**REQUEST FOR CORRECTION OF**
**ATSDR MIXTURES GUIDANCE DOCUMENT**
**(Submitted electronically on December 5, 2005)**

The Kansas Corn Growers Association, the Triazine Network, and the Center for Regulatory Effectiveness ("Petitioners") file this Request for Correction ("RFC") under the Information Quality Act ("IQA") and under the applicable IQA Guidelines.[1]

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***

[1] The IQA is codified at 44 U.S.C § 3516 Historical and Statutory Notes. The applicable IQA Guidelines are the government-wide Guidelines published by the Office of Management and Budget ("OMB"), http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2002_register&docid=R2-59-filed.pdf; the Department of Health and Human Services ("HHS") Guidelines, http://www.hhs.gov/infoquality/part1.html; and the joint Guidelines published by the Agency for Toxic Substances and Disease Registry and the Centers for Disease Control and Prevention ("CDC"): http://www.hhs.gov/infoquality/cdc.html

***Guidance").*** [2]

ATSDR uses the Mixtures Guidance for various regulatory purposes, including the development and dissemination of profiles of human health hazards from various chemical mixtures ("Profiles"). [3] According to ASTDR, 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. [4]

The Mixtures Guidance violates the IQA"s Utility and Objectivity Standards for the following reasons:

- it recommends 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"; and

- 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).

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[2] ATSDR disseminates the Mixtures Guidance at the Agency's website, http://72.14.207.104/search?q=cache:bH7BV1wBXzAJ:www.atsdr.cdc.gov/interactionprofiles/ipga.html+%22Assessment+of+Joint+Toxic+Action+of+Chemical+Mixtures%22&hl=en, and elsewhere.

[3] *E.g*., ATSDR's draft Interaction Profile for Atrazine, Deethylatrazine, Diazinon, Simazine, and Nitrate, 69 FR 76768 (Dec. 22, 2004) ("draft Atrazine Profile"). The draft Atrazine profile is available online at http://www.atsdr.cdc.gov/interactionprofiles/ip10.html.

[4] *Id*.; *see* http://www.atsdr.cdc.gov/iphome.html; 42 U.S.C. § 9604(I)(3)(CERCLA).

ATSDR states in its IQA Guidelines that the Agency "*provides assurance that information [ATSDR disseminates] is accurate, reliable, and unbiased*."[5]

ATSDR cannot assure that Profiles based on the Interaction-based HI are "accurate, reliable and unbiased."

Consequently, the Mixtures Guidance, which recommends use of the Interaction-based HI Formula, and all draft and final Profiles based on this Formula violate the IQA and ATSDR's IQA Guidelines.

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."* [6]

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."*

Petitioners request the following relief under the IQA and IQA Guidelines.

First, ATSDR should withdraw the Mixtures Guidance 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.

**BACKGROUND ON INTERACTION-BASED HI FORMULA**

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[5] CDC/ATSDR Guidelines, Parts II, V.A.

[6] Mixtures Guidance, page B-10 (emphasis added).

When there are no empirical data on the human health hazards of a particular chemical mixture, then the Mixtures Guidance recommends use of the Interaction-based HI Formula to perform qualitative risk assessments of both cancer and noncancer health effects. [7]

This Formula takes the HI as its base, and modifies it to address pairwise interaction among chemicals in the mixture. By itself, the HI cannot address interaction because the HI assumes dose additivity only. Under the modified HI - the Interaction-based HI Formula-- an analyst or a group of analysts make a subjective judgment whether chemical interaction will occur, the direction of the interaction, and the toxicological relevance of the interaction to humans.

The Mixtures Guidance does not require that a mixture's toxicological effects predicted by the Interaction-based HI Formula be compared to observed data for that mixture.

The Interaction-based HI Formula has never been demonstrated to be accurate, reliable and unbiased for any mixture by comparison of the Formula's predicted toxicological results with observed data.

The HI method and the BINWOE modification of it are discussed in more detail below.

***HI***

The Mixtures Guidance describes the HI as follows:

"*The hazard index approach uses the assumption of dose additivity to assess the noncancer health effects of a mixture from the data on the components. EPA has adopted the term "hazard index" for this approach, which appears to have originated in 1972 (see Section 3.5). The approach is used or recommended by a number of agencies (ACGIH 2000; EPA 1986, 1989a; Mumtaz et al. 1994a, 1997; National Academy of Sciences [NAS] 1974; National Research Council [NRC] 1989; OSHA 1993, 2001). Exposures or doses for the various components of the mixture are scaled by a defined level of exposure generally regarded as "acceptable" or "safe" by the agency performing the assessment. The defined levels could be ATSDR MRLs, EPA reference doses (RfDs) or reference concentrations (RfCs),*

[7] Mixtures Guidance, pages xii, 11-12.

*ACGIH threshold limit values (TLVs), or OSHA permissible exposure limits (PELs)* [equation omitted]. *In equation 1(a), E1 is the level of exposure to the first chemical in the mixture and DL1 is some defined level of exposure to the first chemical, E2 and DL2 are the corresponding levels for chemical 2, and the summation can extend to any number of chemicals, signified by the n. Equation 1(b) simply expresses the same idea more succinctly, where i is the ith chemical. Each chemical-specific ratio (e.g., E1 /DL1) is called a hazard quotient (HQ). Therefore, the hazard index can be expressed as the sum of the hazard quotients* [equation omitted]. *When the hazard quotient for a single chemical exceeds unity, concern for the potential hazard of the chemical increases. Similarly, when the hazard index for a mixture exceeds unity, concern for the potential hazard of the mixture increases. Separate hazard indexes are estimated for each pathway and exposure duration of concern. For a given duration, hazard indexes are summed across pathways that affect the same receptor population. The obvious advantage of this method is its simplicity. Because it is based on the assumption of dose additivity, the hazard index method is most appropriately applied to components that cause the same effect by the same mechanism of action. In practice, it may be applied to components with different target organs (sometimes as a screening measure). The method is frequently applied to components with the same critical target organ or critical effect (effect that is the basis for the MRL, RfD, or other health guideline), without regard to mechanism of action."* [8]

***BINWOE Modification of the HI***

The Mixtures Guidance explains the BINWOE modification of the HI as follows***:***

"*As noted above, the hazard index method does not incorporate information on interactions among components of the mixture. A weight-of-evidence (WOE) method proposed by Mumtaz and Durkin (1992) was the first systematic attempt to address this need.*

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"*The method evaluates data relevant to joint action for each possible pair of chemicals in the mixture in order to make qualitative binary weight-of-evidence (BINWOE) determinations for the effect of each chemical on the toxicity of every other chemical. Two BINWOEs are needed for each pair: one for the effect of chemical A on the toxicity of chemical B, and another for the effect of chemical B on the toxicity of chemical A. The BINWOE determination is a classification that indicates the expected direction of an interaction (greater than additive, less than additive, additive, or indeterminate), and scores the data qualitatively, using an alphanumeric scheme that takes into account*

[8] Mixtures Guidance, pages 11-12.

*mechanistic understanding, toxicological significance, and relevance of the exposure duration, sequence, bioassay (in vitro versus in vivo), and route of exposure. The alphanumeric terms in the classification scheme can then be converted to a single numerical score, by multiplying the corresponding direction factor by the data quality weighting factor. Although the earlier publications of the WOE method did not discuss the need for BINWOE determinations to take into account target organ (Durkin 1995; Mumtaz and Durkin 1992), experience in application of the WOE method, including preparation of the ATSDR interaction profiles and a study by Mumtaz et al. (1998), has indicated that the WOE evaluations should be target-organ specific."* [9]

**ATSDR'S RECOMMENDED USE OF THE INTERACTION-BASED HI FORMULA VIOLATES THE IQA OBJECTIVITY AND UTILITY STANDARDS BECAUSE THIS FORMULA HAS NEVER BEEN VALIDATED: *i.e.*, IT HAS NEVER BEEN SHOWN TO BE ACCURATE AND RELIABLE AND UNBIASED BY COMPARISON WITH OBSERVED DATA**

***The Interaction-based HI Has Never Been Shown to be Accurate, Reliable and Unbiased***

ATSDR abandoned any attempt to use the Interaction-based HI Formula for quantitative risk assessments because the Formula is not accurate or reliable or unbiased:

"*Subsequent experience with the algorithm that is used to generate the interactions-adjusted hazard index has revealed, however, that it does not handle changes in the proportions of mixture components in a reasonable manner. The method remains useful in the qualitative prediction of whether hazard may be greater or less than indicated by the hazard index (Sections B.1.2 and B.2.2). A modification to the WOE method was developed (ERG and Durkin 1995; EPA 2000) in order to explicitly incorporate information on the magnitudes of the pairwise interactions into the risk assessment. This modified method addresses some of the limitations of the original method, but introduces a new set of limitations: greater judgment may be required in the scoring of the weight-of-evidence and information on the magnitude of interactions is rarely available.*" [10]

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[9] Mixtures Guidance, page 16.

[10] Mixtures Guidance, page B-1.

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"*Therefore, ATSDR has discontinued the use of the algorithm and will use a qualitative WOE approach (Section B.2.2), as suggested by Mumtaz and Durkin (1992), until an appropriate algorithm can be developed or selected, and fully evaluated.* ***The WOE algorithm 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."*** [11]

Petitioners understand that ATSDR has abandoned any attempt 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 Mixtures Guidance makes this recommendation despite the fact that the Formula did not perform well for any purpose when ATSDR tried to corroborate it with observed data, and despite the fact that the corroboration tests were themselves fatally flawed. The Mixtures Guidance explains:

"*The WOE [i.e., the Interaction-based HI Formula] underestimated the relative liver weights in the same animals. The observed dose-response for relative liver weight was slightly greater than dose additive. Thus, the WOE method did not predict toxicity to a target organ that was different from the one for which the BINWOEs were derived. The WOE method slightly overpredicted the observed dose response for relative kidney weight in male rats for a mixture of dissimilarly acting nephrotoxins (in female rats, the data variability was so great that the exponential model did not fit the observed responses) (Mumtaz et al. 1998). Although these results are suggestive, limitations of this test of the complete WOE method include the substantial variability in the responses of individual animals, small numbers of animals per group, testing of only two dose levels of the mixtures, and lack of rationale for using relative organ weight as an index of toxicity (several other indicators of renal and hepatic toxicity were monitored in the studies that provided the experimental data [Jonker et al. 1993, 1996])."* [12]

***ATSDR's Recommended Use of the Interaction-based HI Formula, and ATSDR's Use of this Formula in Profiles, Violate the IQA and IQA Guidelines.***

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[11] Mixtures Guidance, page B-10 (emphasis added).

[12] Mixtures Guidance, page B-11.

The IQA, the OMB Guidelines, the HHS Guidelines, and the CDC/ATSDR Guidelines all impose the same Accuracy and Reliability standards on the Mixtures Guidance and on Profiles based on the Mixtures Guidance.[13] These standards must be met before publicly disseminating the Mixtures guidance.[14] The HI/BINWOE method does not meet them.

The CDC/ATSDR IQA Guidelines state that ATSDR toxicological profiles will always be considered influential information under the Guidelines. [15] The Mixtures Guidance must also always be considered influential under the IQA Guidelines because it is always used to produce the toxicological profiles. Influential information is subject to the most rigorous quality standards under the IQA.

The CDC/ATSDR DQA Guidelines state that:

> *"CDC will ensure that disseminated information meets the standards of quality set forth in the OMB, HHS and CDC guidelines. It is CDC's policy to ensure and maximize the quality, objectivity, utility, and integrity of information that it disseminates to the public. We strive to provide information that is accurate, reliable, clear, complete, unbiased, and useful."*
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> "*CDC provides assurance that information is accurate, reliable, and unbiased."*[16]

The above-quoted Guidelines include ATSDR within their use of the term CDC, and "*all practices and procedures specified [in the Guidelines] apply to both agencies."* [17]

Applying this IQA Standard, how can ATSDR assure the public that Profiles based on the Interaction-based HI Formula are Aaccurate, reliable, and unbiased?"

The answer to this rhetorical question is that ATSDR cannot.

Consequently, the Mixtures Guidiance's recommendation that the Interaction-based HI

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[13] *E.g*., OMB Guidelines, Parts II, III, V; HHS Guidelines, Part I.A through I.D; CDC/ATSDR Guidelines, Parts III, V.

[14] *E.g*., CDC/ATSDR Guidelines, Part II.

[15] CDC/ATSDR Guidelines, Part VII.

[16] CDC/ASTDR Guidelines, Parts II, V.A.

[17] CDC/ATSDR Guidelines, Part I.

Formula be used to generate draft and final Profiles, and all draft and final Profiles based on that recommendation, violate the IQA and ATSDR's IQA Guidelines.

In ATSDR's own words, the Interaction-based HI Formula should not be used for any risk assessment purpose, quantitative or qualitative, until and unless the Formula has been "*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. "* [18]

## PETITIONERS ARE AFFECTED PARTIES

Petitioner Kansas Corn Growers Association represents Kansas corn producers across Kansas and the United States on a variety of issues that concern its members. It is a member of the Triazine Network.

Petitioner Triazine Network is a coalition of over 1000 local and state agricultural associations and farmers located throughout the United Sates. It includes growers of various crops on which atrazine is used. The Triazine Network's goal is to ensure that atrazine is regulated and assessed on the basis of sound science and data. The Network filed comments on ATSDR's draft Atrazine Profile**.**

ATSDR's draft Atrazine Profile is based on the Interaction-based HI Formula, as recommended by the Mixtures Guidance. [19]

ATSDR's draft Atrazine Profile could hinder the Network members' use of atrazine.

Petitioner Center for Regulatory Effectiveness ("CRE") is a regulatory watchdog organization. One of CRE's missions is to ensure that government action is based on sound science and data. To this end, CRE has advocated compliance with the IQA and IQA Guidelines in numerous contexts. CRE filed comments on the draft Atrazine Profile. CRE's comments made IQA and IQA Guidelines arguments against the Profile.

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[18] Mixtures Guidance, page B-10.

[19] *E.g*, draft Atrazine Profile, pages ix-x, 1, 14-15, 23-27. The draft Atrazine Profile cites the draft 2001 ATSDR Mixtures Guidance as requiring use of the Interaction-based HI Formula. E.g., draft Atrazine Profile, page 14. For purposes of the issues raised by this IQA Request for Correction, the draft Mixtures Document is the same as the final ATSDR Mixtures Guidance.

## CORRECTIONS REQUESTED

First, ATSDR should withdraw the Mixtures Guidance and revise it to state clearly that the Interaction-based HI Formula should not be used to assess health hazards from chemical mixtures.

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

## CONTACT PERSON

Please contact Scott Slaughter at The Center for Regulatory Effectiveness, Suite 700, 11 DuPont Circle, NW, Washington, D.C. 20036, 202/265-2383, Slaughter@mbsdc.com regarding this Request for Correction.

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