



Agency for Toxic Substances
and Disease Registry
Atlanta, GA 30333

SEP 12 2006

Mr. Scott Slaughter
11 Dupont Circle, NW, Suite 700
Washington, D.C. 20036

Dear Mr. Slaughter:

Below is a response to the issues you raised on behalf of the Kansas Corn Growers Association, the Triazine Network, and the Center for Regulatory Effectiveness ("Petitioners") in your Request for Correction ("RFC") filed under the Information Quality Act ("IQA") and under the applicable IQA Guidelines on December 5, 2005.

Part I – Response to Written Request for Correction:

Petitioner's Request:

The petitioners request correction of the following information disseminated by the Agency for Toxic Substances and Disease Registry (ATSDR):

Guidance Manual for the Assessment of Joint Toxic Action of chemical Mixtures, US Dept. Of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Division of Toxicology (May 2004) ("Mixtures Guidance").

Petitioner Comment 1:

The request for correction states that "ATSDR uses the Mixtures Guidance for various regulatory purposes, including the development and dissemination of profiles of human health hazards from various chemical mixtures. According to ATSDR, the Mixtures Guidance and Profiles based on it will be used in regulatory action required by the Comprehensive Environmental Response Compensation and Liability Act, and by the Food Quality Protection Act."

ATSDR Response:

ATSDR is not a regulatory agency and no statements were made in ATSDR's documents [i.e., in the *Guidance for the Assessment of Joint Toxic Action of Chemical Mixtures* (hereafter referred to as the Mixtures Guidance Manual) or in the interaction profiles] indicating that the conclusions/recommendations made, would be used for regulatory purposes. The assessment of joint action of chemical mixtures provides guidance to ATSDR health assessors who are

reviewing chemical contaminant levels in air, water, food, or soil. The qualitative guidance informs health assessors to adjust screening levels for contaminants if they occur in combination.

ATSDR was established by the Comprehensive Environmental Response Compensation and Liability Act of 1980 (CERCLA) (42 USC 9604(i)). ATSDR is directed in various provisions of CERCLA to evaluate the potential health effects of exposure to multiple hazardous substances commonly found in combination at hazardous sites. Following the last set of public comments on interaction profiles, ATSDR no longer cites the Food Quality Protection Act (FQPA) as a mandate for its mixtures activities because FQPA is not the authorizing statute for ATSDR.

Petitioner Comment 2:

ATSDR states in its IQA Guidelines that the Agency “provides assurance that information [ATSDR disseminates] is accurate, reliable, and unbiased.” ATSDR cannot assure that Profiles based on the Interaction-based HI are “accurate, reliable, and unbiased.” (Cited as CDC/ATSDR Guidelines, Part II, V.A. in a footnote).

ATSDR Response:

It is ATSDR’s highest priority to provide the public with quality information that is consistent with Office of Management and Budget (OMB), Department of Health and Human Services (HHS), and Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (CDC/ATSDR) guidelines for ensuring quality, objectivity, utility, and integrity of information disseminated by Federal agencies. OMB, HHS, and CDC/ATSDR define quality as being composed of utility, objectivity, and integrity. Outlined below are the measures undertaken by ATSDR to ensure each of the criteria which collectively constitute quality:

- Utility – utility is defined by the OMB, HHS, and CDC/ATSDR guidelines as usefulness of the information for the intended audience. Federal agencies should consider the uses of the information from the perspective of the public.

ATSDR’s Mixtures Guidance Manual presents a practical screening approach to assess potential health hazards from chemical mixtures. It is based upon and integrates ATSDR interaction profiles, toxicological profiles, and research on chemical mixtures, along with site-specific exposure information. The Mixtures Guidance Manual presents a scientifically rigorous screening methodology to assess the joint toxic action of chemicals within mixtures.

The intended users of the Mixtures Guidance Manual are presented in the first paragraph of the executive summary: “The *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures* (Mixtures Guidance Manual) is intended to assist environmental health scientists and toxicologists of ATSDR’s Division of Toxicology and Environmental Medicine in determining whether exposure to chemical mixtures at hazardous waste sites may impact public health. It serves a basis for interaction profiles, as the basis for health assessments and health consultations.” Further, it is stated that “[t]his guidance is designed to be used in conjunction with the ATSDR Public Health Assessment Guidance Manual, which provides the primary guidance for public health

assessment.” The information is of utility for the health assessors and the methodology has been successfully used on multiple occasions (e.g., Toms River, Tar Creek, VBI 70, IBM Endicott, and Conrail).

In summary, the intended audience of the Mixtures Guidance Manual is clearly stated and the Mixtures Guidance Manual is used by the intended audience.

- Objectivity - according to the HHS, and CDC/ATSDR guidelines, objectivity consists of two elements: 1) “Whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner. This involves whether the information is presented within a proper context” (the agency may need to disseminate supporting information to ensure an accurate, clear, complete, and unbiased presentation). Identification of sources of disseminated information is needed. Data should have a full, accurate, transparent documentation, and error sources affecting data quality should be identified and disclosed to users. 2) Whether there is “a focus on ensuring accurate, reliable, and unbiased information” (use of sound research methods).

The OMB Bulletin also states: “If data and analytic results have been subjected to formal, independent, external peer review the information may generally be presumed to be of acceptable objectivity.” Similarly, the CDC/ATSDR Guidelines confirms: “Objectivity is achieved through existing review and clearance procedures and, in many cases, the peer review of disseminated information.”

The Mixtures Guidance Manual was subjected to extensive internal review and clearance and to external peer-review. This included an expert peer-review panel that met on May 30-31, 2000 to evaluate ATSDR’s approach described in the Mixtures Guidance Manual. The panel consisted of experts in the field of chemical mixtures with representatives from the governmental agencies both domestic (e.g., US EPA, CDC, NIEHS, Pacific Northwest National Laboratory) and foreign (Health Council of the Netherlands), academic institutions from the USA (e.g., Colorado State University, University of Louisiana) and from other countries (e.g., University of Montreal, Charles University of Prague), and from the industry (e.g., The Netherlands Organization for Scientific Research (TNO), Statoil Research Center of Norway, Burdock and Associates, Inc). The BINWOE method was specifically reviewed by the peer-reviewers. A list of the peer reviewers and their comments is available from ATSDR upon request.

Further, to ensure the transparency and objectivity of its action, ATSDR made all the interaction profiles and the Mixtures Guidance Manual available for public comment. A summary of the public comments and ATSDR’s response is available upon request. The availability of the Mixtures Guidance Manual was announced in the Federal Register on May 24, 2002. Following close cooperation with EPA, NIEHS, and NIOSH, the Mixtures Guidance Manual was finalized and released to public in 2004. The Mixtures Guidance Manual was also endorsed by the Health Council of the Netherlands (2002).

In regards to reliability, the Mixtures Guidance Manual is consistent with contemporary science. It is based upon the principal of replication of results thus generating increased confidence in conclusions. Consistent with the application of the scientific method, as new insights emerge that merit inclusion in any of the ATSDR documentation, they will be incorporated as required by CERCLA section 104 (i).

- Integrity – Integrity is defined as the “protection of information from unauthorized access or revision, to ensure that the information is not compromised through corruption or falsifications.”

Some of the controls used at CDC/ATSDR include access control, user authentication, encryption, access monitoring, provision of unalterable electronic content, and audit trails. ATSDR takes precaution that the information in the documents disseminated on CD-ROM or on the ATSDR’s web site cannot be tampered with.

Petitioner Comment 3:

The request for correction states that the Mixtures Guidance Manual violates the IQA’s Utility and Objectivity Standards by its recommendation to use of the Hazard Index or Risk Quotient Method (“HI”), as modified by a Binary Weight of the Evidence (“BINWOE”) analysis to include pairwise interactions (“Interaction-based HI Formula”).”

ATSDR Response:

As stated in the response to comment 2, ATSDR toxicological profiles and interaction profiles undergo agency-wide review and independent external peer-review. The BINWOE methodology itself was peer-reviewed and endorsed by independent reviewers. All information in the BINWOEs themselves is based upon peer-reviewed scientific literature and identification of sources of disseminated information is provided in the interaction profiles’ reference list. Possible sources of error affecting data quality are identified in the justification of the BINWOE evaluation and disclosed to users. The quality of data is reflected by the classifications of the mechanistic understanding and toxicological significance. The BINWOE determinations include evaluation of peer-reviewed information regarding toxicity and target organs, pharmacokinetics, and mechanism of action of the individual chemicals; interaction data on each chemical pair; and interactions and mechanistic data on related chemicals. Further, ATSDR expresses the confidence in the derived BINWOEs as high, medium, or low to ensure correct interpretation of the results. All BINWOEs derived in interactions profile are reviewed by the ATSDR workgroup which consists of representatives from different ATSDR’s divisions and of an EPA representative. Further, the BINWOEs are externally peer-reviewed together with the entire document. These measures ensure utility and objectivity of these documents.

ATSDR uses the BINWOE modified HI to further characterize interactions and to categorize the technical information on mixtures at the sites as additive (i.e., $1+1 = 2$), greater-than-additive (e.g., $1 + 1 = 3$), and lower-than-additive (e.g., $1 + 1 = 0.5$). This is stated explicitly in the ATSDR’s “guidance manual” (page 17).

In addition, it should be noted that the term “Risk Quotient Method” used by the petitioner is not

used by ATSDR nor is it used in broader scientific community.

Petitioner Comment 4:

The request for correction states that “The Interaction-based HI Formula has never been validated (e.g., it has never been demonstrated to be accurate, reliable, and unbiased by comparison of Formula-predicted data with observed data).”

ATSDR Response:

The BINWOE approach for two mixtures has been validated in animal experiments (Mumtaz et al. 1998). The authors concluded that the BINWOE approach can be used to estimate qualitatively the joint toxicity of simple mixtures. Further, the study clearly demonstrated that for the toxicants with similar mechanism of action, in particular, the BINWOE approach correctly adjusted for the observed interactions in experimental studies. There is no question that atrazine, deethylatrazine, and simazine are chemicals with similar mechanism of toxic action and, therefore, the methodology applied is highly appropriate and supported by empirically based studies.

Petitioner Comment 5:

The request for correction states that “ATSDR has abandoned all use of the Interaction-based HI Formula for quantitative risk assessment because, in ATSDR’s own words, this formula “and other approaches of this type must be tested to ensure that they behave in a reasonable and consistent manner with regard to the underlying assumptions and that their predictions are reasonable representations of experimental or known exposure outcomes.”

The request for correction further states that “ATSDR has abandoned any attempt to use the Interaction-based HI Formula for quantitative risk assessments” and to validate the Interaction-based HI Formula by corroboration with observed data. Yet the Mixtures Guidance still recommends use of the Formula for qualitative risk assessments. The Interaction-based HI Formula should not be used for qualitative risk assessments either until and unless the formula’s predictions have been demonstrated to be “reasonable representations of experimental or known exposure outcomes.”

ATSDR Response:

While ATSDR does not employ a quantitative HI approach, ATSDR did not “abandon” the method but from the very start ATSDR recommended a qualitative approach. The Mumtaz and Durkin (1992) approach represented an advancement in mixtures risk assessment at the time. When the approach was tested for consistency of applications, individuals and groups tend to develop fairly similar scores (Mumtaz et al. 1995). The theoretical predictions were further validated in an experimental study conducted in cooperation between ATSDR and TNO (Mumtaz et al. 1998).

The challenges posed by the Mumtaz and Durkin (1992) approach for the mixtures (i.e., BINWOE) adjusted HI included the lack of a guidance on selecting the uncertainty factor for interactions, the complexity of steps for BINWOE determination, and the fact that the magnitude of the interaction is not included. In conclusion, ATSDR developed a qualitative categorized

approach to decisions- an alternative to the quantitative BINWOE approach.

Petitioner Comment 6:

The request for correction suggests that ATSDR should withdraw the Mixtures Guidance Manual and revise it to state clearly that the Interaction-based HI Formula should not be used to assess human health hazards from chemical mixtures.

Second, ATSDR should withdraw all final and draft Profiles that use or rely on the Interaction-based HI Formula. For example, ATSDR should withdraw the draft Atrazine Profile.

ATSDR Response:

As outlined above, the Mixtures Guidance Manual has met the standards of the HHS Information Quality Guidelines and withdrawal is not warranted. Similarly, the ATSDR draft and final interaction profiles are based upon methods published in the peer-reviewed literature. Further, these interaction profiles are based upon scientific studies that have been peer-reviewed in scientific journals. We do not believe that withdrawal of the draft Atrazine profile is warranted. The draft profile will undergo a thorough review, including a public comment period, before it is finalized.

If you wish to appeal this response to your request for correction, you may submit a written appeal or electronic request for reconsideration within 30 days of receipt of our response. The appeal must state the reasons why the agency response is insufficient or inadequate. You must attach a copy of your original request and the agency's response to it. Also, clearly mark the appeal with the words, "Information Quality Appeal" and send the appeal:

By Mail:

Centers for Disease Control and Prevention
Management Analysis and Services Office
1600 Clifton Road, N.E.
Mail stop F-07
Atlanta, Georgia 30333
Fax: (770) 488-4995

By Website Electronic Submission:

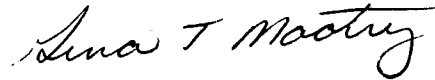
<http://www2.cdc.gov/PublicInquiry/PIAppealForm.asp?theID=35>

By Electronic-Mail:

<mailto:InfoQuality@cdc.gov>

If you have any further questions or concerns, please do not hesitate to contact me at (404) 498-0003.

Sincerely,

A handwritten signature in black ink that reads "Gina T. Mootrey". The signature is written in a cursive, flowing style.

Gina T. Mootrey, D.O., MPH
Acting Associate Director for Science
National Center for Environmental Health /
Agency for Toxic Substances and Disease
Registry

Attachment

References

Health Council of the Netherlands 2002. Exposure to combinations of substances: a system for assessing health risks. Gezondheidsraad 2002/05, Den Haag, ISBN 90-5549-430-5.

Mumtaz MM, Durkin PR. 1992. A weight-of-evidence approach for assessing interactions in chemical mixtures. *Toxicol Ind Health* 8:377-406.

Mumtaz MM, Cibulas W, De Rosa CT. 1995. An integrated framework to identify significant human exposures (SHELs). *Chemosphere* 31:2485-2489.

Mumtaz MM, De Rosa CT, Groten J, et al. 1998. Estimation of toxicity of chemical mixtures through modeling of chemical interactions. *Environ Health Perspect* 106(Suppl 6):1353-1360.