Summary of Review Panel Meeting
1,3-Butadiene Risk Assessment Document

Sponsored by Health Canada
November 30, 1998
Ottawa, Ontario, Canada

Review Panel (Roles and Expertise):

Michael L. Dourson (Review Panel Chairperson, General Risk Assessment and Toxicology)
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Harvey Clewell (Risk Assessment, Biostatistics, and Modeling)
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Meeting Notes and Summary:

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Representing Health Canada, Priority Substances Section, Environmental Substances Division, Environmental Health Directorate, Health Protection Branch, Tunney’s Pasture, Ottawa, Ontario, K1A 0L2:

Bette Meek (Section Head)
Kathy Hughes
(Primary Document Author)
Michael Walker (Statistician)

Other Public Attendees:
Background – Purpose of the Assessment:

The information presented in this section was taken from the background documentation provided to the review panel.

The Canadian Environmental Protection Act (CEPA) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List that identifies substances, including chemicals, groups of chemicals, effluents and wastes that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" as defined in Section 11 of the Act, which states:

"...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions

a) having or that may have an immediate or long-term harmful effect on the environment;

b) constituting or that may constitute a danger to the environment on which human life depends; or

c) constituting or that may constitute a danger in Canada to human life or health."

Based on initial screening of readily accessible information, the rationale for assessing 1,3-butadiene (hereafter referred to as butadiene) provided by the Ministers’ Expert Advisory Panel on the Second Priority Substances List (Ministers’ Expert Advisory Panel 1995) was as follows:

"1,3-Butadiene is present at low levels in indoor and outdoor air throughout the country. Sources include motor vehicle emissions and the manufacture of plastics and synthetic
rubbers. The substance is carcinogenic and genotoxic in animals. It may be carcinogenic in humans. It is important to assess the potential risk to human health and the environment."

Supporting documentation and the content of the health-related sections of the summary assessment report were prepared by K. Hughes, M.E. Meek, D. Moir and M. Walker of Health Canada, based, in part, on background information prepared (1994) by BIBRA Toxicology International:

Sections of the Supporting Documentation on genotoxicity and reproductive and developmental toxicity were reviewed by D. Blakey and W. Foster, respectively, of the Environmental Health Directorate of Health Canada. A review of the exposure assessment included in the critical epidemiological studies was prepared under contract by M. Gerin and J. Siemiatycki of the Institut Armand-Frappier.

In the first stage of external review, background sections of the Supporting Documentation pertaining to human health were reviewed and written comments were provided by the following 10 individuals primarily to address adequacy of coverage (December, 1997). The principal criterion for selection was likely familiarity with recent, relevant data in critical areas including toxicity (particularly genetic toxicity), epidemiology and metabolism. Names, affiliations and relevant areas of expertise of first stage reviewers were as follows:

J. Aquavella, Epidemiologist, Monsanto Company

M. Bird, Toxicologist, Exxon Biomedical Sciences, Inc.

J.A. Bond, Researcher, kinetics and metabolism, development of PBPK model on butadiene, Chemical Industry Institute of Toxicology

I. Brooke, Toxicologist, Principal evaluator for UK assessment and rapporteur for the EU assessment on butadiene, U.K. Health and Safety Executive (U.K. HSE)

G. Granville, Toxicologist, Shell Canada Ltd.

R. Keefe, Toxicologist, Imperial Oil Ltd.

A. Koppikar, Epidemiologist, Principal evaluator for U.S. EPA assessment of butadiene, U.S. Environmental Protection Agency (U.S. EPA)

R.J. Lewis, Toxicologist, Exxon Biomedical Sciences Inc.
K. Peltonen, Researcher, kinetics and metabolism, Investigated formation of adducts with butadiene and metabolites
Finnish Institute of Occupational Health (FIOH)

F. Ratpan, Genetic toxicologist, Nova Chemicals

In a subsequent stage of external peer review, a second draft of the Supporting Documentation, which incorporated comments from the first stage review in addition to the first draft of the sections on Hazard Characterization and Dose-Response Analyses, was forwarded for written review to 23 individuals and groups (March, 1998). The charge to these reviewers was to address specifically the adequacy of coverage and accuracy of reporting and defensibility of conclusions with respect to hazard characterization and dose-response analyses. These reviewers were selected to broadly reflect the range of scientific views of the research community addressing butadiene in critical areas including metabolism, genetic toxicity, epidemiological study and dose-response analyses, the latter particularly for that based on epidemiological data. Additional reviewers in each of these areas were selected who were not involved in research on butadiene, per se, but rather offered experience relevant to a more distanced assimilation of the data for purposes of development of the Hazard Characterization and Dose-Response analyses. Responses were obtained from all but one reviewer (E. Frome). Second stage reviewers were as follows:

R.J. Albertini, Genetic toxicologist, Principal investigator of transitional epidemiological study on biomarkers for butadiene, University of Vermont, Information Department, BIBRA International, U.K.

J. Bucher, Deputy Director, Environmental Toxicology Program, U.S. National Toxicology Program

B. Davis, Head, Ovarian Toxicity/Carcinogenicity Group, Environmental Toxicology Program, U.S. National Toxicology Program

E. Delzell, Epidemiologist, Principal author of critical epidemiological study of styrene-butadiene rubber workers, University of Alabama at Birmingham

B.J. Divine, Epidemiologist, Principal author of key epidemiological study of butadiene monomer workers, Texaco

A.A. Elfarra, Researcher, kinetics and metabolism on butadiene, University of Wisconsin-Madison

E. Frome, Senior statistician, Oakridge National Laboratory

B.D. Goldstein, Academic researcher, Environmental and Occupational Health Sciences Institute, New Jersey
R.F. Henderson, Researcher, kinetics and metabolism on butadiene, Lovelace Respiratory Research Institute

R.D. Irons, Researcher, mechanism of action of lymphohematopoietic carcinogens, University of Colorado Health Sciences Center

J. Lubin, Senior statistician, National Cancer Institute

J. Lynch, Consulting industrial hygienist, Directly involved in developing the exposure estimates for the critical study of styrene-butadiene rubber workers and transitional epidemiology study on butadiene biomarkers, Exxon Biomedical Sciences, Inc. (retired)

R.L. Melnick, Toxicologist, Toxicokinetic modeling, Principal investigator in critical cancer bioassay in animals; U.S. National Toxicology Program

A.G. Renwick, Researcher, kinetics and metabolism, University of Southampton

J. Siemiatycki, Epidemiologist, Institut Armand-Frappier


J.A. Swenberg, Researcher - DNA adducts in workers exposed to butadiene, University of North Carolina

R. Tice, Genetic toxicologist, Integrated Laboratory Systems, Inc.

J. B. Ward Jr., Genetic toxicologist, Researcher on genetic effects in workers exposed to butadiene, University of Texas Medical Branch

The revised documentation was also forwarded to several of the same individuals who provided review in stage 1, primarily to access their input with respect to defensibility of conclusions in the Hazard Characterization and Dose-Response Analyses (additional comments were not received from two of these individuals). These reviewers included:

- J. Bond, CIIT
- I. Brooke, U.K. HSE
- A. Koppikar, U.S. EPA
- K. Peltonen, FIOH

Charge to Reviewers of the Technical Oversight Panel of November 30, 1998:
The reviewers were requested to review the critical evaluation from each external reviewer and evaluate the disposition of comments by Health Canada, with particular attention to their areas of expertise.

The reviewers were requested to review the critical evaluations from each external reviewer and evaluate the disposition of comments by Health Canada. In addition they were charged with paying particular attention to their area of expertise. As part of the summary of external peer review comments and issues, Health Canada developed and iterated a number of key points for consideration by the review panel. The panel was asked to provide comment on other issues that were relevant to the adequacy of the incorporation of the comments of the peer reviewers. The issues (1-12) stated below are verbatim as presented to the review panel by Health Canada. The paragraph, which follows the identified issue, is a synopsis of the review panel’s discussion.

Review Panel Comments on the Identified Principal Issues:

1. Inclusion of additional (primarily) recent studies. Wherever possible (i.e., where adequate documentation could be acquired), data considered relevant to the assessment were included and the nature of the source of the information clearly indicated. None of the suggested additions materially affected the overall conclusions. However, research by two groups (i.e., Matanoski et al., (epidemiological study) and Meng et al., (genotoxicity studies in rats and mice)), contributed to the weight of evidence for critical endpoints, as indicated in the revised Hazard Characterization.

Additional references were recommended for inclusion by several of the external reviewers. The panel reviewed the updates made to the risk assessment with Health Canada. Some references were not included if they did not enhance the discussion or had been previously cited in other sections of the document. For example, Melnick, recommended that four references be added. Two were and two were not because the latter were secondary reviews of primary reports from the literature, which had already been cited in the assessment. Clewell commented favorably on Health Canada’s ability to resolve the issues and in particular the consideration given to the expert reviewer’s recommendations. Dourson, on behalf of the assembled review panel, declared that Health Canada had considered and addressed the reviewer’s comments appropriately and adequately addressed issue 1.

2. Improved documentation of the methodology for quantification of dose-response analyses was suggested by 2 reviewers (BIBRA Toxicology International and Jonathan Ward). Jack Siemiatyci also requested clarification on several aspects of the dose-response analyses. It is reassuring, though, that Leslie Stayner and colleagues of NIOSH (who conducted the dose-response analyses based on the same critical epidemiological study for the U.S. EPA assessment of butadiene) considered the exposure-response analyses to be "extremely thorough and highly defensible". Similarly, J. Lubin of NCI considered the analyses to be "thorough and complete" and had no "substantive criticisms" concerning this section. The
documentation in this area has been expanded and members of the Review Panel with relevant expertise are invited to review its adequacy.

Clewell responded that the documentation as it relates to clarification of the methodology used in the report had been improved from the version originally submitted to the expert reviewers even though the documentation was adequate in the first draft. Still there is a need to adopt appropriate nomenclature throughout the document to clearly distinguish between estimates of exposure for humans and animals. In particular, a standard nomenclature should be used to distinguish animal NOAELs and BMCs from the human equivalent calculated concentrations. Health Canada replied that a number of different analyses were performed and they all yielded similar results. The details of the analyses utilized are included in the revised document. Clewell offered an opinion that the modeling still needs to be more fully documented. In fact the results would appear to be counterintuitive – the models are different in the range of the data, yet the results (TC 05) are similar. Health Canada agreed to incorporate the suggested changes. The panel agreed that Health Canada had addressed the comments to the extent possible.

3. Two reviewers (John Bucher, NIEHS and Leslie Stayner, NIOSH) question why the mouse lymphomas were not used for quantification of dose-response. In fact, the quantitative values were included in the previous draft documentation for comparison. However, they were not highlighted, due to the fact that while they were considered qualitatively relevant to humans, they were not considered quantitatively relevant due to the greater sensitivity of the mice to induction of these tumors associated with the presence of an endogenous virus. Since (as John Bucher indicates), these values are not limiting, they have no material impact on the outcome of the dose-response analyses. No change was introduced. (Jonathan Ward supported the case to exclude the lymphomas for quantitative characterization of dose-response).

The panel agreed that Health Canada had addressed this issue by a footnote to the appropriate table. Clewell further noted that the mouse lymphoma data were appropriately addressed and that Health Canada had handled the endpoints quite well both in the table and in the text. The issue was determined by the panel to be appropriately addressed.

4. Weight of epidemiological evidence for causality for leukemia associated with exposure to butadiene. Comments in this regard were provided by Elizabeth Delzell and Jack Siemiaticki. The former suggests that characterization of the association between butadiene and leukemia as strong in the study by Delzell et al. may be an overstatement in view of the imprecise and weak exposure-response relationship in the overall cohort and the moderately strong but imprecise association in the highest exposure groups, based on only 5 leukemia decedents. She also suggests that though there is evidence of internal consistency in this study, the available data do not fulfill the criterion of external consistency. She also points out that the epidemiological finding of no leukemia excess in monomer workers seriously threatens coherence (This can be contrasted with the
comments of Jerry Lynch, an industrial hygienist who indicates that the possible reason for the variation in results in monomer and SBR workers may be related to exposure; this is mentioned also by R. Irons). Jack Siemiatycki feels that latency is irrelevant in assessing causality. In addition, Leslie Stayner felt that there should be a more definitive conclusion concerning the weight of evidence of carcinogenicity in human populations. This isn’t required, however, for Priority Substances; moreover, it was considered important that conclusions concerning the potential carcinogenicity of this compound be made on the basis of all available evidence, including that in toxicological studies in animal species. There were conflicting opinions (E. Delzell and B. Goldstein) as to whether leukemias and lymphomas should be considered jointly or separately in the assessment of weight of evidence. Members of the Review Panel with relevant expertise are invited to review the adequacy of the revised discussion of the weight of evidence for causality for leukemia associated with exposure to butadiene, based on the comments of the external peer reviewers.

Erdreich pointed out that the weight of evidence for causality is a complicated issue and that the evidence for causality is always a problem when using epidemiological data. For example, questions can always be asked such as: What is the statistical criteria? How are the differences determined? Can one separate biological plausibility when assessing causality, especially in a risk assessment? For example, one must emphasize the precision of the estimate and separate that from the statistical significance. The process for assessing the weight of epidemiological evidence for causality is conceptually no different from the overall weight of evidence process. The standard guidance for assessing epidemiological data to reach a public health decision includes biological plausibility, often considered separately from the conclusion based on the epidemiological evidence. Health Canada’s procedure to assess all available evidence, without presenting a specific conclusion based on epidemiological data, is certainly appropriate.

Health Canada stated that there was a difficulty in reconciling opinions. Erdreich in turn indicated that the lymphoma/leukemia issue was handled very well by Health Canada in the text. There are many difficult issues surrounding the leukemia problem with butadiene, but certainly the weight of evidence, although not strong, exists for leukemia. The epidemiological data is not complete and the document explains this very well. However, Erdreich thought that it is important for Health Canada to also address the issue about the bone marrow stem cells and their relation to the origin of lymphoma/leukemia.

The Panel recognized that the range of opinions expressed by the reviewers in this difficult and complex area, but felt that Health Canada had expressed the problem quite well. This is further illustrated by the fact that the weight of evidence of the available data, including the issue of coherence due to the lack of consistency of observed cancers between the monomer and rubber workers, is handled well in the text. Clewell added that there were a variety of opinions presented by the expert reviewers, which made it difficult to totally resolve the inconsistencies associated with the opinions expressed. Overall, the document finds the middle ground and expresses the problems quite well.
Erdreich suggested that the data be additionally addressed in the uncertainty section. However, a good job was done with a difficult array of data. Erdreich also stated that she will provide editorial comment to this section to make it more understandable to the first time reader. Dourson emphasized that Health Canada used both the epidemiological and animal toxicity data in their conclusions to this section, a point that should not be lost on the readers.

The review panel was satisfied with the way in which Health Canada approached this difficult issue.

5. Ron Melnick indicates that rather than the tumor rates adjusted for intercurrent mortality which exaggerate effects seen at the end of the bioassay, the potency calculations should be based on the Poly-3 survival adjusted tumor rates, considered to be a more reliable means of accounting for intercurrent mortality. The tumorigenic concentrations for mice have been recalculated on this basis.

Clewell stated that it was heartening to see that the comments and suggestions of the reviewer had been acted upon by Health Canada and this consequently had made for a stronger document. Clewell also pointed out that the NTP endorses the Poly-3 approach as a preferred method. The review panel agreed with the changes made to the document.

6. One of the reviewers (R.J. Albertini) suggested that the dose-response relationship for micronuclei in the mice in NTP bioassay be modeled. These analyses have been run and a description of the approach and results added to the section on Dose-Response Analyses. Members of the Review Panel with relevant expertise are invited to review the adequacy of conduct and presentation of these analyses. Another reviewer (Jonathan Ward) suggested modeling of the dose-response relationship for male mediated reproductive effects on the basis that there are more men than women occupationally exposed to butadiene. These analyses were not conducted since ovarian atrophy appears to be the most sensitive reproductive endpoint.

Dourson asked whether TC\textsubscript{0.05} meant a 5% increase over the control level (i.e., 5% over 1.26 micronuclei per 100 cells or excess risk normalized by background rate). If so, what does this mean biologically. Otherwise, the modeling of micronuclei seemed appropriate and the description given by Health Canada was reasonable. Dourson also indicated that Figure 5 should state that the BMCs are in units of mg/m\textsuperscript{3}, so as not to be confused with the dose scale in ppm. Clewell suggested that the observation of increased micronuclei is an interesting fact, but that the modeling does not provide any additional information to enhance the risk assessment. Therefore, it should have a supportive role and be mentioned in the text where appropriate. Health Canada agreed that the modeling did not lead to any meaningful risk assessment statement and there is not a good biological reason for doing multiple modeling exercises.

Dourson thought that the response by Health Canada to the issues of modeling of the dose-response relationship for male mediated reproductive effects seemed appropriate.
This was based on the description of these effects (found on text pages 9 and 10). Dourson suggested that acquisition of the historical control data of Anderson et al. (1993) and Brinkworth et al. (1998) might be informative to see if the effects 12.5 ppm are related to butadiene exposure or are more likely due to background.

The Review Panel agreed that no further work should be attempted here under the scope of this particular document.

7. Though the reproductive/developmental toxicologist at Health Canada (Warren Foster) is convinced of the relevance of the observed changes, Barbara Davis of NIEHS expresses concern that the diagnosis of ovarian atrophy in the 2 year cancer bioassay in mice may represent a senile rather than a toxic effect, based on review of some of the slides from the terminal sacrifice in the study. In view of the fact that such effects were observed in other studies and since similar changes were reported at the interim sacrifices, it was suggested that some of the slides from these intermediate time points be examined. Unfortunately, Dr Davis’ schedule has not permitted this additional work and it is necessary currently to complete the assessment. The text of the document has been modified to characterize the uncertainty about the significance of the endpoint, though, in view of the observation of these lesions at early intermediate time points in the study and evidence of similar effects in other studies, quantitative characterization of exposure-response has been retained. Additional work in this area as well as research to better characterize female mediated reproductive effects have been recommended. (B. Goldstein also indicates that he has "some concern" about the use of the ovarian toxicity for quantification on the basis that the low BMC is not "internally compatible" with the tumor data but provides no additional amplification).

The Panel considered the data an unequivocal effect. Dourson pointed out that Table 15 clearly shows an increasing trend in both the incidence and severity of ovarian lesions. Whether this is due to a direct toxicity effect on the organ, or perhaps indirectly by way of an overall oxidation of the organism, is not particularly important. Making the animal (or its organs) prematurely senile is considered an adverse event. Dourson suggested that additional analyses of these data would make an interesting project (but not necessarily by Health Canada). He also suggested that instead of a BMD analysis, a categorical regression approach for these data would be more appropriate since there is a qualitative and quantitative progression of the effect. Clewell also pointed out that Health Canada was using a BMD approach, which would obscure trends such as changes in severity.

For the purposes of the document, human cancer is the critical effect. No other development of the reproductive data needs to be undertaken. The Review Panel deemed the approach to comments taken by Health Canada to be appropriate. No further action is warranted by Health Canada.

8. Two of the reviewers (Leslie Stayner and Ron Melnick) mention that, to their knowledge, there is no evidence that dimethylthiocarbamate is carcinogenic. It
had been stated in the previous draft that though the biological plausibility of a potential association between exposure to this compound and leukemia is recognized it is not possible to draw any conclusion concerning its role in the observed increases in leukemia in the styrene butadiene rubber industry at this time in view of the current lack of quantification of exposure levels of this substance in the plants examined. An additional qualification concerning absence of data on its leukemogenic potential, based on these comments as well as on a literature search conducted by the Department, has been added.

Dourson asked Health Canada to more fully explain what was done to address this issue. Health Canada replied that literature searches were undertaken, but that no evidence was found in the literature to indicate that dimethyldithiocarbamate was carcinogenic. A statement to that effect was included in the document. Health Canada will also provide a review of the work and search strategy performed on the literature for the carcinogenicity of dimethyldithiocarbamate in the Appendix of the final version of the Assessment Report.

The Review Panel did not request any additional work on this issue and felt it was adequately handled in light of the conflicting suggestions of previous reviewers.

9. Three of the reviewers (B. Divine, E. Delzell and R. Irons) indicate that workers in tire manufacturing where there have been increases in LHC, either have insignificant exposure to butadiene or that this is not documented. A qualification has been added that, while there are no quantitative data on exposure to butadiene in these cohorts, styrene butadiene rubber was the most important synthetic rubber produced in these plants.

The Panel commented that the text had been improved considerably since the first draft by the addition of the qualification. Erdreich thought that the current version of the document had revisited and adequately addressed these issues but noted that the version of the document sent to the expert reviewers did not adequately present the tire manufacturing data which should be considered non-informative regarding 1,3-butadiene. However, she also stated that there is no quantifiable exposure data available which may affect the confidence of the risk assessment.

The Review Panel did not have any other comments and the issue was determined to be adequately addressed.

10. Two of the reviewers (B. Divine and E. Delzell) indicated that they considered there to be undue emphasis on positive outcomes seen on one cohort or subgroup within a cohort. Wherever possible, negative results for the cancers of interest within the entire cohort have been added to the text. Assimilation of the quantitative data for cancers of interest for the Hazard Characterization and Dose-Response Analyses included both positive and negative results.
Erdreich replied that it is misleading to label entire studies as positive or negative, rather, the magnitude of the association (odd ratio or SMR) as well as the precision of the estimate (confidence interval) should be considered. To assess consistency, the trends and patterns in the data need to be considered. The tables in the document that were added in the most recent version of the risk assessment demonstrate the precision of the estimate and the points raised were handled well.

The Review Panel agreed with the comments of Erdreich and no further action by Health Canada is required.

11. At an earlier stage, one of the internal reviewers and one of the second stage external reviewers (Ron Melnick) recommended that a description of variations in the nature of process and thereby, exposure in the two principal industries in which the epidemiological studies have been conducted, be added. While it was not considered a priority previously, information included in the comments from one of the external reviewers (J. Lynch) are extremely helpful in this regard.

The panel stated that the document provided ample discussion on the exposure issues. In addition, the panel stated that this discussion of the data is important to the document and that the exposure issues were addressed appropriately. The issue was handled in the best way possible and no further action by Health Canada is required.

There were a number of suggestions (BIBRA Toxicology International, Andy Renwick, Jonathan Ward) concerning additional need for comparison and interpretation of the dose-response estimates. This is, indeed, an integral component of assessments conducted for Priority Substances, though not considered relevant for inclusion in second stage external review. Some of the relevant text in this regard and characterization of uncertainties have been included in the current draft of the Assessment Report.

Clewell responded that when using epidemiological data, one needs to break out from convention, i.e., does the 5% incidence level relate appropriately to the incidence in the epidemiological studies. Clewell pointed out that it was actually necessary to extrapolate upwards from the epidemiological data to obtain a TC.05. An additional risk level closer to the range of the epidemiological data should also be calculated and presented, e.g., the TC.005, in order to better characterize risk exposures of environmental relevance. It was also suggested that the data on ovarian lesions be analyzed by categorical regression even though the quantitative dose-response analysis for cancer would likely drive the risk characterization and was therefore not considered critical for this assessment. The panel was not sure why the TC.05 effect level was selected. Health Canada replied that the TC.05 was developed by biostatisticians to compare with other tumor data. In Canada, both cancer and non-cancer effects may be used to develop an effect level.

Clewell further expounded upon the cross-species scaling of butadiene. Health Canada had applied a cross-species dosimetry adjustment for both the cancer and non-cancer risk assessments for butadiene. The dosimetric adjustment assumes that the chemical in question is highly water soluble and is rapidly metabolized such that there is no re-entry
of the chemical in venous blood into the lung. Butadiene is relatively insoluble in water and is relatively slowly metabolized and thus does not meet the assumptions of the dosimetric adjustment. Thus, according to the Us EPA’s methodology, a default cross-species dosimetry of 1 is used. Use of this default ratio is estimated to be conservative by a factor of 2. Clewell therefore recommended that the adjustment for a ventilation to body weight ratio for butadiene not be constructed and utilized in this assessment.

The panel was comfortable with the discussion of the dose response estimates in the document. The significance of the ovarian effects needs further exploration. However, it is not necessary for this document at this time and any work performed on the severity and/or incidence of ovarian tumors needs to be undertaken as a separate task and not necessarily by Health Canada.

**Review of Individual Expert Reviewer Comments:**

Dourson polled each of the Review Panel members for each Expert Reviewer comment(s) to insure that the individual issues raised were appropriately addressed. The panel commented on the breadth and detail of each review that the Expert Reviewers provided. In all cases the panel felt that issues raised by the expert reviewers were in most cases appropriately handled in the body of the document. (The few exceptions are mentioned above in the individual issue discussions). For those issues that did not result in changes or additions to the document, the Review Panel agreed with the rationale used by Health Canada to not amend the document. The Panel suggested that the discussion of likely heterogeneity in the human population due to complexity of metabolic pathways be emphasized less and also suggested that the terminology used in the dose-response analyses with respect to unadjusted and human equivalent doses be clarified and standardized throughout. Finally, the Review Panel also agreed with the disposition of comments by Health Canada on the Health Risk Assessment for 1,3-Butadiene.