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July 19, 2004

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Dr. C.W. Jameson
National Toxicology Program
Report of Carcinogens
79 Alexander Drive
Building 4401
P.O. Box 12233
Research Triangle Park, NC 27709

RE: National Toxicology Program; Call for Public Comments on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Twelfth Edition. 69 FR 28940; 5/19/2004.

Dear Dr. Jameson:

I am writing on behalf of CropLife America in response to the subject *Federal Register* (FR) notice. I comment specifically on the nomination for the listing of atrazine in the National Toxicology Program's (NTP) *Report on Carcinogens* (RoC). CropLife America questions the process and resources being utilized by the National Institute of Environmental Health Sciences (NIEHS) since atrazine has been thoroughly reviewed over the past 10 years by the EPA and has been found "Not Likely to be Carcinogenic to Humans."

CropLife America is the national trade association representing the developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. As a matter of policy CropLife America does not comment on individual products marketed by our member companies. However, CropLife America believes that the decision-making process in nominating atrazine for the RoC is flawed, and wants to make certain that such a process does not become the precedent for inappropriate handling of other compounds in the future.

The nomination of atrazine to the RoC fails to meet the legal requirements of the Public Health Service Act §301(b)(4), and clearly falls outside the listing criteria published by the NTP (<http://ntp-server.niehs.nih.gov/NewHomeRoc/ListingCriteria.html>).

The NIEHS should have considered the IARC findings in their entirety before nominating atrazine for listing in the RoC. The NIEHS nomination is inadequate.

According to this FR notice, NIEHS nominated atrazine citing the 1999 IARC monograph as the sole basis. The nomination cites an "IARC finding of sufficient evidence of carcinogenicity in animals (Vol. 73, 1999)", but NIEHS conspicuously fails to note that the preceding sentence in the IARC monograph stated, "[t]here is *inadequate evidence* in humans for the carcinogenicity of atrazine." Although IARC's Overall Evaluation was clearly explained on the same page of the IARC monograph, NIEHS failed to cite it. IARC explained that there was "strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumors in Sprague-Dawley rats is not relevant to humans." IARC concluded that "Atrazine is *not classifiable as to its carcinogenicity to humans (Group 3)*." For the RoC process, NIEHS should have discussed openly the IARC monograph conclusions on the relevance of the animal data. The IARC Overall Evaluation addresses the full weight of the scientific evidence, but the NIEHS nomination does not. NTP should ensure that the "Background Document" that will be submitted to the NIEHS/NTP RoC Committee (RG1) considers carefully in full the IARC monograph that reviewed atrazine (Vol. 73, 1999) and the supporting references. I believe the weight of the evidence clearly shows that atrazine does not meet the NTP criteria for listing in the RoC.

NIEHS should also have cited other public scientific deliberations on atrazine's potential carcinogenicity. Particularly, NIEHS should have considered the careful deliberations already undertaken by the U.S. Environmental Protection Agency (EPA), before nominating atrazine for listing in the RoC.

The RG1 "Background Document" needs to include the conclusions of the EPA Atrazine Interim Reregistration Eligibility Decision (IRED) review (published January 31, 2003, revised October 31, 2003; <http://www.epa.gov/pesticides/reregistration/atrazine/>); reviews of atrazine by EPA's FIFRA Scientific Advisory Panel (SAP) (June 27, 2000; <http://www.epa.gov/oscpmont/sap/2000/index.htm#062700> and July 17, 2003; <http://www.epa.gov/oscpmont/sap/2003/index.htm#071703>); and the substantial literature supporting each of these deliberative documents. Considerable effort went into the EPA decisions on the cancer classification of atrazine.

Human studies and extensive mechanistic animal studies have explained clearly why the Sprague-Dawley rat mammary tumor findings are not relevant to human risk assessment. The animal studies show that mammary tumors occurred in the Sprague-Dawley rat exposed to atrazine, but not in the Fischer 344 rat or CD-1 mouse. Only in the Sprague-Dawley rat was the neuroendocrine system shown to respond to atrazine in a manner that led to accelerated reproductive senescence and mammary tumor development. Atrazine is neither genotoxic nor inherently estrogenic. There is strong evidence that this mechanism for mammary tumorigenesis in Sprague-Dawley rats is not relevant to humans. The studies supporting these conclusions should also be included in the NTP search of the peer-reviewed published literature for the RG1 Background Document.



In fact, in the October 2003 IRED revision EPA states:

“Even though the epidemiological evidence and animal data, when viewed separately, do not support a positive cancer finding for atrazine, EPA examined the totality of animal and human data to determine if that approach showed that atrazine was likely to cause a carcinogenic response in humans. Specifically, EPA reviewed the available animal data to determine if a mechanism could be identified which supports the biological plausibility of atrazine as a human carcinogen taking into account the tumors that were identified in the epidemiological data. This review showed that (1) lymphomas, including NHL, were generally not seen in atrazine animal bioassays; (2) a mechanistic role for atrazine contributing to NHL has not been identified in laboratory studies; (3) tumors at any endocrine site other than mammary gland tumors in female SD rats (e.g. prostate, ovarian tumors) have not been identified in atrazine bioassays; (4) the SAP concluded in 2000 that the mammary gland tumors in rats caused by atrazine are produced via a mechanism not relevant to humans; and (5) the endocrine tumors that have been raised in epidemiological studies (other than mammary gland tumors) cannot be biologically tied to atrazine’s mode of action (i.e., decrease prolactin, decrease luteinizing hormone (LH) and suppression of ovulation). Thus, at this time, joint consideration of the available animal cancer and mode of action data and epidemiological studies, does not indicate that atrazine is likely to cause cancer in humans.”

EPA’s conclusions should be incorporated into the NTP Background Document as reason to discontinue review of this chemical.

This nomination of atrazine was inadequate, highly selective, and inappropriate as submitted. The nomination relied on a single sentence taken out of context and therefore inconsistent with the Overall Evaluation in a carefully constructed IARC document. The nomination ignored the balance of the IARC review as well as extensive EPA review activities that reached the same conclusion. The nomination should be rejected upon further review. This review process should not proceed beyond the internal RG1 committee review because the evidence is clear and consistent that atrazine does not pose a cancer risk to humans and should not be listed as either a “known human carcinogen” or a “reasonably anticipated human carcinogen.”

When scientific judgment is used and all relevant information is considered, atrazine clearly fits in the circumstances where, although there is evidence of activity in one animal model of tumorigenicity, there are “compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.” (see p.2, <http://ntp-server.niehs.nih.gov/NewHomeRoc/ListingCriteria.html>). The nomination of atrazine for the RoC should be rejected under the existing procedures and criteria.



Dr. C.W. Jameson
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Sincerely,

[Redacted]

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Senior Vice President
Applied Toxicology & Risk Sciences
THE WEINBERG GROUP INC.

cc: Kenneth Olden, Ph.D., Director, NIEHS
Stephen L. Johnson, Deputy Administrator, EPA
Adam Sharp, Associate Assistant Administrator, OPPTS/EPA
Jay Vroom, President, CropLife America

