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Safeguarding Scientific Evaluations by Governmental Agencies:

Case Study of OSHA and the 1,3-Butadiene Classification

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Using the example of the industry pressures on OSHA that preceded the Agency's downgrading the carcinogenic potential of butadiene from "human carcinogen" to "possibly carcinogenic to humans" in the face of scientific evidence, the author warns of the danger to public health of the infringement on governmental agencies' decision making by special-interest groups. *Key words*: butadiene; carcinogenicity classification; government agencies; OSHA; toxicity classification; industry influence.

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Recent reports have raised concern about the ability of governmental and international agencies to maintain independence from the influence of industry when evaluating data related to the carcinogenic risks of chemicals to humans.[1–3] Tomatis, a former Director of the International Agency for Research on Cancer (IARC), discusses the strong pressure that industry attempts to exert on IARC carcinogeneity evaluations because of the effects of these evaluations can have on their profits.[2]

Huff also has expressed concern about the influence of industry on IARC evaluations in downgrading evidence of carcinogenicity.[1] He specifically cites the decision regarding 1,3-butadiene (butadiene) arrived at during the February 1998 IARC working group meeting as "the prime example of overt industry influence on the IARC Monographs process." He reports that IARC initially voted to list butadiene as a "human carcinogen," but that after one or two working group members left the meeting, the vote was retaken and industry's desired outcome of downgrading the evidence of cancer to "probably carcinogenic" was achieved. He notes that the epidemiology subgroup voted to list butadiene as a "human carcinogen," while the entire working group, influenced by industry and made up of chemists, toxicologists, and in-vitro experts, subsequently voted to downgrade the evidence of cancer in humans.

Sass[3] has raised the same issue about industry influence on cancer evaluations at the U.S. Environmental Protection Agency (EPA). She reports on the unbalanced industry representation on the EPA Scientific Advisory Board (SAB) panel that reviewed the EPA butadiene-risk assessment. This influence led to an unprecedented investigation by the U.S. General Accounting Office (GAO) of EPA procedures in the selection of SAB panel members. The GAO report concluded that EPA needed to improve its policies to balance the composition of EPA SAB panels to ensure independence from outside influences.[4] According to Sass, "The SAB report, issued in November 1998, rejected EPA staff scientists' recommendations to classify butadiene as a human carcinogen, instead recommending the less-protective classification of 'probable human carcinogen.'"[3] Subsequent to the GAO report,[4] the EPA followed staff scientists' opinion and concluded that butadiene was indeed "carcinogenic to humans."[5]

The reports cited above raise very important issues about the independence of government and international organizations in carrying out scientific evaluations. This is not a new problem; however, the magnitude of the current influence of industry and its consultants on governmental deliberations goes well beyond what is healthy for our environment, the general public, and blue-collar workers in particular. The morale of the career civil servants who attempt to function in this political environment is also an important and often overlooked casualty in these situations.

INDUSTRY'S INFLUENCE ON OSHA'S CANCER EVALUATION FOR BUTADIENE

To further illuminate the issue, I review an example of industry influence on the cancer evaluation made by the Occupational Safety and Health Administration

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(OSHA) in the preamble to its Final Standard for Occupational Exposure to 1,3-Butadiene.[6] As part of a negotiation to complete the standard and to avoid a legal challenge by industry as well as delay in the approval of the standard during the Office of Management and Budget (OMB) review process, OSHA changed its interpretation of the evidence related to the carcinogenic effects of butadiene to humans. Specifically, just prior to publication of its final standard, OSHA changed its conclusion that "butadiene causes an increased risk of death from cancers of the lymphohematopoietic system" in humans and instead stated that butadiene was a "probable human carcinogen." This is an important if subtle modification. The classification of a substance as a "known carcinogen" means that there is sufficient evidence to conclude that it causes cancer in people. Classification of a substance as a "probable carcinogen" or a "suspect carcinogen" means that data linking the substance to cancer in humans are weaker and thus subject to more uncertainty and debate.. This changed classification in the preamble to the final standard did not result in any change to the regulatory provisions of the standard. It does, however, raise the issue of governmental responsibility to communicate the full extent of a hazard to workers, to the public, and to employers, who may not have been part of the "negotiated interpretation" of the cancer hazard. The downplaying of the cancer hazard may also unnecessarily impede compensation to workers who develop lymphohematopoietic cancer as a result of butadiene exposure.

DEVELOPMENT OF THE OSHA STANDARD FOR 1,3-BUTADIENE

The OSHA Butadiene Proposal (1990)

In 1990, the Occupational Safety and Health Administration (OSHA) proposed to lower the workplace permissible exposure limit (PEL) for butadiene from a time-weighted average (TWA) of 1,000 ppm to 2 ppm. The proposal also included a short-term exposure limit (STEL) of 10 ppm, to be measured over a 15-minute sampling period. Ancillary provisions related to exposure monitoring, medical surveillance, worker training and education, personal protective equipment, etc., also were included. This proposal was based on evidence that butadiene induced cancer in experimental animals and also was associated with an increased risk of death from cancer of the lymphohematopoietic system, which had been demonstrated in five epidemiologic studies of workers.[7] For its preliminary quantitative cancer risk assessment, OSHA used data from the National Toxicology Program (NTP), namely, the "NTP I" study, as it was referred to by OSHA. This study demonstrated that inhalational exposure of mice to butadiene at levels that were both above and below the OSHA PEL of 1,000 ppm induced cancers of the lung, heart, liver, mammary gland, ovary, and forestomach, as well as lymphomas.[8]

For its "best" estimate of the quantitative cancer risk to humans, OSHA relied on data showing the induction of heart hemangiosarcoma in female mice from the NTP I study. Modeling the dose response from this butadiene-induced tumor site indicated an excess risk of 147 cancer deaths per 1,000 workers exposed over an occupational lifetime to the 1,000 ppm butadiene PEL. Expressed in another way, 14.7% of the workforce exposed to the PEL would be estimated to die from cancer. The excess lifetime occupational cancer risk estimated by OSHA to result from exposure to the "proposed" PEL of 2 ppm was five extra cancer deaths per 1,000 workers.

OSHA considers a risk of one extra cancer death per 1000 workers over an occupational lifetime of 45 years to be a significant risk to worker health.[7] OSHA has not characterized the significance of risk below this level because it has had difficulty in reducing exposures to get below the "significant risk" level due to problems of "economic feasibility" with the health standards it had promulgated since the Supreme Court's decision on benzene.[9] All of the health standards promulgated by OSHA since the 1980 Supreme Court decision on benzene have resulted in significant (one or more per 1,000 workers' occupational lifetime) risks of cancer remaining from exposures to the new permissible levels, even though the risks have been greatly reduced by the promulgation of the new standards.[11]

OSHA held public hearings on the 1990 proposal in January and February 1991. The post-hearing comment period closed in February 1992. Subsequently, the standard lay dormant at OSHA as the Bush and Clinton administrations had little interest in completing the butadiene standard.

Development of the OSHA Final Butadiene Standard (1996)

In light of all of the effort that had gone toward the development of the butadiene proposal, and the recognition that a new standard was needed to protect exposed workers from a significant risk of developing cancer, an OSHA career civil servant raised the possibility of bringing together representatives of the manufacturers and users of butadiene as well as the unions that represented workers involved in its manufacturing in order to determine whether a mutually agreed upon standard could be negotiated. These entities met and produced an outline for a voluntary agreement for provisions of a standard to be included in the OSHA Final Standard. In March 1996, OSHA published the agreement and reopened the butadiene record for 30 days to allow the public to comment on the joint recommendations. The recommendations addressed the PEL and a number of ancillary provisions such as exposure monitoring and goals, medical surveillance, hazard commu-

nication, and respiratory protection. OSHA Health Standards staff was charged with completing the documentation of the health hazards related to butadiene as well as the quantitative risk assessment in order to determine the significance of the risk of exposure to butadiene and the significance of the reduction in risk that could be achieved by the new standard.

The OSHA Office of Regulatory Analysis was responsible for calculating the health benefit, in terms of cancer deaths avoided, to be derived from the new butadiene standard through use of OSHA's preferred quantitative risk-assessment analysis results.

OSHA's Disconnect between Its Evaluation of the Epidemiologic Data and Its Conclusion about Evidence of Causality

OSHA had strong confidence that epidemiologic studies had demonstrated that butadiene caused lymphohematopoietic cancers in workers. To come to this conclusion, it had examined the results of six epidemiologic studies, or groups of studies, of exposed workers. The first of these was a series of studies of workers employed in the styrene–butadiene rubber (SBR) industry, conducted by the University of North Carolina. These studies, not designed to evaluate butadiene per se, demonstrated an elevated risk of lymphohematopoietic malignancies in this industry. The elevated risk for these malignancies, however, could not be linked solely to butadiene, as benzene and other solvents were also present in the workplace.

In the second group of studies, OSHA examined the mortality experience among workers employed in a Texaco butadiene-manufacturing facility located in Texas. Divine updated this study population through 1985 and found a statistically significant excess of mortality from lymphosarcoma and reticulosarcoma combined.[6] The sub-cohort of these workers employed before 1946 (wartime workers) demonstrated a statistically significant excess of death from the same cancers and, according to OSHA, the risk was even higher than that for the total group. OSHA found these findings consistent with those from an earlier study of these workers by Downs. OSHA characterized the findings from this study population as providing several notable results. OSHA determined that the statistically significantly elevated risk of death from lymphosarcoma was consistent with the excess of lymphomas seen in the mouse studies.[6] OSHA also noted that the relative risks for these cancers were the highest in the groups of workers that had experienced the heaviest exposures to butadiene. Finally, OSHA determined that the observation of the significantly elevated rate of malignancy in workers employed for less than ten years was a "notable result."

OSHA also evaluated the National Institute for Occupational Safety and Health (NIOSH) cohort of workers employed at adjacent SBR facilities located in Texas. For plant A, OSHA found that while the overall mortality was significantly decreased, e.g., the standardized mortality ratio, or SMR, was equal to 80, the risks for lymphopoietic cancers (SMR = 155), lymphosarcoma and reticulum-cell sarcoma (SMR = 181), and leukemia (SMR = 203) were all elevated, although none of these results was statistically significant. The subgroup of workers who had begun employment in the war years, however, did demonstrate borderline significantly elevated rates of death for these cancers, e.g., lymphohematopoietic cancer (SMR = 212) and leukemia (SMR = 278). Because the highest rates of mortality for these malignancies occurred among workers whose exposures had begun during World War II, when exposures were thought to have been the highest, OSHA thought these findings were noteworthy. OSHA concluded that the NIOSH study "by itself" did not demonstrate that occupational exposure to butadiene *causes* cancer. It is reasonable to interpret this statement to mean that along with other evidence, this study provided supportive evidence to an overall evaluation that butadiene *does cause* cancer in humans.

The fourth and fifth studies evaluated by OSHA, sponsored by the International Institute of Synthetic Rubber Producers (IISRP), were the cohort study of SBR workers conducted by Matanoski et al., followed to 1982, and the case–control study for lymphohematopoietic cancers nested within this cohort, conducted by Santos-Burgoa and Matanoski. Regarding the cohort study, OSHA agreed with the conclusions of the authors that the risk of death from lymphohematopoietic cancers seemed to be higher in the SBR industry than in the general population and seemed to be associated with three different work areas in the plants. In the nested case–control study, OSHA noted that the odds ratio (OR) for leukemia was 6.8 and statistically significant and was even higher in the matched-pair analysis, OR = 9.35 (95% CI = 1.10–42.23). Butadiene exposure above the group mean also was associated with an OR of 2.30 for all lymphohematopoietic cancers. OSHA entertained several lines of criticism from the IISRP about the study and ultimately rejected them. It is ironic that IISRP sponsored the study, approved the study design and method, and then disagreed with the findings at OSHA hearings.

The sixth epidemiologic study of butadiene-exposed workers evaluated by OSHA was that of Delzell et al.[12] This study, also sponsored by the IISRP, included workers from seven of the eight plants previously studied by Matanoski et al. and the two plants studied previously by NIOSH as mentioned above. According to OSHA, "one of the most important findings of the research of Delzell et al. was strong and consistent evidence that employment in the SBR industry produced an excess of leukemia." OSHA noted that both white and black hourly workers with 10+ years of employment and 20+ years of latency had significantly elevated mortality

ratios for leukemia, SMRs = 192 and 436, respectively. It further stated that the study demonstrated a dose–response relationship between cumulative butadiene exposure and relative risk of leukemia.

In its Summary and Conclusions of the epidemiologic evidence, OSHA listed "seven criteria" that it said could be used to judge the presence of a *causal relationship* between occupational exposure to butadiene and cancer of the lymphohematopoietic system. The "seven criteria" that OSHA listed were taken from a paper by Sir Austin Bradford Hill[13]: temporal relationship; consistency; strength of association; dose–response relationship; specificity of association; biological plausibility; and coherence. (It is important to note that Hill never called them "criteria" but rather referred to them as "things to consider.") In the preamble to the Final Butadiene Standard, OSHA indicated that the epidemiologic, animal, and mechanistic data met all of its "criteria for a causal relationship." The preamble to the OSHA standard clearly shows that the OSHA staff evaluating the data believed that exposure to butadiene in the workplace caused lymphohematopoietic cancer in humans (Table V-4, titled "Evidence That 1,3-Butadiene is a Human Carcinogen"). Yet, in a following section of the preamble on bone-marrow effects, OSHA stated that "epidemiologic studies of the styrene–butadiene rubber (SBR) industry *suggest* that workers exposed to BD are at an increased risk of developing leukemia, or lymphoma, two forms of hematologic malignancy." Finally, in the "Significance of Risk" section, it states "OSHA has concluded that butadiene is a *probable human carcinogen.*"[6] The latter characterization of butadiene's cancer risk to humans misrepresents OSHA's evaluation of the epidemiologic data and is a reflection of a negotiation with the butadiene industry on the final standard.

The Data Relied Upon by OSHA for Its Quantitative Risk Assessment

Between the time of OSHA's proposal in 1990 and March 1996, a second butadiene-inhalation study of cancer in animals was conducted by the NTP,[14,15] and updated results from a number of epidemiologic studies were introduced into the record. In the NTP II study, the animals were exposed to butadiene levels closer to those prevailing in the workplace. The span of exposure levels was 0, 6.25, 20, 62.5, 200 and 625 ppm for six hours/day, five days/week for up to 105 weeks. This study again demonstrated the induction of tumors at essentially the same sites shown in the earlier NTP study, including lung tumors from exposure to 6.25 ppm butadiene—a level 160 times lower than the OSHA exposure limit permitted at the time.

In its Final Butadiene Standard, OSHA set limits of 1 ppm for the eight-hour TWA and 5 ppm for the STEL,[6] along with the ancillary provisions that are usually included in OSHA standards. In the preamble to its final standard, OSHA stated that the estimated cancer risks to workers based on NIOSH analyses of animal cancer data in the NTP II study ranged from 0.9 to 30 excess cancer deaths per 1,000 workers over an occupational lifetime. Risk assessments from other entities also were cited. Based on results from the NTP II study, OSHA also calculated its own cancer risk estimates for butadiene in relation to a PEL of 1 ppm. Based on male mouse data, the excess cancer risks to humans were 1.3 per 1,000 using lymphomas as the cancer effect and 6.4 per 1,000 using the lung cancer response. Based on female mouse data, the estimated excess cancer risks were 6.0 per 1,000 using lymphomas as the cancer effect and 8.1 per 1,000 using lung cancer as the site.

OSHA also evaluated the quantitative risk of cancer to workers exposed to butadiene based on the updated epidemiologic data.[6] For this evaluation, it relied on the risk assessment performed by NIOSH that was based on the cohort study of workers exposed to butadiene in the synthetic rubber industry by Delzell et al., as submitted to the International Institute of Synthetic Rubber Producers on October 2, 1995. Utilizing the relative-risk model that best fit the data reported by Delzell et al.,[12] NIOSH calculated the maximum likelihood estimate (MLE) of risk associated with occupational lifetime exposure to 1 ppm butadiene to be eight extra leukemia deaths per 1,000 workers. OSHA concluded that the risk of leukemia demonstrated by the Delzell et al.[12] study was concordant with the quantitative risk estimates based on the animal cancer studies mentioned above. At this point in its evaluation of occupational cancer risk related to butadiene exposure, OSHA departed from its past policy of relying on epidemiologic data when dose–response information was available from both toxicologic and epidemiologic studies.[16,17] Instead, OSHA relied upon animal cancer data to estimate quantitative cancer risks to workers exposed to butadiene. OSHA's choice of cancer risk from animal studies instead of leukemia risk from epidemiologic studies to express its quantitative risk assessment misinforms workers about the severity of the cancer hazard from exposure to butadiene by understating the risk.

OSHA's Benefits Analysis

In each standard promulgated by OSHA, it is required that the Agency provide an estimate of the benefits of the standard. Since the Supreme Court decision on benzene,[16] when issuing health standards, OSHA has traditionally used its quantitative risk assessments to determine the benefits of the standard. In other words, it estimates the number of lives that might be saved, or illnesses prevented, by any change in practice that would be required by the standard. In its preliminary quantitative risk estimate of cancer deaths related to the proposed 2 ppm TWA for butadiene,[7] OSHA esti-

misleading the public erodes trust in the Agency and government in general.

The Persistent Attempt of Butadiene Industry Representatives to Influence Cancer Evaluations of National and International Governmental Agencies

The involvement of the butadiene industry in the carcinogenicity evaluations of its product by various governmental and international agencies appears to represent a consistent effort to minimize the knowledge of its cancer-causing properties in humans. As mentioned above, IARC also changed its evaluation that butadiene was a "human carcinogen" to one that concluded that butadiene was "probably carcinogenic to humans."[1] This change in evaluation allegedly occurred after overnight lobbying by industry and IARC staff.[1] Thus, the industry was successful in influencing both IARC and OSHA.

The butadiene industry's efforts to minimize knowledge of the carcinogenic potential of butadiene failed to change the views of either the EPA or the NTP. The EPA Butadiene Scientific Advisory Board panel, with much industry representation, rejected EPA staff scientists' conclusion that butadiene is a human carcinogen and instead recommended a weaker cancer classification.[3] The selection process for the EPA Butadiene SAB panel, however, was criticized by the GAO as needing to be changed to achieve balance in the composition of members, in order to ensure independence from outside influences. In the end, EPA maintained its "carcinogenic to humans" classification for butadiene.

In 1997, the NTP, through the Federal Register, solicited public input into its cancer classification for butadiene as a substance "known to be a human carcinogen." Subsequently, the NTP evaluated all comments and concluded that butadiene was a human carcinogen. This evaluation included a final review by the NTP Board of Scientific Counselors, a non-governmental scientific review body. In May 1998, the Chemical Manufacturers Association (CMA) wrote to the Director of the NTP in response to its final notice about its cancer classification of butadiene. The CMA, representing the major domestic producers, users, and importers of butadiene, requested that the NTP not list butadiene as a "known carcinogen." The CMA supported its position in part by citing the IARC's February 1998 butadiene evaluation and the EPA SAB panel's butadiene evaluation mentioned above.[24] The NTP rejected the CMA arguments.

While it is beneficial for science to have critical review of scientific study results, it is not beneficial to public health to have industries and their consultants apply political pressure on national and international governmental agencies in order to downgrade evidence of cancer risks during reviews of scientific evidence related to the toxicity of the chemicals that they manufacture and sell.

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