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July 1, 2004

Via mail and e-mail <jameson@niehs.nih.gov

Dr. C. W. Jameson
Report on Carcinogens
National Toxicology Program
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Via mail

Mr. John T. Burklow
Associate Director for Communications
Office of the Director
National Institutes of Health
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9000 Rockville Pike
Bethesda, MD 20892

Re: Report on Carcinogens/Vinyl Chloride/
Information Quality Act Request for Correction

Dear Dr. Jameson and Mr. Burklow:

The National Toxicology Program (NTP) recently asked for public comment on 21 substances or groups of substances being considered for possible listing in the Report on Carcinogens (RoC), Twelfth Edition. 69 Fed. Reg. 28940 (May 19, 2004). One of these is "vinyl mono-halides as a class," including vinyl chloride. Vinyl chloride is listed in the Tenth and previous editions of the RoC as a "known human carcinogen."

The Vinyl Chloride Health Committee (VCHC) of the American Chemistry Council represents the U.S. manufacturers of vinyl chloride.¹ The VCHC writes to call to your attention inaccurate statements being disseminated by NTP and the National Institute for

¹ Members of the Health Committee include The Dow Chemical Company, Formosa Plastics Corporation, U.S.A., Georgia Gulf Corporation, Oxy Vinyls, LP, PPG Industries, Inc., and PolyOne Corporation.



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Environmental Health and Safety (NIEHS) in the Tenth and previous RoC editions. In connection with the request for comments on the 12th RoC, and pursuant to the Information Quality Act (IQA), the VCHC hereby requests that these inaccurate statements be corrected in the 11th, 12th, and future editions of the RoC.²

The entry for vinyl chloride in the 10th RoC states:

Carcinogenicity

Vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC, 1987). Vinyl chloride has been associated with tumors of the liver, brain, lung, and hematolymphopoietic system. A large number of epidemiological studies and case reports have substantiated the causal association between vinyl chloride and angiosarcoma of the liver. Several studies also confirm that exposure to vinyl chloride causes other forms of cancer, i.e., hepatocellular carcinoma, brain tumors, lung tumors, and malignancies of the lymphatic and hematopoietic system. Exposure to poly(vinyl chloride) dust was associated with an increased incidence of lung tumors in one study; the authors suggested that trapped vinyl chloride monomer was responsible. Melanoma occurred in excess in one study but it has not been mentioned in others. Slightly elevated risks for gastric and gastrointestinal cancer (other than liver cancer) were indicated in some studies, but these were not confirmed in others.

Vinyl chloride was listed in the First RoC as a *known human carcinogen* based on epidemiological evidence showing a clear association between historical high workplace exposure to vinyl chloride and angiosarcoma of the liver. Recently published updates of the large epidemiological data base in North America and Europe confirm this association. Those reports, however, do not provide support for, much less "confirm," that "exposure to vinyl chloride causes . . . hepatocellular carcinoma, brain tumors, lung tumors, and malignancies of the lymphatic and hematopoietic system." Recent reviews of the epidemiological data base and studies of the U.S. facility that had reported a significant increased incidence in brain cancers support the conclusion that vinyl chloride exposure is not causally associated with brain cancer or the other tumors mentioned in the quoted passage from the RoC, other than liver tumors. The erroneous statement in the 10th RoC is also inconsistent with the Toxicological Review of Vinyl Chloride currently available on EPA's Integrated Risk Information System (IRIS). <http://www.epa.gov/iris/subst/1001.htm>.

² The 11th RoC has not been published and its text is not available. The VCHC specifically requests NTP/NIEHS to make the requested revisions prior to publication as part of the IQA predissemination review process for the Eleventh Edition of the RoC.

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The current evidence on vinyl chloride and cancers other than liver is discussed below. The VCHC requests that the statement quoted above be revised to read in the 11th and future editions of the RoC as follows:

Vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC, 1987). Vinyl chloride has been associated with tumors of the liver, brain, lung, and hematolymphopoietic system. A and a large number of epidemiological studies and case reports have substantiated the causal association between vinyl chloride and angiosarcoma of the liver. Several studies also confirm that exposure to vinyl chloride causes other forms of cancer, i.e., hepatocellular carcinoma, brain tumors, lung tumors, and malignancies of the lymphatic and hematopoietic system. Exposure to poly(vinyl chloride) dust was associated with an increased incidence of lung tumors in one study; the authors suggested that trapped vinyl chloride monomer was responsible. Melanoma occurred in excess in one study but has not been mentioned in others. Slightly elevated risks for gastric and gastrointestinal cancer (other than liver cancer) were indicated in some studies, but these were not confirmed in others.

Review of Scientific Evidence

Virtually every scientific analysis published in the past fifteen years has concluded that there is not a strong association between vinyl chloride and any form of cancer other than liver cancer. These include a recent review by Aaron Blair, Chief of the Occupational Studies Section of the National Cancer Institute, which states that epidemiological evidence shows a strong exposure-response relationship for angiosarcoma of the liver, but not for other types of cancer.³ Thus, Blair reached the same results that Sir Richard Doll had published ten years earlier.⁴ A more recently published review reaches the same conclusion: "Occupational vinyl chloride exposure has not been conclusively causally linked to any adverse health outcome, with the exception of angiosarcoma of the liver."⁵

³ Blair A and Kazerouni N. Reactive Chemicals and Cancer. *Cancer Causes and Control* 1997; 8:473-90.

⁴ Doll R. Effects of exposure to vinyl chloride: an assessment of the evidence. *Scand J Work Environ Health* 1988; 14:61-78.

⁵ McLaughlin JK and Lipworth L. A critical review of the epidemiologic literature on health effects of occupational exposure to vinyl chloride. *J Epidemiol Biostat* 1999; 4:253-75.

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Recently published updates of cancer incidence in American and European industry-wide cohorts of workers exposed to vinyl chloride further support the conclusion that vinyl chloride exposure is not causally associated with brain cancer or the other tumors mentioned in the quoted passage from the 10th RoC. The European study was conducted by scientists affiliated with the National Institute of Occupational Safety and Health (NIOSH) and the International Agency for Research on Cancer of the World Health Organization. It found no evidence of an increase in cancers other than angiosarcoma of the liver.⁶ Specifically, with regard to brain cancer, which “was of a *priori* interest on the basis of findings in some prior studies,” “[e]vidence for an association of brain cancer with VC [vinyl chloride] exposure in the current study was generally negative.”

An update of the American cohort has also been published.⁷ This study had identified an excess of mortality from brain cancer, but noted “the size of that excess has decreased with time . . . substantially during the most recent follow-up period,” and that “no firm conclusion may be made about an association with vinyl chloride.”

Other researchers have concluded that the brain cancer excesses reported in U.S. vinyl chloride studies were related to a cluster at a single facility. This facility, in Louisville, Kentucky, has been the subject of a number of investigations, most notably by NIOSH scientists who concluded that the excess brain cancers observed at the facility were not related to vinyl chloride exposure.⁸ Most recently, researchers studying this facility concluded:

This study confirms that workers from the Louisville plant have experienced excess mortality from brain cancer, particularly those hired prior to 1950. Although the relationship between VC [vinyl chloride] exposure and liver cancer, primarily angiosarcoma, is clear, the same cannot be said for brain cancer. This same Louisville brain cancer cluster has been repeatedly identified in multiple studies of the VC industry, potentially suggesting an exposure disease relationship. Based on

⁶ Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, *et al.* Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. *Epidemiology* 2001; 12:710-8.

⁷ Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of 10109 men in the North American vinyl chloride industry, 1942-72; update of cancer mortality to 31 December 1995. *Occup Environ Med* 2000; 57:774-81.

⁸ Wu W, Steenland K, Brown D, Wells V, Jones J, Schulte P, *et al.* Cohort and case-control analyses of workers exposed to vinyl chloride: an update. *J Occup Med* 1989; 31:518-23.

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the current findings in the review of the literature, there is little evidence that VC exposure causes brain cancer.⁹

The foregoing discussion applies equally to cancers of the lung and hematolymphopoietic system. Epidemiologic evidence for these associations is even weaker than that supporting an association between vinyl chloride and brain cancer. Indeed, a meta-analysis published by the authors of the most recent updates of the European and American cohorts indicates that the only causes of death in the two "multicenter" studies which had standardized mortality ratios (SMRs) greater than 2 and 95% confidence intervals (CIs) that did not span unity were liver and soft-tissue cancers. All others, including brain, lung, and lymphatic/hematopoietic system, were not consistent with a causal relationship.¹⁰

On the basis of the strength of the human evidence, the EPA Toxicological Review of Vinyl Chloride available on IRIS states the following conclusion:

Blair and Kazerouni (1997) indicated that the data in humans suggested VC is not likely to be associated with cancers other than the liver. Further attempts to estimate cancer risk based upon tumor induction in animal bioassays at other sites, such as mammary glands, resulted in much greater uncertainty because responses were quite variable and not always statistically significant, and because the magnitude of the cancer risk estimated was, with few exceptions, considerably less than the risk of liver tumors. Finally, although cancer incidence was reported to be significantly increased at two other sites in a recent epidemiology study (CMA, 1998a), the association is weak and any estimated increase in mortality from cancer at these sites is likely to be less than for liver cancer.

Information Quality Act Requirements

The IQA was enacted in December 2001 as a rider to the Treasury and General Government Appropriations Act for Fiscal Year 2001. P.L. No. 106-554, § 515; USCCAN (114 Stat. 2763) 29. See 44 U.S.C. § 3516 note.

⁹ Lewis R, Rempala G, Dell LD, Mundt, KA. Vinyl chloride and liver and brain cancer at a polymer production plant in Louisville, Kentucky. *J Occup Environ Med* 2003; 45 (5): 533-37.

¹⁰ Boffetta P, Matisane MD, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. *Scan J Work Environ Health* 2003; 29(3): 220-29.

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The Office of Management and Budget (OMB) issued guidelines for federal agencies under the IQA in January 2002. 67 Fed. Reg. 369 (Jan. 3, 2002) (OMB Guidelines). The OMB Guidelines direct all affected agencies to “adopt a basic standard of [information] quality (including objectivity, utility, and integrity).” *Id.* at 376. “Objectivity” means “accurate, reliable and unbiased information.” *Id.* at 377. For scientific information, “the original and supporting data shall be generated, and the analytic results shall be developed, using sound statistical and research methods.” *Id.* Data and analytical results that have been subjected to formal independent peer review are presumed to be “of acceptable objectivity,” though this presumption is rebuttable. *Id.* Any agency that disseminates “influential scientific information” must provide in its guidelines for “a high degree of transparency about data and methods to facilitate the reproducibility of such information by qualified third parties.” *Id.* And, any agency that disseminates “influential scientific information” in the form of an “analysis of risks to human health, safety and the environment” must “adopt or adapt the principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996.” *Id.*

The National Institutes of Health have adopted IQA guidelines that apply generally to information disseminated by the Institutes and specifically to “guidelines or authoritative health information,” of which a “prime example” is “the Report on Carcinogens prepared by the National Toxicology Program of the National Institutes of Environmental Health Sciences.” <http://www.hhs.gov/infoquality/NIHinfo2.htm>, at 7 (NIH Guidelines). The NIH Guidelines require that such information be “objective,” *i.e.*, “accurate, reliable, and unbiased.” *Id.* at 2. They also establish a predissemination review process, as well as procedures for the public to request correction of information disseminated. *Id.* at 17-21.

The continued publication of erroneous statements concerning the carcinogenicity of vinyl chloride can have serious consequences for the manufacturers and users of vinyl chloride. NTP considers the RoC to be an “authoritative” source of information to support regulatory decisions, including the determination of health risks. Moreover, the RoC has been used by private parties in litigation as evidence of health risks.

The current description of the carcinogenicity of vinyl chloride is not “objective,” as defined in the OMB and NIH Guidelines. Specifically, it is not “accurate, reliable, and unbiased.” As discussed in the “Review of Scientific Evidence” section above, the association claimed in the RoC between vinyl chloride and various human cancers other than angiosarcoma of the liver is inconsistent with the published reviews and studies.

The description of vinyl chloride in the RoC is "influential," as defined in the OMB and NIH Guidelines, because it is intended to and does have a significant impact on both public policy and private sector decisions. For example, the information is used to establish regulatory requirements, to develop human health risk assessments, and to set environmental cleanup standards. It is also used by private sector firms who may decide that it supports product deselection. These are impacts with huge financial implications for public and private resources.

Finally, the OMB Guidelines require that influential information concerning an analysis of risks to human health, safety, or the environment must meet the standard for risk assessments adopted by Congress in the Safe Drinking Water Act (SDWA) Amendments of 1996.¹¹ These SDWA quality principles clearly are not met by a description that is

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- ¹¹ A. The substance of the information is accurate, reliable, and unbiased. This involves the use of:
- i. The best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and
 - ii. Data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).
- B. The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, is comprehensive, informative, and understandable. In a document made available to the public, the OMB Guidelines specify:
- i. Each population addressed by any estimate of applicable human health risk or each risk assessment endpoint, including populations if applicable, addressed by any estimate of applicable ecological risk;
 - ii. The expected risk or central estimate of human health risk for the specific populations affected or the ecological assessment endpoints, including populations if applicable;
 - iii. Each appropriate upper-bound or lower-bound estimate of risk;
 - iv. Each significant uncertainty identified in the process of the assessment of risk and studies that would assist in resolving the uncertainty; and
 - v. Peer-reviewed studies known to the agency head that support, are directly relevant to, or fail to support any estimate of risk and the methodology used to reconcile inconsistencies in the scientific data.

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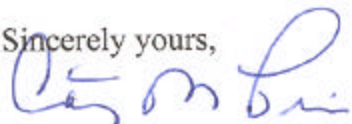
inconsistent with reviews and assessments published in the scientific literature or adopted by other government agencies after more recent review of the scientific data base.¹²

Conclusion

Preparation of the 12th RoC provides an opportunity for NTP to review the issues raised in this comment and make the corrections needed. Because the 11th RoC has not yet been published, and given the long lapse between publication of the 11th and 12th RoC, NTP must also make the corrections requested as part of its predissemination review process for the 11th RoC.

Please contact Elizabeth Festa Watson (703-741-5629), the VCHC Manager, if we can provide additional information in support of this comment/request for correction.

Sincerely yours,



Courtney M. Price
Vice President, CHEMSTAR

¹² Curiously, the NIH Guidelines do not appear to include any requirements based on the SDWA quality principles. With regard to the RoC, the NIH Guidelines take the position that "the RoC does not present assessments of carcinogenic risks." *Id.* at 16. The VCHC believes that NIH is required to adapt the SDWA quality principles in its IQA guidelines. Resolution of that issue is not necessary to grant the relief requested, however, since the 10th RoC's characterization of vinyl chloride does not meet even the basic standard of quality required under the IQA.