Environmental Health Perspectives
Vol. 86, pp. 149–153, 1990

Cancer Risk Assessment of 1,3-Butadiene

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This paper discusses the Environmental Protection Agency's (EPA) risk assessment of 1,3-butadiene. The assessment focuses on estimation of increased cancer risk to populations living near industrial sources of 1,3-butadiene emissions rather than occupationally exposed populations. Incremental cancer risk estimates based on extrapolation from laboratory animal data are presented. Pharmacokinetic data published since the EPA's 1985 assessment are incorporated, which somewhat alters the earlier assessment of cancer risk. Characterization of emission sources, estimates of ambient air concentrations, and population exposure are also discussed.

The estimate presented in this paper of excess cancer cases resulting from point source exposure to 1,3-butadiene is decreased to approximately 40% of the estimate published in 1985 from 6.4 in 10 to 2.5 chances in 10 for a lifetime exposure to 1 ppm. The current estimate is no more than eight additional cancer incidences in the general population. Increased risk to the most exposed individuals is not anticipated to be greater than 1 in 10. This reduction in the risk estimate is due to a change in the estimate of 1,3-butadiene potency (i.e., incremental unit risk estimate) based on incorporation of new pharmacokinetic data.

Background

1,3-Butadiene is a colorless gas used in the production of polymers, elastomers, and other chemicals. Some 1,3-butadiene products are as follows: automobile tires, high-impact plastic used in automobiles, appliance parts and pipes, and synthetic fibers. It is produced as a coproduct in the production of ethylene, by oxidative dehydrogenation of *n*-butenes, or by dehyrogenation of *n*-butanes. Automobile exhause also contains 1,3-butadiene (*1,2*).

Due to its volatility, 1,3-butadiene is primarily an air contaminant. Because of potential carcinogenic effects associated with 1,3-butadiene exposure (*3*), in 1984 EPA initiated a review to determine the potential impact on public health from exposure to 1,3-butadiene present in the ambient air. The results of this review are the topic of this paper and are being used to determine if air emissions of 1,3-butadiene should be regulated by EPA under the Clean Air Act.

Hazard Identification

The first element in conducting a cancer risk assessment is the evaluation of the weight of evidence that a given chemical is likely to produce an adverse health effect in humans. The effect of greatest emphasis in this assessment is cancer, both because of the seriousness of the effect and because of the strength of the evidence.

Epidemiologic studies of the potential health hazards associated with 1,3-butadiene exposure are limited. Until recently the data have been considered inconclusive and inadequate for classification or quantifying risks. Some excess cancers of the lymphatic and hematopoietic tissues were, however, seen in some studies (*4–6*). More recent information (*7–10*) provides additional confirmatory evidence that 1,3-butadiene exposure is associated with these lymphatic and hematopoietic system cancers in humans, but accurate contemporary exposure estimates are lacking.

Three lifetime inhalation carcinogenicity studies have been carried out in mice and rats (*3,11–14*). There were significant increases in the incidences of primary tumors in both species, both sexes, and at multiple organ sites; dose-response trends were observed in all three studies. There are marked differences, however, in both affected tumor sites and sensitivity between exposed mice and rats, with mice being much more sensitive. In the rat study (*14*), groups of male and female Sprague-Dawley rats were exposed for 2 years, 6 hr/day, 5 days/week to 0, 1000, and 8000 ppm 1,3-butadiene via inhalation. Significantly decreased survivals were observed in both the male and female 8000-ppm dose groups. Increased tumors were observed in males in Leydig cells and pancreatic exocrine and Zymbal glands, with increases being statistically significant only at the highest concentration and only for the two former sites. Female rats showed increased mammary, uterine, Zymbal gland, and thyroid gland follicular cell tumors. Other than increases in common mammary gland tumors, response was generally less than 10%. For more details see Owen et al. (*15*).

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In comparison to the statistically significant but small increases in rats, the cancer response, in both male and female B6C3F$_1$ mice, at comparatively lower concentrations of 625 and 1250 ppm was both massive and rapid and included as many as seven primary tumor sites (*3,12,13*). Survival in both sexes at both treatment doses was affected to the point where the studies had to be terminated after 60 and 61 weeks. Early tumors, especially malignant lymphomas and hemangiosarcomas of the heart, were responsible for most of these deaths. Other statistically increased tumor sites included lung and forestomach (both sexes) and liver, mammary glands, and ovarian glands (females). [Information from a recently completed study in B6C3F$_1$ mice by Melnick et al. (*11*) provides additional evidence of the carcinogenicity of 1,3-butadiene at lower concentrations.]

Based on the previous evidence of positive cancer response in two animal species and inadequate epidemiologic data, EPA in 1985 classified 1,3-butadiene as a "probable" human carcinogen, Group B2 according to EPA's Guidelines for Carcinogen Risk Assessment (*16,17*). The authors of this paper believe that epidemiologic evidence provided at this symposium (*8–10*) will result in an EPA reclassification upgrade for 1,3-butadiene from Group B2 to Group B1. The Group B1 classification is indicative of a probable human carcinogen based on limited human data and sufficient animal data. The Group B2 classification is indicative of a probable human carcinogen based on animal data only.

Dose-Response Assessment

The second element in a cancer risk assessment is the estimation of the carcinogenic potency of the substance in humans, which is expressed as the "incremental unit risk," sometimes shortened to the "unit risk." The incremental unit risk estimate for an air pollutant is defined as the lifetime probability of excess cancer risk, i.e., the risk, in excess of the background rate, that is estimated to occur because of exposure to one unit of the agent per volume of air.

Choice of Model

Since risks at low ambient exposure levels cannot ordinarily be estimated directly either by experiments in laboratory animals or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from higher to lower exposures and from animals to humans. Several different extrapolation models will usually fit the observed data reasonably well, but they may lead to large differences in the extrapolated risk at low doses.

At present, mechanisms of the carcinogenesis process are largely unknown and data are generally limited. If a carcinogenic agent acts by accelerating or enhancing the same carcinogenic process that leads to the background occurrence of cancer, the added effect of the carcinogen at low doses is expected to be virtually linear (*18–21*); although at high doses nonlinear effects usually occur. In the absence of evidence to the contrary, EPA has chosen to extrapolate to low exposures using this linearity assumption and has chosen a model for animal to human extrapolation called the linearized multistage model (*22*). This procedure fits the most pertinent animal data set(s) to a polynomial of suitable degree and then extrapolates to low doses using an upper-limit linear term consistent with the data.

For each assessment the EPA reviews the available evidence on carcinogenic mechanisms and other biological or statistical evidence that indicates the suitability of a particular extrapolation model. When the compound is mutagenic, the multistage model is used as an application of the mutation theory on cancer. When the compound is a promutagen, as 1,3-butadiene appears to be, the linearized multistage model is still appropriate; an adjustment must be made, if possible, for the target organ dose of the active metabolite(s).

It should be emphasized that the linearized multistage procedure leads to a plausible upper limit of excess risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the low dose risk.

Choice of Data Set

An estimate of the carcinogenic potency of 1,3-butadiene to humans was made based on the most sensitive animal species. In this case, since the cancer responses in the male and female mice were so similar (*3–13*) both sets of results were used by taking the geometric mean of the 95% upper-limit estimates derived from each sex by the use of the linearized multistage model.

To derive estimates of target tissue dose, the data from an unpublished study (*23*) on male mouse total body burden were used in EPA's risk assessment (*17*). However, following EPA's publication, additional experiments and further analysis by the National Toxicology Program (NTP) led to a publication of final results (*24*) that differ from those in the unpublished report. The risk assessment presented at this meeting used these final results for the body burden and absorption estimates. Estimates of total body burden were used instead of estimates of target organ dose because of the high number of affected sites and the different dose and time-response characteristics of the different tumor sites.

In calculating internal doses from external exposures, estimates of the low-exposure retention of 1,3-butadiene and/or metabolites following 6-hr exposures to mice were 20% over a two order of magnitude range of concentration (up to 7 ppm). At the higher exposures of 70 and 930 ppm, retention decreased to 8% and 4%, respectively (*24*). Since metabolic clearance of 1,3-butadiene in mice (and rats) follows linear pharmacokinetics below exposure concentrations of about 1000 ppm (*25,26*), the decreases at high concentrations in micromoles body burden/ppm exposure concentration after a 6-hr exposure are assumed to result from decreased lung absorp-

tion. When body burden doses are adjusted for this decreased absorption at higher atmospheric concentrations, potency estimates in the female rat and female mouse are within a factor of three of each other, but estimates based on the male mouse are still between one to two orders of magnitude greater than those based on the male rat.

Using the linearized multistage model to extrapolate from the cancer response in the NTP mouse bioassay (*13*), a correction factor for early termination, and the estimates of body burden based on the data of Bond et al. (*24*), the upper-limit incremental estimate of carcinogenic potency for humans, assuming a 70-year continuous exposure, is 2.5×10^{-1} per ppm. This means that if a person were exposed to 1 ppm for 70 years, the increased probability of getting cancer is not likely to exceed 2.5 chances in 10. This estimate of potency is decreased from the 6.4×10^{-1} per ppm unit risk estimate published in 1985 (*14*).

Exposure Assessment

The third element in a risk assessment is the evaluation of exposure. In this case, the evaluation focuses on exposure of people living near 1,3-butadiene-emitting facilities. Exposure assessment, as was performed for this assessment, requires two steps: *1*) identification and characterization of the sources and their emissions and *2*) use of available data from step 1 in a computerized model of air dispersion. This model produces estimates of 1,3-butadiene concentrations in air and the numbers of people exposed to these estimates of concentration.

The United States production of 1,3-butadiene in 1987 was approximately 3 billion pounds annually (*1*) and substantial amounts are imported. Annual emissions from all industrial 1,3-butadiene sources are estimated to be approximately 12 million pounds per year. These emissions arise primarily from process vents or stacks and fugitive sources (e.g., equipment leaks). Source characterization data has been provided by industry in response to EPA's request for information under the authority of Section 114 of the Clean Air Act. These data and engineering judgment have been used to characterize the sources. Types and amounts of emissions, numbers of stacks, release temperatures, and velocity are parameters that affect the estimates of air dispersion and are inputs to the exposure modeling.

The Human Exposure Model (HEM) was used to estimate exposure to 1,3-butadiene emissions (*27*). The term "exposure" means the sum of the products of the estimated ambient air concentration of 1,3-butadiene and the estimated numbers of people exposed to those concentrations. A Gaussian dispersion model contained within the HEM was employed to estimate ambient concentrations of 1,3-butadiene within a 50-km radius of specific emission sources. Exposure estimates are limited to 50 km because it is felt that the dispersion algorithm is most accurate within this distance. Exposure may occur at distances greater than 50 km, but the half-life of 1,3-butadiene has been estimated to be relatively brief—approximately 4 hr. While the half-life is sufficient to allow for a 50-km dispersion, there is expected to be minimal impact on populations living at greater distances. This is in contrast to pollutants with long half-lives (e.g., carbon tetrachloride, cadmium) where impact on populations beyond 50 km may be substantial.

An additional input to the HEM modeling is a 5-year average of weather from the National Weather Service station closest to each facility. Wind speed, direction, and turbulence are important in the air dispersion modeling. By combining population and estimated ambient air concentrations, the HEM produced estimates of exposure at selected radial distances from each identified source and summed the exposure estimates for each source.

Approximately 52 million people are estimated to live within 50 km of industrial 1,3-butadiene sources. Each plant was modeled without consideration of other plants that may be within the 50-km radius. Modeling each plant separately, as was done here, may somewhat underestimate the intensity of exposure and overestimate the total number of exposed individuals in areas where more than one plant exists.

There are little ambient monitoring data available for 1,3-butadiene. Reported monitoring data range from less than 1 to 10 ppb in urban air (*28,29*). The modeled exposure concentrations appears to be consistent with monitored off-site concentrations. Modeled estimates of fenceline concentrations and occupational monitoring of fenceline concentrations are also similar (*30,31*).

Risk Characterization

By combining the estimates of public exposure to emissions of 1,3-butadiene from point sources with the unit risk for 1,3-butadiene, two types of quantitative estimates of the risk to public health have been produced. The first type of risk estimate, called aggregate cancer incidence, is characterized as the excess number of cancers predicted to occur in the exposed population. This is the summation of all the cancer risks estimated by combining the products of the predicted ambient concentrations of 1,3-butadiene and the estimated number of people exposed to those concentrations. The aggregate incidence is expressed as incidences of cancer among all of the exposed population after 70 years of continuous exposure; for convenience, it is often divided by 70 and expressed as annual cancer incidence.

The second type of risk estimate, called "maximum individual risk," is the estimated upper bound excess cancer risk predicted for the individual(s) exposed continually for 70 years to the highest estimated ambient air concentration.

No more than 8 annual cancer incidences, or no more than 560 cancer incidences per 70 years, nationwide are currently being estimated to result from nonoccupational exposure to concentrations of 1,3-butadiene from industrial emissions. Risk to the most exposed persons

are not expected to be greater than one in ten. These estimates are based on the upper 95% limit unit risk estimate and the results of the HEM exposure modeling analysis. A significant amount of uncertainty exists in the estimates of maximum individual cancer risk and annual cancer incidence. Sources of uncertainty in the risk assessment include species differences in sensitivity to 1,3-butadiene, the adequacy of the source characterization, the dose-response model used to perform low-dose extrapolation and estimate potency, and the air dispersion modeling and exposure. Reducing these uncertainties with better data could either raise or lower the current estimates of risk.

Conclusions

The EPA has concluded that air exposure from industrial emissions of 1,3-butadiene increases the risk of cancer in the exposed population. This is based on the weight of evidence of carcinogenicity, the estimate of cancer potency, the quantity of emissions, the estimated ambient air concentrations, and the proximity of large populations to emitting sources.

The estimate presented in this paper of excess cancer cases resulting from point source exposure to 1,3-butadiene is decreased to approximately 40% of the estimate published in 1985 (*32*), from 6.4 chances in 10 to 2.5 chances in 10 to lifetime exposure to 1 ppm. The current estimate is no more than eight additional annual cancer incidences in the general population. Increased risk to the most exposed individuals is not anticipated to be greater than one in ten. This reduction in the risk estimate is due to a change in the estimate of 1,3-butadiene potency (i.e., unit risk estimate) based on incorporation of new pharmacokinetic data. The emissions estimates, weight of evidence classification, and estimates of cancer potency presented in this paper may change subsequent to the analysis of anticipated new data.

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