# Industry Efforts to Weaken the EPA's Classification of the Carcinogenicity of 1,3-Butadiene

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Industry's success in negotiating away science at the level of governmental regulatory agencies is eroding the integrity of the regulatory process. Maneuvers used by industry to weaken the U.S. Environmental Protection Agency's classification of the carcinogenicity of butadiene are described. *Key words*: butadiene; carcinogenicity classification; government agencies; EPA; IRIS; IARC; industry influence.

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In 1998 the International Agency for Research on Cancer (IARC) re-evaluated 1,3 butadiene, an industrial carcinogen and widespread air pollutant, as a "probable" human carcinogen in a controversial second vote, after voting to classify it as a human carcinogen on the previous day. In late 2002 the U.S. Environmental Protection Agency (EPA) revised its estimate of the cancer-causing potency of 1,3-butadiene to a value eightfold lower (less potent) than the previous determination (1985), and fourfold lower than the value derived from the most recent experimental data (2002). This opened the door to weaker pollution cleanup standards. The available evidence indicates that there were extensive industry efforts to influence the expert scientific committees used in both the EPA and IARC processes to reassess butadiene, and that these efforts may have resulted in a significant weakening of the scientific assessments.

1,3-Butadiene is among the most hazardous air pollutants both because it is widespread and because it has known adverse impacts on human health (for more detail, see the hazard ranking for butadiene on the Web site <www.Scorecard.org>[12]). Butadiene has been shown in laboratory studies to be a multisite carcinogen[1–5] and in occupational studies to be associated with leukemia and non-Hodgkin's lymphoma.[6–8] It is classified as a "known" human carcinogen in the U.S. Department of Health and Human Services 10th Report on Carcinogens (RoC), "based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information, which indicate a causal relationship between occupational exposure to 1,3-butadiene and excess mortality from lymphatic and/or hematopoietic cancers."[9]

Butadiene is produced industrially at approximately 3 billion pounds annually in the United States and 12 billion pounds worldwide.[10] It is used primarily in the production of synthetic rubber and plastics, and is also a byproduct of cigarette smoke and the incomplete combustion of fuels, including gasoline, diesel fuel, and jet fuel. The U.S. EPA Toxics Release Inventory (TRI) reports that 1.9 million pounds (871,000 kg) of 1,3-butadiene were released into the air from industrial sources alone in 2002, the most recent year for which data are available, primarily from the chemical and allied products sector (1.7 million pounds).[11,12] However, industrial sources account for less than 2% of butadiene air emissions, with approximately 78% coming from mobile sources, primarily incomplete combustion of gasoline and diesel engine exhaust. A recent study of children in the United Kingdom reported a significant association between deaths from leukemia prior to age 16 and living near an area of elevated 1,3-butadiene air pollution (RR = 3.81).[13] The magnitudes of human health risks from butadiene are clearly relevant both to human health and to the profitability of numerous powerful sectors, including the oil and synthetic rubber industries.

### *EPA Assessment Based on Occupational Cancer Mortality Studies*

Many of the EPA assessments of regulated chemicals are publicly available on its database, the Integrated Risk Information System (IRIS), which contains EPA's scientific positions on potential human health effects from environmental contaminants. While IRIS data are not enforceable regulatory standards per se, information on IRIS is considered by regulators at the state and federal levels and others worldwide in setting pollution-cleanup standards and various exposure standards for air, water, and soil.[14] The widespread use of IRIS assessments is demonstrated by the fact that the database receives over a half million visits monthly, from well over 50 countries.*[15]

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*For the month April 1, 2005, the IRIS database Web site had an approximate average of 20,000 requests daily, and 612,000 requests for the month. These requests came from over 29,000 distinct electronic hosts, originating from over 100 countries.

EPA completed its review of butadiene for the IRIS database in 2002,[16] classifying it as a human carcinogen based primarily on epidemiologic data, including a study of over 13,000 adult male workers from six rubber-manufacturing plants by Macaluso, Delzell, and colleagues, sponsored by the International Institute of Synthetic Rubber Producers.[6,17] The study concluded that exposure to butadiene in the synthetic rubber industry produced a dose-related increase in deaths from leukemia among workers under age 70. These conclusions are in agreement with a number of other occupational epidemiologic studies available at the time, including a study of a relatively small cohort of butadiene-production workers in a U.S. chemical manufacturing plant with elevated lymphatic and hematopoietic cancer deaths (SMR = 1.8; 95% CI, 0.7–3.6).[18,19]

### *EPA Rejects Outside Peer Review Recommendation to Downgrade Cancer Classification*

One of the final stages in the completion of an EPA risk assessment is peer review. The Scientific Advisory Board (SAB) committee reviewing the 1998 external-review draft butadiene assessment included so many corporate officials and consultants that it became the subject of a Congressional investigation (detailed later in this commentary). The SAB report, issued in November 1998, rejected EPA staff scientists' recommendation to classify butadiene as a human carcinogen, instead recommending the less-protective classification of "probable" human carcinogen, citing the lack of a consistent dose–response relationship for the leukemia and lymphosarcoma cases, and possible confounding from co-exposure to styrene and other factors.[22] The contribution to dosimetry that could have been made from the extensive rodent data was not utilized (the difference in risk estimates derived from animal versus occupation data is discussed in the following section). In its final assessment, EPA retained the more health-protective classification of human carcinogen. However, EPA did accept the SAB recommendation that EPA base its estimate of carcinogenic potency (slope of the dose–response relationship) primarily on exposure estimates derived from the occupational study, despite the acknowledged weaknesses. The authors had acknowledged that the occupational study suffered from a lack of individual exposure data, that "misclassification of exposure levels is likely," and "only limited efforts were feasible to estimate a range of credibility for the exposure estimates."[6] Moreover, because this was a mortality study it may have significantly undercounted incident cases of cancer, as the five-year survival rate for leukemia has reached 44% among the U.S. white population.

### *EPA Recalculates and Reduces Its Estimate of Butadiene Risk*

In its 2001 draft assessment, EPA initially calculated a continuous lifetime risk estimate of 0.03/ppm based on leukemia deaths reported in the occupational study. This value, 30 cancer cases per 1,000 people exposed at a continuous lifetime (70-year) exposure to 1 ppm butadiene, was strongly protested in letters sent to EPA from public health officials representing air quality agencies in the northeastern states,[23] the California EPA,[24] and the Natural Resources Defense Council.[25] Among other concerns, the letters noted that an estimate of the carcinogenic potency of butadiene based solely upon the occupational evidence of a cohort of adult males would not represent the possible differential responses in women and children exposed to butadiene in non-occupational settings. In the final assessment (2002) this value was adjusted to a more potent risk estimate; first to 0.04/ppm to extrapolate from a mortality study to incidence, and then raised twofold to a final value of 0.08/ppm to adjust for animal evidence of a potential risk of breast cancer in women (female rats and mice had significant excess mammary tumors), a risk not captured in the all-male worker study. Unfortunately, no adjustments were made for data showing that butadiene is a more potent carcinogen in the lung in female mice than in male mice.[5] (See Table 1.)

The final EPA 2002 risk estimate of 0.08/ppm predicts an excess of 80 cancer cases per 1,000 people at a continuous lifetime exposure to 1 ppm butadiene. This is about one fourth as potent as the EPA risk estimate that had been based on animal data,[5] 0.3/ppm, which had predicted an excess of 300 cancer cases per 1,000 people at a continuous lifetime exposure to 1 ppm butadiene (EPA, 2002; see Table 1). By evaluating butadiene as a less potent carcinogen, EPA sets the stage for weaker regulatory standards. Were EPA to have followed its Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (issued as a Draft in 2003 and finalized in March 2005), the lifetime estimate of excess cancers would further increase approximately 1.6-fold (from 0.08/ppm to 0.13/ppm) due to the increased susceptibility to cancer when exposures to mutagenic agents occur during early childhood.

### *OSHA's Newest Workplace Exposure Limit is Still Inadequately Protective*

Using the same data available to EPA, in November 1996 the US Occupational Safety and Health Administration (OSHA) reduced the workplace permissible exposure limit from 1,000 ppm to 1 ppm, after overwhelming data had demonstrated that the earlier standard failed to provide adequate protection for workers.[20] Unfortunately, OSHA's own calculations suggest that even the new standard may be inadequately protective, allowing between 1.3 and 8 excess leukemia deaths per 1,000 workers with an occupational lifetime exposure (45 years, five days/week, eight-hours/day time-weighted average) to 1 ppm butadiene (see Table 1).[20] A nested case–control

**TABLE 1—Regulatory Agencies' Assessments of 1,3-Butadiene Carcinogenicity**

| Regulatory Agency | Risk Estimate | Estimated Excess Cancer Cases per 1,000 People/Workers Exposed to 1 ppm 1,3-Butadiene* | Basis |
|---|---|---|---|
| Previous EPA (1985) | 0.64/ppm | 640 cases (continuous lifetime exposure)<br>90 worker cases (occupational lifetime exposure) | NTP I rodent study (male and female mice data) |
| EPA (2002; not used) | 0.3/ppm | 300 cases | NTP II rodent study (all cancer risk; estimate would have been 0.14/ppm for risk based only on female mouse lung) |
| Final EPA (2002) | 0.08/ppm | 80 cases | Delzell et al. occupational study (0.03/ppm leukemia mortality; 0.04/ppm adjusted for incidence; 0.08/ppm adjusted for potential female breast cancer risk) |
| NIOSH | 0.008/ppm | 8 worker deaths | Delzell et al. (leukemia mortality) |
| NIOSH (1993) | | 1–30 worker deaths | NTP II rodent study (male mouse lymphoma risk is lower; female mouse lung risk is upper) |
| Final OSHA (1996) | 0.008/ppm | 1.3–8 worker deaths | NTP II rodent study (1.3 derived from male mouse lymphoma data; 8 derived from female mouse lung data) |

*A total lifetime exposure (EPA) is approximately 70 years, and includes exposure through childhood and into old age. An occupational lifetime exposure (NIOSH; OSHA) is approximately 45 years, assumes exposure is to working-age adults only, and is limited to a 40-hour workweek, 8 hours per day, time weighted average (8-hour TWA).

study of synthetic rubber production workers published the year after the standard was issued reported a significantly elevated risk of leukemia at the allowable standard of 1 ppm (OR = 1.5 at 1 ppm, 95% CI = 1.07–2.10).[7] The OSHA standard is likely to result in a disproportionate and preventable cancer burden among workers, while favoring industry arguments of technological and economic feasibility constraints.

EPA calculations are based on cancer cases, whereas OSHA calculations are based on cancer deaths. Also, EPA calculations are adjusted for a continuous lifetime exposure of 70 years, whereas OSHA calculations are adjusted for an occupational lifetime of 45 years beginning at 20 years of age, five days/week, eight hours daily. It is interesting that OSHA (1996) determined that the risk estimates from epidemiology and animal data were concordant (0.008/ppm; eight excess cancer deaths per 1,000 workers exposed to 1 ppm over an occupational lifetime), whereas EPA calculated an almost fourfold difference between risk estimates derived from the epidemiology (0.08/ppm) and animal (0.3/ppm) data. Using the same data sets, the National Institute for Occupational Safety and Health (NIOSH) calculated excess cancer death risk estimates from the animal data risk estimates (0.001–0.03/ppm) that bracketed the estimates from epidemiology (0.008/ppm) (see Table 1). The discrepancy with the EPA estimates is due in part to different assumptions used by NIOSH and OSHA to extrapolate from animal data to human risk, including body-weight adjustment factors and length of a full mouse lifetime.

### *EPA Outside Peer Review Rife with Conflict*

Committees of nongovernmental scientists that provide peer review for EPA are required by the Federal Advisory Committee Act (FACA) to be both independent and balanced in perspective, and are subject to the criminal financial conflict-of-interest statute and the U.S. Office of Government Ethics regulations. However, in June 2001, the U.S. General Accounting Office (GAO) reported on problems of financial conflicts among members of the Scientific Advisory Board (SAB) that had reviewed butadiene, and gross incompetence at EPA.[26] The GAO report stated, "[T]he staff office would be better able to assess panelists' impartiality and ensure that panels are properly balanced if it had an understanding of the work performed by the panelists for law firms and industry, particularly for chemical companies."[26] The GAO report concluded that EPA did not identify panelists who owned stock in companies that manufactured or distributed butadiene; this information is required for federal conflict-of-interest determinations. Although EPA collected almost no information about contractual work, research funding, or expert services in toxic tort litiga-

tion, the EPA staff director told GAO he believed that when the butadiene SAB was formed, six panelists (40%) reflected an industry perspective, six (40%) reflected a "broad middle" perspective, and three (20%) reflected an environmental perspective.† How the EPA official made this assessment is unclear, as the SAB meeting minutes provided conflict-of-interest disclosure statements for only ten of the 15 panelists; the GAO could not find out why there were no records for five panelists, including the panel chair. One of the panelists listed under the academic/medical category disclosed prior consulting work for the Chemical Industry Institute of Toxicology (CIIT), in addition to work on a study of butadiene funded by the Chemical Manufacturers Association and the International Institute of Synthetic Rubber Producers. GAO's documentation of poor identification of conflicts of interest, inadequate assurance of independence and balance, and very limited public access to information regarding panelists reveals a startling breach of public trust.

### *IARC Evaluation of Butadiene Raises International Backlash*

The 1998 evaluation of butadiene by the International Agency for Research on Cancer (IARC) meeting also raised concern. An article by the former Director of IARC[27] and a letter signed by 29 scientists worldwide, including the chair of the butadiene evaluation group and a former Chief of the IARC chemical evaluation program, [28] documented global concern regarding the butadiene evaluation by IARC. At this meeting, the classification of butadiene by the scientific expert group was the result of a controversial second vote. The group initially had voted 17–13 to classify butadiene as a human carcinogen, but a highly unusual next-day vote resulted in classification of butadiene as a probable human carcinogen by a narrow margin of 15–14. The second vote was highly controversial for a number of reasons: the subgroup of epidemiologists at the IARC meeting had concluded that there was sufficient evidence for butadiene carcinogenicity in humans, but this evaluation was overturned by panelists in the other subgroups; the second vote occurred without any further discussion; one of the scientists who had voted in the majority was not present for the second vote; and scientists present at the meeting noted that observers and committee members allied with the oil and rubber industries were able to persuade, outside the meeting, two others to reverse their votes.[28] The chair of the committee was denied his request that the public record disclose that a substantial portion of the committee, including the majority of epidemiologists, had concluded that there was sufficient epidemiologic evidence to determine that 1,3-butadiene is carcinogenic to humans.

Issues of credibility and transparency during IARC chemical evaluations attracted international attention from scientists, public health professionals, and unions.[29–34] The significance of IARC classifications is tremendous. For example, whether or not a cancer case is compensated as work-related may be influenced by whether or not the exposure was to a chemical listed by IARC as carcinogenic to humans.

### *Integrity of Regulatory Process Is Being Eroded through Negotiating Away Science*

In 2003, the new chief of the IARC chemical evaluation program developed and implemented a rigorous set of disclosure and financial-conflict guidelines to re-establish the program's scientific credibility and transparency.[35] EPA has also taken significant steps towards improving the credibility of its Science Advisory Board in response to criticisms raised in the GAO report. Nonetheless, the broader problem of federal scientific advisory committees suffering a purge of independent public health experts and an influx of industry influence has increased under the Bush Administration.[36–38] In 2004, over 60 prominent scientists, including Nobel laureates, leading medical experts, former federal agency directors, and university chairs and presidents, signed a statement critical of the misuse of science by the Bush administration.‡[39] An editorial in the *Lancet* warned, "Members of expert panels need to be impartial and credible, and free of partisan conflicts of interest, especially in industry links or in right-wing or religious ideology. Any further right-wing incursions on expert panels' membership will cause a terminal decline in public trust in the advice of scientists."[40] An editorial in *Nature* condemned this practice, under the title, "All the President's Yes-men?"[41] In a letter to the *New York Times*, Russell Train, the EPA Administrator to

†EPA's Science Advisory Board at a public meeting held on April 30 and May 1, 1998: Mark J. Utell (Chair), University of Rochester Medical Center; Cynthia Bearer, Case Western Reserve University;. John Doull, University of Kansas Medical Center; David G. Hoel, Medical University of South Carolina; Abby A. Li, Monsanto Company;. Michele Medinsky, Chemical Industry Institute of Toxicology; Lauren Zeise, California Environmental Protection Agency; Dr. Richard Albertini, University of Vermont; Elaine Faustman, University of Washington; Karl Kelsey, Harvard School of Public Health; R. Jeff Lewis, Exxon Biomedical Sciences, Inc.; Judith MacGregor, Toxicology Consulting Services; David Parkinson, Long Island Occupational and Environmental Health Center, Port Jefferson, NY; Roy Short, New York University Medical School; James Swenberg, University of North Carolina; Genevieve Matanoski, The Johns Hopkins University; Ronald Melnick, National Institutes for Environmental Health Sciences. Matanoski and Melnick were non-voting consultants.

‡The Union of Concerned Scientists coordinated a statement signed by over 60 leading scientists Nobel laureates, leading medical experts, former federal agency directors, and university chairs and presidents voicing their concern over the misuse of science by the Bush administration. The statement was publicly released on February 18, 2004.

Presidents Nixon and Ford, wrote, "I can state categorically that there never was such White House intrusion into the business of the E.P.A. during my tenure. . . . But the interest of the American people lies in having full disclosure of the facts, particularly when the issue is one with such potentially enormous damage to the long-term health and economic well-being of all of us."[42]

The evaluation and scientific peer review of butadiene is but one example of lobbying by corporate polluters to weaken government assessments and regulatory standards. As the new Administrator takes charge at EPA, he would do well to learn from the butadiene reassessment by making sure that the science at EPA is unsullied by financial influences that will ultimately undermine both the public health and the public trust. In this endeavor, IARC's new guidelines on disclosure and conflicts of interest[36] may serve as a template for EPA, the National Academies, and other scientific and regulatory agencies that convene expert advisory committees.

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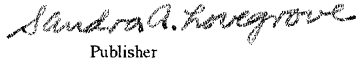

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