butadiene monomer (*Divine and Hartman 1996*) or in the most recent SBR workers study (*Delzell et al. 1995*).

Findings for multiple myeloma and Hodgkin's disease have not been indicative of a relationship with butadiene exposure (*Divine and Hartman 1996, Delzell et al. 1995*).

The SBR workers study by Delzell and colleagues (*1995, 1996, Macaluso et al. 1996*), while conducted according to very high standards, has limitations that preclude the use of exposure estimates at face value for risk assessment. These limitations include the underestimation of exposures (*Macaluso et al. 1997*), the, as yet, undetermined impact of peak exposures, and the potential impact on results of other exposures in the SBR industry.

I hope these comments are helpful to the Agency in its deliberations. In addition to these general comments, hereafter I offer a number of specific comments on the text of the EPA review.

Specific Comments on the Text of EPA's Health Assessment of 1,3-Butadiene

Section 7.1.1 Texaco Cohort

In general, the comments will only refer to latest version of this study (Divine and Hartman 1996) since all of the earlier data are included in this version.

Page 7-3, lines 1-2: Note that the Texaco study was originally designed to be similar in methodology to the Meinhardt *et al.* (1982) study. This is why the authors did a stratified analysis of World War II and post-war workers. In the study by Meinhardt *et al.* (1982), the war/post war comparison was related to a process change⁴; no such change took place after the war in the butadiene monomer industry.

Page 7-5, footnote: During the process of updating the file from Downs and colleagues (1987), it was discovered that some employees were in the file more than once and that some workers who had been assumed to be male were in fact female. Over the course of the study updates, errors were corrected, and new eligible employees were added.

Page 7-6, lines 16-25: The categorization of workers into the four exposure groups was based on each employee's complete work history, instead of the last assigned department. An employee could be in more than one exposure group throughout his employment at the plant, except for those in the background exposure group. The group assignment for each job (and later the exposure class assignment) was reviewed with plant industrial hygienists and long time employees.

Page 7-7, lines 17-20: Note that vital status follow-up was done using the Social Security Administration death records, company benefit records, and the Health Care Finance Administration records through the end of 1994 and the National Death Index through the end of 1993. Only persons known to be alive from one of these sources (except NDI) was assumed to be alive at the study end date. Those known to be alive as of 1979 or later and for whom no NDI match was found were assumed to be alive as of 1993. Of those lost to follow-up (n=574), all but 28 were known to be alive as of the end of 1993. The 28 were lost to follow-up as of the date last employed.

Page 7-7, lines 23-32: The exposure classification for the survival analyses was based on combining the exposure class for each job (As explained above, the exposure class was assigned using more information than just recent industrial hygiene data. Each job classification used in the study was reviewed by long-term plant employees and industrial hygienists, and the exposure classification was based on their knowledge of the job and the tasks associated with it.), the length of time in each

⁴ The process change was not an important predictor of leukemia risk in the Delzell *et al.* study (1995, 1996, Macaluso *et al.* 1996, Sathiakumar *et al.*, *in press*) which combined the plants studied by Meinhardt with the plants studied by Matanoski *et al.* (1990).

job, and a weight for the calendar time when the job was held (exposures were judged to have been higher in the past so that the earlier calendar times had higher weights).

Page 7-8. Line 9: There is a reference here and numerous times later in the report to a “prewar” subcohort. There is no prewar subcohort. The plant started operation during World War II, and so the earliest employees are the wartime cohort.

Note that the increase in lymphosarcoma in the wartime cohort is higher in the short-term workers than in the long-term workers. Since all of the employees in the wartime cohort started working at approximately the same time, they all had the same potential for exposure to butadiene during the war years. Overall, the long-term wartime subcohort would be expected to have had the highest exposures to butadiene, but they do not have an excess of lymphosarcoma.

Section 7.1.1 Union Carbide Cohort

Page 7-9, line 33: It is not true that only individuals who worked in butadiene production during World War II were included in this cohort. There were 364 men whose department codes indicated that they worked in a butadiene area of the plants during the time butadiene was produced. Of these, 277 worked in butadiene production only during World War II (1943-1946) at the Rubber Reserve plant. There were also 87 individuals who worked at two other plants that produced butadiene, one from 1941-1965 and one from 1959-1971. This misstatement about only working during World War II is also found on pages 7-32, 7-34, and 11-6.

Page 7-10, lines 11-14: This sentence is awkward. In addition, it should be noted that duration of employment was divided into less than 2 years and greater than 2 years because of the short period of time that the largest facility was in operation. Analyses based on this division do not provide information on exposure potential or on the presence or absence of a dose-response effect.

Page 7-10, lines 15-17: The investigators stated that the lymphosarcoma decedents had “no common exposures to other chemicals”. The three cases from the Rubber Reserve Plant would all have had potential exposure to acetaldehyde because it was present in the process in this unit. In addition, two of the three also worked at one time in the acetaldehyde unit. The only lymphosarcoma case without this exposure was the one from the South Charleston plant.

Page 7-10, line 20: There is no qualitative exposure information for this cohort. In fact, there isn’t even any job specific information for these cohort members. The only information is the department code.

Page 7-12, Table 7-1: Under strengths and limitations of the Divine and Hartman study (1996), it is first stated that “exposure estimation useful” and second that the “major limitation is no exposure estimation available in prewar subcohort”. Again, there is no “prewar” subcohort. If the author(s) mean the wartime subcohort, the exposure estimation efforts were done similarly for everyone in the cohort regardless of when they started employment.

Page 7-13, Table 7-1: Under 1,3-butadiene exposure assessment for the Ward *et al.* study (1995), it is stated “jobs where only 1,3-butadiene exposure occurred”. The cohort was picked using department codes referring to butadiene production during calendar times when butadiene was being produced. Nothing is known about employees’ exposure potential in this study. Also, see note regarding Page 7-10, lines 15-17.

Section 7.3 Summary and Discussion

Page 7-31, lines 11-15: Although the overall mortality rate in the butadiene cohorts may be slightly affected by the “healthy worker effect”, it is unlikely to be a strong effect since the major cohorts are very aged. There is even less reason to suspect that the “healthy worker effect” had any impact on lymphohematopoietic cancer (LHC) rates or any other cancer mortality rate. Thus, the cancer SMRs seen in these cohort studies are not likely to be underestimations of risk.

Section 7.3.1. Monomer Production

Page 7-31, line 24: Again, it should be noted that the exposure classifications were based on more than just recent industrial hygiene sampling data. See the note on Page 7-7, lines 23-32.

Page 7-31, line 31: Note that the SMR for lymphosarcoma is not statistically significant for the total cohort in the Divine and Hartman (1996) update.

Page 7-32, line 3: This sentence needs to have the word “excess” moved from after the word “latency” to after “lymphosarcoma,”.

Page 7-32, line 9: Again, the exposure to butadiene was presumed based on department codes, not job categories. There is no job specific information for this study.

Section 7.3.3. Relevant Methodologic Issues and Discussion

Page 7-34, lines 7-9: Percy states that the death certificate statement of leukemia as a cause of death has “both a high detection and confirmation rate” (See table 3). Most of the inaccuracy for leukemia involves mis-specification of the exact cell type. The detection rate for NHL is 83.2 percent and the confirmation rate is 88.4 percent. The detection and confirmation rates for Hodgkin’s Disease and multiple myeloma are even higher. Thus, while there is some inaccuracy in death certificate diagnoses of the lymphopoietic cancers, the data is not as unreliable as implied here.

Table 3
Detection and Confirmation Rates for Lymphopoietic Cancers
from the Third National Cancer Survey (Percy *et al.* 1982)

ICD8	Primary Site	#	% detected	% confirmed
200-202	non-Hodgkin's lymphoma	1562	83.2	88.4
201	Hodgkin's disease	572	86.7	92.5
203	multiple myeloma	699	96.6	98.1
204	lymphocytic leukemia	743	79.9	86.3
205	myeloid leukemia	1107	76.2	92.2
206	monocytic leukemia	98	57.1	53.8
207	other and unspecified leukemia	204	73.0	34.3

Page 7-34, lines 11, 14: Neither Cowles *et al.* (1994) nor Ward *et al.* (1995) did any job classification or exposure estimation. The tone of the write-up suggests that Ward *et al.* (1995) did more than Cowles *et al.* (1994).

Page 7-34, lines 17-18: See notes on page 7-10, lines 11-14 and page 7-10, line 15-17.

Page 7-34, lines 25-28: The exposure estimation developed for Divine and Hartman (1996) was used for the survival analyses which found no association between the semi-quantitative estimates of butadiene exposure and any of the lymphohematopoietic cancers.

Page 7-34, lines 32-33: Note that at least one of the lymphosarcoma decedents in the Meinhardt *et al.* (1982) study also worked at the butadiene monomer facility in Divine and Hartman (1996).

Page 7-34, lines 33-35: While Meinhardt *et al.* (1982) provide information on the length of employment for the leukemia decedents, there is no similar information for the lymphosarcoma decedents. Thus, there is no information to determine whether the excess of lymphosarcoma in the short-term workers, but not in the long-term workers, in Divine and Hartman (1996) is consistent with the findings of Meinhardt *et al.* (1982).

Page 7-36, lines 21-23: This statement is an unverified conjecture which is not supported by the actual exposure estimates in this study. The long-term workers were once short-term workers during the same time period and had the same high exposures as the short-term workers.

Page 3-36, lines 21-36: The author's application of the criteria of strength of association and consistency reflect a very selective "pick and choose" approach. My previous comments about consistency apply here. In addition, the strength of association evaluation (and obviously the consistency evaluation) should focus on individual lymphopoietic cancers. That was unanimous sentiment for evaluating the evidence this way at the recent IARC meeting.

Page 7-36, lines 24-29: This analogy between the rodent findings and the epidemiologic findings for lymphosarcoma among short term monomer workers is wild conjecture, not worthy of a regulatory proceeding. The rodent study involved controlled exposures for two groups of rodents such that the total dose was equivalent but exposure time was not. The epidemiologic situation involved workers with intermittent exposure of unknown level and intensity. There is no evidence that the short term workers had equivalent exposures over a shorter time period as did long term workers. In fact, the available data suggest that long term workers had the same exposure as short term workers plus additional exposures in their subsequent jobs.

Page 7-38, lines 9-11: The statement from Linet (1985) that exposures to a particular chemical (or drug or radiation) can cause many types of lymphohematopoietic cancers is not referenced. Other than for ionizing radiation, is there any other evidence that this is true? It certainly is not true for the chemotherapy drugs such as cyclophosphamide which only cause an excess risk of acute myelogenous leukemia.

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