UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
AIR AND RADIATION

MAY -9

Center for the Evaluation of Risks to Human Reproduction
P.O. Box 12233, MD EC-32
Research Triangle Park, NC 27709

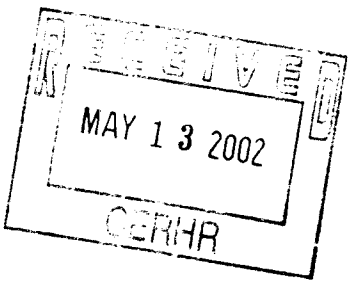
Dear Dr. Shelby:

We are pleased to comment on the reports prepared by the Expert Panel on 1-bromopropane and 2-bromopropane, and wish to thank the Panel and the Center for the Evaluation of Risks to Human Reproduction itself for undertaking this important review.

Attached you will find EPA's comments as prepared by our contractor ICF Consulting. Please do not hesitate to contact me at birgfeld.erin@epa.gov or 202-564-9079 with any questions regarding these comments.

Sincerely,

Erin Birgfeld
Global Programs Division



CONSULTING

MEMORANDUM

To: Erin Birgfeld

From: Kara Altshuler, Reva Rubinstein, Mark Wagner

Date: April 30, 2002

Re: Responses to the Final CERHR Report on 1-Bromopropane
Deliverable under Contract Number 68-D-00-266, WA 1-05 Task 02

First, we wish to congratulate the Expert Panel for tackling the challenging job of distilling the varied toxicological studies available regarding 1-bromopropane and presenting a thoughtful and well-balanced report. At the request of EPA, we have prepared this response to the NTP – CERHR[1] Expert Panel Report on the Reproductive and Developmental Toxicity of 1-Bromopropane (1BP).

In general, ICF agrees with the Expert Panel's interpretation of systemic and reproductive and/or developmental findings of the reviewed studies. We agree with the Expert Panel that the lack of a developmental study in rabbits is a deficiency in the overall database. We also concur with the Expert Panel that mechanistic and metabolism studies regarding 1BP and structurally similar haloalkanes would bolster the overall database regarding these solvents.

ICF disagrees with the selection of certain Lowest Adverse Effect Concentrations (LOAECs), however. The text in the following sections identify endpoints of concern noted by the Expert Panel and presents our responses to the toxicological relevance of these endpoints.

General Systemic Effects

From the two-generation inhalation toxicity study by Stump (2001), the Expert Panel identified a LOAEC of 250 ppm for 1BP based on kidney effects. This LOAEC was based on increased mineralization of the pelvis of the kidney for all dose groups. We note that although the incidence of mineralization of the kidney pelvis was increased in all dose groups, mineralization of all areas of the kidney combined was only increased in the high-dose group (750 ppm) compared to the controls. Further, the severity of mineralization in any part of the kidney did not increase above a category of minimal, with the exception of two 750 ppm females with the category of mild pelvic mineralization. Mineralization of the kidney, in both the parenchyma and pelvis, is not a particularly sensitive endpoint in the rat. It is a rather common occurrence in chronic toxicity studies using rats (Lord and Newberne, 1990; Owen and Heywood, 1986) and mice (Chandra and Frith, 1994). Further, the CERHR report does not describe why the incidence of pelvic mineralization should be of greater toxicological interest than that in other locations within the kidney.

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Developmental Effects

The report notes that bent or wavy ribs were reported as a developmental finding in the offspring of male and female rats that inhaled ~1000 ppm 1BP in the two-generation inhalation study (Stump, 2001). The report further indicates that this endpoint is a fetal aberration rather than a frank malformation. ICF concurs with the position of the report regarding the toxicological significance of the changes in ribs.

The report indicates that the Expert Panel performed a benchmark dose (BMD) analysis to determine if reduced pup weight in the F_1 generation at the low dose (Stump, 2001) was related to compound administration. The BMD estimated the concentration at which the pups would exhibit a 5% decrease in weight compared to the control group. The $BMDL_5$ value was determined to be 305 ppm. This value indicates that reduced fetal body weights at 103 ppm in the study were likely not related to administration of 1BP and the concentration of ~500 ppm would be the LOAEC for skeletal variations (reduced skull ossification).

The report further compares the BMD of 561 ppm derived by the Expert Panel for skeletal variations with the LOAEC for this endpoint (~500 ppm) and states that the values are consistent. While these two values are numerically comparable, they do not represent a toxicological consistency. Rather, the LOAEC is the dose at which the response reaches an arbitrarily assigned cutpoint for statistical significance and is the product of a hypothesis test. Unlike the LOAEC, the BMD is the product of an estimation procedure that takes into account the response of exposed animals at all doses. By definition, the BMD defines the dose at which a certain level of response is expected. It is more appropriate for this study, therefore, to compare the $BMDL_5$ for reduced pup weight to the $BMDL_5$ for skeletal variations to determine if these effects would be expected at similar exposure concentrations of 1BP.

Reproductive Effects

The CERHR report identified 250 ppm as a LOAEC in the Stump (2001) study based on decreased prostate weight in the F_0 males and increased estrous cycle length in the F_1 female offspring. ICF notes that while mean absolute prostate weights were decreased at 250 ppm and higher doses, there was no dose related trend as the mean absolute weights were the same at the three highest doses (1.14±0.169 g, 1.14±0.232 g, 1.14±0.178 g at 250, 500, and 750 ppm respectively). The biological endpoint that is of more interest, however, is the relative prostate weight because a reduction in body weight might result in a concomitant reduction in the weights of certain organs, including the prostate. ICF determined the mean relative prostate weights for exposed dose groups and did not observe a clear dose-related response. For example, the relative prostate weights are 0.0040, 0.0039, 0.0036, 0.0035, and 0.0035 at 0, 100, 250, 500, and 750 ppm, respectively. ICF did not perform a statistical analysis to determine if any of these values is significantly different from the control mean. A clear dose-related decrease in relative prostate weight is not represented by these data and the values at 250 ppm represent a decrease of only 10% relative to controls. Therefore, ICF does not believe that the reduced absolute prostate weights should be considered as an endpoint to determine a LOAEC for this study.

The CERHR report identified 250 ppm as a LOAEC in females based on increased estrous cycle length in F_1 female offspring. The estrous cycle length in the F_1 females (4.9 days at 250 ppm compared to 4.5 days for controls) was considered to be increased by the author of the two-generation inhalation study (Stump, 2001); however, he did not subject the data to statistical analyses. We acknowledge the possibility that the slightly increased estrous cycle length may be a result of 1BP exposure. Because the estrous cycle length of 4.9 days is well within the range of the historical controls (4.1-5.1 days) of the study laboratory (Stump, 2001), the effect cannot be conclusively attributed to exposure without a statistical analysis. The study report notes the lack of cycling in some females which may have caused difficulty in accurately determining the average estrous cycle length for each affected group. ICF agrees that lack of estrous cycling could affect the accuracy of cycle length measurements, thereby skewing the mean cycle length to be longer as compared to historical laboratory controls. Because these data are lacking, it is our opinion that this effect should not inform a LOAEC of 250 ppm.

The CERHR report indicates that a LOAEC for male reproductive effects was determined to be 200 ppm based on reported decreases in absolute and relative seminal vesicle weight in male rats exposed to varying doses of 1BP in a 12 week whole body inhalation study (Ichihara et al., 2000). While this study

provides important data concerning the hormonal and histological changes in the reproductive organs of male rats following 1BP exposure, the study design and/or reporting are deficient in several areas. First, the study did not conform to Good Laboratory Practice (GLP) standards and as such is not comparable to other studies that are GLP compliant. The limited number of animals (9) decreases the statistical strength of the findings. Most importantly, the study is lacking a detailed description of how long it took the inhalation chambers to reach the target concentration of 1BP and clear the 1BP post-exposure (and whether the rats were present in the chambers during these periods). Without these data, it is unclear that the exposure concentrations noted in the Ichihara et al. (2000) study are accurate. It is our belief that the Stump (2001) study provides a more reliable basis for selection of LOAECs, as well as provides a more appropriate data set upon which to develop a BMD analysis.

ICF has prepared a BMD analysis (ICF, 2002) for 1BP using the data from the Stump (2001) study. The BMD analysis included several endpoints in the F_0 and F_1 generations of rats including hepatocellular centrilobular vacuolation in males and females from both generations and effects on sperm motility in males of both generations. $BMDL_{10}$ values were determined according to the following endpoints: 169 ppm for sperm motility in F_1 males and 110 ppm for hepatocellular centrilobular vacuolation in F_1 males. It is noteworthy that both $BMDL_{10}$ values were lower than the $BMDL_5$ value of 305 ppm determined by the Expert Panel (CERHR 2002). Thus the endpoints analyzed by BMD at ICF are more sensitive than that chosen by the Expert Panel.

ICF believes that the BMD approach is the best method for determining toxicity values for potentially hazardous compounds for which exposure is expected in both the workplace and the general environment. This approach has been embraced by the EPA (EPA, 1995) as the most appropriate methodology as it is not associated with the limitations of the NOAEL/LOAEL approach (Crump, 1984; Kimmel and Gaylor, 1988). It is our contention that such measures as Reference Concentrations (RfCs) and occupational exposure limits, can and should be estimated using BMD methods when possible.

Errata

The CERHR report states in Section 1.2.4.2 that "1-BP is being considered [under the SNAP Program] as a possible replacement for CFC-113, methyl chloroform, and HCFC-141b for non-aerosol solvent cleaning of metals and electronics and for adhesives, coatings, aerosol propellant, and solvent applications." This statement should read that "1-BP is being considered as a possible replacement for CFC-113 and methyl chloroform in non-aerosol solvent cleaning of metals and electronics. It is also being considered as a replacement for methyl chloroform, CFC-113 and HCFC-141b in aerosol solvents and adhesive applications."

The CERHR report indicates in Section 1.2.4 (Human Exposure) that the EPA is currently recommending an 8-hour time weighted average (TWA) exposure limit for 1BP of 50-100 ppm. EPA has stated that this is no longer the case given the availability of additional data, referred to here and in ICF (2002).

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