

**DISPOSITION OF PUBLIC COMMENTS ON THE INTERACTION PROFILE FOR  
ATRAZINE, DEETHYLATRAZINE, DIAZINON, NITRATE, AND SIMAZINE**

Agency for Toxic Substances and Disease Registry,  
U.S. Department of Health and Human Services,  
Atlanta, Georgia

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**Comments submitted by:**

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**Submitter A.**

Comment 1     Scientifically Syngenta finds no justification for the creation or publication of this Draft Interaction Profile. First ATSDR cites a mandate from the Comprehensive Environmental, Response, Compensation, and Liability Act (CERCLA) to assess whether adequate information on health effects is available for *priority hazardous substances*.

Syngenta has reviewed the latest list (2003) of *priority hazardous substances* as well as earlier lists and find that neither atrazine, deethylatrazine, nor simazine have been listed as priority substances for ATSDR. Therefore the decision to assess these chemicals in a mixture interaction is inappropriate.

Response     Both ATSDR and EPA’s authorities under CERCLA primarily involve responses to releases of hazardous substances as defined by CERCLA. This definition references lists of substances required under CERCLA and other environmental laws, including the Clean Water Act, Clean Air Act, and the Solid Waste Disposal Act. Pesticides covered by FIFRA are not excluded from this definition, and several pesticides and related compounds are found on the referenced lists. 42 USC 9601(14).

ATSDR is directed to compile a list of priority hazardous substances that are commonly found at National Priorities List sites and “which, in their sole discretion, they determine are posing the most significant potential threat to human health due to their known or suspected toxicity to humans and the potential for human exposure to such substances at facilities on the National Priorities List or at facilities to which a response to a release or a threatened release under this section is under consideration.” 42 USC 9604(i)(2).

From the featured mixture of atrazine, deethylatrazine, diazinon, nitrate, and simazine, diazinon is # 114 on the ATSDR’s Priority List of Substances at NPL Sites and nitrate is # 222 . It should be noted that only the first 275 substances are included on the published list. For example, atrazine is ranked #397 on the Priority List, but because of its widespread use, a toxicological profile for atrazine was developed (ATSDR 2003). For health assessments, ATSDR “may consider additional information on the risks to the potentially affected population from all sources of such hazardous substances including known point or nonpoint sources other than those from the facility in question.” In developing health assessments and supporting documents such as Interaction Profiles, for use by public health officials conducting health assessments and other site-specific responses, the agency may clearly consider and evaluate other sources of exposure to hazardous substances, such as from drinking water sources. 42 USC 9604(i)(6)(G). Atrazine is a widely used pesticide that was found in 91%-98% of surface waters (ATSDR

2003). The EPA estimated that about 70,800 rural domestic drinking water wells are contaminated with atrazine. Therefore, it is only appropriate to evaluate atrazine together with other contaminants as a mixture.

Comment 2 The formation of N-nitrosoatrazine in the stomach, again while theoretically possible, has not been demonstrated, even at high doses of nitrate and atrazine. Finally, when nitrosoatrazine or nitrososimazine were administered for a lifetime to rats and mice that exceeded maximum tolerated doses, no excess incidence of tumors were observed. Therefore ASTDR proposed interaction profile between atrazine and nitrate based upon carcinogenic potential is unwarranted.

Response As for the formation of N-nitrosoatrazine, following information can be found in the interaction profile: “The formation of N-nitrosoatrazine from atrazine and nitrite has been demonstrated in human gastric juice (pH 1.5–2.0) during 1.5–12 hours of incubation at 37 °C (Cova et al. 1996). The percent formation peaked at 3 hours, and gradually declined thereafter, due to degradation of N-nitrosoatrazine to atrazine. Peak formation of N-nitrosoatrazine was 2% from 0.05 mM atrazine and 0.5 mM nitrite, 23% from 0.05 mM atrazine and 3 mM nitrite, and 53% from 1 mM atrazine and 3 mM nitrite. The levels of nitrite used were similar to peak gastric levels of nitrite (1.77 mM) in subjects who ingested a salad-type meal containing 1.15 mM of nitrate (Walters et al. 1979).

The formation of N-nitrosoatrazine from atrazine and nitrite also has been demonstrated *in vivo*. Approximately 0.04% conversion occurred within 15 minutes in mice gavaged with 1,000 µg atrazine followed by 500 µg nitrite (Krull et al. 1980). At 500 µg atrazine and 500 µg nitrite, N-nitrosoatrazine was found in some but not all of the mice, and at 250 µg atrazine and 500 µg nitrite, N-nitrosoatrazine was not detected. The *in vitro* studies conducted as part of this study resulted in conversion of about 0.4% of the atrazine to N-nitrosoatrazine during incubation of 500 µg atrazine with 500 µg nitrate at 37 °C and pH 3 for 2 hours. According to Seiler (1977), the pH of the mouse stomach is approximately 4–5.”

As for the induction of cancer, the submitter did not provide a reference for the cited study. However, ATSDR found out that: “N-nitrosoatrazine was clastogenic in cultured human lymphocytes at concentrations 10,000 times lower than required for atrazine clastogenicity and 1,000 times lower than required for nitrate clastogenicity in the same assay (Meisner et al. 1993). In addition, N-nitrosoatrazine was mitogenic, whereas atrazine and nitrate were not. In a Chinese hamster cell line derived from lung fibroblasts, N-nitrosoatrazine caused chromosomal aberrations when tested at a concentration 17-fold lower than an atrazine concentration (250 mg/L) that did not cause chromosomal aberrations in the same study (Ishidate 1983; Ishidate et al. 1981). Results of these studies

indicate that N-nitrosoatrazine is more clastogenic than atrazine or nitrate, and stimulates cell division whereas atrazine and nitrate do not. This raises a concern that the formation of N-nitrosoatrazine through chemical interaction may be a greater-than-additive interaction in terms of genotoxic and proliferative effects. Implications for carcinogenicity or other effects are less clear. However, Preussmann and Stewart (1984) reported that 86% of the 232 N-nitrosamines that had been tested for carcinogenicity in animals gave positive results. Many of the remaining 14% had been tested at below the maximum tolerated dose and/or in only one species, so the apparent negative results were not definitive.” ATSDR added a conclusion that “...the issue of atrazine/nitrate and simazine/nitrate combinations and potential cancer risk in humans is still unresolved and further research is needed”.

Comment 3 In addition in a study conducted by NIEHS, mixtures of atrazine, simazine and nitrate at 100-fold higher levels than environmental concentrations did not cause any reproductive (mice), general or developmental toxicity (rats) (Heindel, et al. 1994).

Response In the quoted article, Heindel et al. 1994 (Fundam Appl Toxicol 22:605-21) described assessments of reproductive and developmental toxicity of two complex mixtures in rats. One mixture contained aldicarb, atrazine, dibromochloropropane, 1,2-dichloropropane, ethylene dibromide, simazine, and ammonium nitrate. The other consisted of alachlor, atrazine, cyanazine, metachlor, metribuzin, and ammonium nitrate. Evidently these are completely different mixtures than the one featured in the interaction profile. Both mixtures contain chemicals that are structurally unrelated. Therefore, it is inappropriate to apply inferences drawn from the Heindel et al. (1994) study to the mixture addressed in this interaction profile.

Comment 4 The interaction profile proposed by ATSDR for diazinon and atrazine based upon enhanced acute toxicity in selected aquatic invertebrates is likewise unwarranted based on the fact that environmental concentrations or estimated human doses of atrazine or total chlorotriazine is substantially below those concentrations need to induced P450 enzymes capable of modulating diazinon acute toxicity. Furthermore, it is not clear why ATSDR chose these two chemicals to showcase interaction out of the myriad of combinatorial effects that could be considered between xenobiotics that co-occur, especially considering the fact that there is empirical evidence that all most environmental concentrations of atrazine and diazinon are below their respective standards.

Response As outlined in the Guidance Manual for the Assessment of the Joint Toxic Action of Chemical Mixtures, the weight-of-evidence evaluation includes assessment of the mechanism of interaction. This includes toxicodynamic and toxicokinetic understanding of the interaction. When the metabolism of both chemicals involves

engagement of the P-450 enzymes, this effect is highly appropriate for consideration. As explained in the interaction profile: “Diazinon is a phosphorothioate organophosphorus insecticide that is metabolically activated through oxidative desulfuration to diazoxon by cytochrome P450. Diazoxon binds to acetylcholinesterase, inhibiting its ability to hydrolyze the neurotransmitter acetylcholine. The resulting accumulation of acetylcholine at the nerve endings causes continual neurological stimulation. This mechanism of action applies to both invertebrates and mammals. Atrazine induced the metabolic activation of a similar phosphorothioate organophosphorus insecticide, chlorpyrifos, and potentiated its acute neurotoxicity to midges (Belden and Lydy 2000). Based on the similarity in structure and mechanism of action of diazinon and chlorpyrifos, a similar mechanism (induction of metabolic activation) can be inferred for atrazine’s potentiation of the acute neurotoxicity of diazinon to midges in the same study. Because the mechanism of interaction is inferred from a similar chemical, a rating of II is chosen for mechanistic understanding.”

Comment 5 ATSDR cites the Food Quality Protection Act (FQPA) as requiring consultation with the Secretary of Health and Human Service (HHS) (which includes ATSDR) in implementing some of the provisions of FQPA. As far as this assertion is concerned, the requirements for consultation with the Secretary of HHS are quite specific in FIFRA/FFDCA as amended by FQPA, generally specified for vector controlling substances. Additionally, EPA under FQPA specifically addresses assessment of chemicals that have a common mechanism of toxicity. While atrazine, simazine and deethylatrazine have been deemed as having a common mechanism of toxicity by EPA, this does not hold true for the other substances described in the Draft Interaction Profile. Further, to Syngenta’s knowledge, the testing of pesticide and fertilizer interactions is not a part of any validated federal toxicological testing protocol, nor any mandate to ATSDR. It appears therefore that the decision by ATSDR to develop this Draft Interaction Profile absent any request from the EPA Administrator is questionable.

Response ATSDR no longer cites the FQPA in this interaction profile. However, as part of its general authorities, ATSDR is directed to “establish and maintain an inventory of literature, research, and studies on the health effects of toxic substances.” In addition, ATSDR shall either independently or as part of other health status survey, conduct periodic survey and screening programs to determine relationships between exposure to toxic substances and illness. (CERCLA 104(i)(1)(B) and (E)). These authorities are interpreted broadly to provide ATSDR the discretion to make scientific and professional determinations as to the type of information and investigations necessary to help determine the relationships between health effects and exposure to hazardous and toxic substances. For further clarification, see response to comment 1.

Comment 6 Although the ATSDR Draft Profile correctly cites The International Agency for Research on Cancer's (IARC 1999a) atrazine classification as *not classifiable as to its carcinogenicity to humans* (Group 3) based on inadequate evidence in humans and sufficient evidence in experimental animals, Syngenta wishes to point out that the IARC went on to evaluate atrazine (and simazine) with the statement: "Therefore there is strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumours in Sprague-Dawley Rats is not relevant to humans." In addition, the EPA Office of Pesticide Programs (2002) classified atrazine and its chlorinated metabolites as *not likely to be carcinogenic to humans*.

Response There is nothing in the interaction profile that would suggest that ATSDR considers atrazine by itself as a carcinogen. As for the carcinogenicity of N-nitrosoatrazine formed from atrazine and nitrite (a metabolite of nitrate), see the response to comment number 2.

Comment 7 The Draft Interaction Profile states in the first sentence of the "Summary" that "Atrazine, deethylatrazine, simazine, diazinon, and nitrate were chosen as the subject mixture for this interaction profile because they frequently occur together in rural well water." The citation for this conclusion is not apparent in the summary but later is shown to be a study by Squillace et al. 2002. In review of the study however it is shown that neither atrazine, deethylatrazine, nor simazine were found at levels greater than their established standards. Additionally, ATSDR states that "diazinon was the most frequently detected organophosphate insecticide", when in fact, in the report cited, it was the only organophosphate insecticide detected, and it was found in a total of one well.

Response A careful review of the Squillace et al. (2002) study would reveal that various combinations of atrazine, deethylatrazine, simazine, and nitrate represent all the top 8 most frequently found mixtures in the drinking water tested (Table 2 of the study).

For the evaluation of mixtures, it is not relevant that the chemicals were found at levels below "their established standards." A number of studies indicate co-exposure to subthreshold doses or environmental doses of chemicals that affect the same target organs (though not necessarily by the same mechanism) can result in adverse effects. A mixture of eight xenoestrogens produced significant effects in a recombinant yeast estrogen screen when the individual components were present at below their no-effect concentrations (Silva et al. 2002). An acute study of a mixture of subthreshold doses of 1,1,1-trichloroethane, trichloroethylene, and tetrachloroethylene in rats resulted in adverse effects on the liver; similar results were obtained in hepatocytes *in vitro* (Stacey 1989). Although cadmium and lead affect the hematological system through different mechanisms, dietary exposures of rats to these metals at doses that did not significantly affect hemoglobin and

hematocrit when given individually, resulted in significant decreases in hemoglobin and hematocrit when given as a mixture (Mahaffey and Fowler 1977; Mahaffey et al. 1981). A series of studies initiated by the NIEHS on a mixture of 25 groundwater contaminants from hazardous waste sites and on a mixture of pesticide and fertilizer contaminants indicated that toxic effects can result from long-term exposure to mixtures in which each of the components is present at doses expected to be subtoxic (Kligerman et al. 1993; Yang 1994). Epidemiological studies of children have indicated that lead and arsenic, and lead and cadmium, may interact at environmental levels of exposure to produce adverse neurobehavioral consequences in children (Marlowe et al. 1985; Moon et al. 1985).

Changes will be made in the interaction profile to clarify the occurrence of diazinon, as well in the technical rationale for the inclusion of diazinon in this interaction profile.

Comment 8 Therefore it is extremely puzzling to Syngenta why these compounds were picked over VOCs, for example, which, as stated by the authors, were detected more frequently than pesticides. ATSDR seems to try to justify its choice of this mixture by ignoring that VOCs were detected more frequently than pesticides and by simply stating that it picked the most frequently occurring *four-chemical* mixture (emphasis added). Based on Squillace et al. 2002, VOCs should have been of much higher priority to ATSDR and therefore this is an extremely questionable choice of compounds for an interaction assessment.

Response As explained in the response to comment number 7, VOCs were not the most often found combinations in the Squillace et al. (2002) study.

In addition, ATSDR already completed two interaction profiles for VOCs: the *Interaction profile for 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene* and the *Interaction profile for benzene, ethylbenzene, toluene, and xylenes (BTEX)*. These interaction profiles are available to the public at [www.atsdr.cdc.gov](http://www.atsdr.cdc.gov)

Comment 9 ATSDR states on Page iii: "A weight-of-evidence approach is commonly used in documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds." Several statements made in the document also support the fact that this proposed Draft Interaction Profile is unwarranted.

Response As stated in the interaction profile, the weight-of-evidence approach of binary combinations is used to evaluate the overall toxicity of the mixture; i.e., the



evaluation provides important “qualitative” information on the predominant direction of all interactions (additivity, more-than additivity, less than additivity). As in the example of this particular interaction profile, the additivity approach is applied when the effect of a mixture can be estimated from the sum of the components, normalized for differences in potency Finney (1971). It usually requires that all components act by the same mechanism and that tolerances are positively correlated, i.e., organisms susceptible to chemical A will also be susceptible to chemical B (EPA 1986, 1990, 2000). In the low-dose region in which dose-response regressions may be linear, which is assumed in absence of data to contrary, dose additivity may hold for components with different (i.e., independent) mechanisms (Svedsgaard and Hertzberg 1994). Dose additivity is the underlying assumption of the hazard index method (“quantitative”) used in the interaction profile. Nothing in the approach described here supports the fact that this interaction profile is “unwarranted.”

Comment 10 Syngenta also notes that ATSDR has cited the EPA IRIS database with regard to atrazine and simazine. Syngenta refers the ATSDR to Federal Register Notice Integrated Risk Information System (IRIS); Announcement of 2004 Program; Request for Information (Vol. 69, No. 26 / Monday, February 9, 2004) which states for atrazine, simazine and diazinon (among others) that the Agency is “deleting from the IRIS agenda, a group of pesticides that will not be assessed through the IRIS process given that the Office of Pesticide Programs (OPP) has a large assessment program evaluating these chemicals. This step is being taken to more efficiently utilize Agency resources.”

ATSDR should take advantage of the EPA OPP’s extensive ongoing review of the triazines which will culminate in a cumulative risk assessment of the group of triazine-containing chemicals. These include atrazine, simazine, desethyl-s-atrazine (DEA), desisopropyl-s-atrazine (DIA), and diaminochlorotriazine (DACT). EPA OPP will complete its assessment on the chlorotriazines in 2006, and therefore it is a waste of federal resource for ATSDR to start a new assessment. In addition, the data do not support the need for a profile that includes diazinon and nitrate.

Response ATSDR is working closely with the EPA OPP in the further development of this interaction profile. Therefore, these efforts are complementary and are being developed in the same timeframe.

#### **Submitter B.**

Comment 1a “ATSDR’s Draft Profile, and any final profile, must meet the requirements of the Data Quality Act (“DQA”) and the applicable DQA Guidelines.”

The submitter supported the above statement by quoting the interaction profile on the lack of data for the entire mixture or some of the mixtures components. The submitter asked “Weight of what evidence?” and further suggested that ATSDR cannot assure the public that its health effects assessments are accurate and reliable.

- Response For a brief explanation of ATSDR’s approach, see response to submitter A, comment 9. This submitter is further encouraged to consult ATSDR’s *Guidance Manual for Assessment of Joint Toxic Action of Chemical Mixtures* ([www.atsdr.cdc.gov](http://www.atsdr.cdc.gov)). This document underwent rigorous peer-reviews and public reviews and was endorsed by scientists from governmental agencies in the U.S.A. (EPA, NIEHS) and Europe (Health Council of the Netherlands). It outlines ATSDR’s strategy for exposure-based assessment of joint toxic action of chemicals and the decision process (in flow-charts) that is to be followed in cases when pertinent data are missing or insufficient.
- Comment 1b “The study relied upon, Squillace *et al.* (2002), actually states that VOCs were detected more frequently than pesticides. Why were pesticides singled out rather than an assessment of VOC mixtures? Diazinon was found in only one well. Therefore, the assessment of a mixture of diazinon with anything in ground water does not appear to be the best use of resources and tax dollars by an Agency that is supposed to be evaluating the effects of substances in combination with other substances with which they are commonly found (Preface to Draft Profile). The Draft Profile has no utility in protecting public health.”
- Response See response to submitter A, comment 8.
- Comment 2 “The Draft Profile does not meet the DQA Accuracy and Reliability requirements. The only way it could possibly meet these requirements is for ATSDR to clearly state that the Draft Profile’s conclusions and analyses may not be accurate and reliable. Any final Profile similar to the Draft would have to include the same disclaimer.”
- Response The submitter does not support this claim with any evidence. The missing data issues were addressed in the response to comment 1b.
- Comment 3 “The Draft Profile does not meet the DQA Utility requirement because it is of no practical value to anyone given that it may not be accurate or reliable. Any final Profile similar to the Draft profile would not meet the DQA Utility requirement for the same reason.”

Response The interaction profile is actually quite useful for health assessors because it provides a conclusion that the hazardous index approach is appropriate for the mixture assessment and provides recommendations applicable in the field.

Comment 4 “CRE cannot find any statutory authority for the Draft Profile or for any final Profile.”

The submitter supports this conclusion by statements: “1) that Profile is not tied to any CERCLA hazardous substance release site; 2) that Profile includes several substances that are not listed CERCLA hazardous substances; and 3) no other federal agency, state or Native American tribe has requested that ATSDR prepare that Profile.” Further the submitter questioned “What “hazardous waste sites” are known to contain the mixtures addressed by the Draft Profile?”

Response The Agency for Toxic Substances and Disease Registry (ATSDR) was established by the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund)(42 USC 9604(i)). While ATSDR is not specifically required to develop and publish Interaction Profiles, 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 Superfund sites and releases. The development of such profiles is legally supported by several provisions within ATSDR’s CERCLA authorities. Although the CERCLA response scheme does impose certain limitations on the substances and circumstances in which ATSDR may undertake activities, ATSDR has a great deal of discretion in determining which substances and combinations may be evaluated and the priority order in which to conduct the evaluations. There is nothing in these limitations that would prohibit ATSDR from developing Interaction Profiles on hazardous substances, as well as pollutants and contaminants and other substances with which they are found. In developing health assessments and supporting documents such as Interaction Profiles, for use by public health officials conducting health assessments and other site-specific responses, the agency may clearly consider and evaluate other sources of exposure to hazardous substances, such as from drinking water sources. 42 USC 9604(i)(6)(G). Both ATSDR and EPA’s authorities under CERCLA primarily involve responses to releases of hazardous substances as defined by CERCLA. This definition references lists of substances required under CERCLA and other environmental laws, including the Clean Water Act, Clean Air Act, and the Solid Waste Disposal Act. Pesticides covered by FIFRA are not excluded from this definition, and several pesticides and related compounds are found on the referenced lists. 42 USC 9601(14). See also response to submitter A, comment 1.

In addition, all of the chemicals featured in the interaction profile are found at hazardous waste sites. Both diazinon and nitrate are on the ATSDR list of Priority

Hazardous Substances. ATSDR has identified seven sites involving the presence of both atrazine and diazinon while atrazine and nitrate were found together at 14 sites. In addition there are at least 3 instances where 2 or more components of this mixture have been involved in complete exposure pathways.

**Submitter C.**

Comment 1. The submitter recommends that ATSDR withdraw its mixtures approach and propose it through the normal notice and comment process of informal rule making. Comments primarily relate to the notice of availability of a “Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures”.

ATSDR’s direct promulgation of a final version of its mixtures approach, in the form of a Guidance Manual, lacks a rationale to forego the informal rule making procedures of proposal and comment that the Administrative Procedures Act requires.

Response ATSDR is not a regulatory agency. Therefore, its scientific assessments are not presented as a “rule”. However, to assure the transparency of its action, ATSDR made all the interaction profiles and the guidance document available for public comments. The availability of the *Guidance Manual for Assessment of Joint Toxic Action of Chemical Mixtures* was announced in the Federal Register on May 24, 2002 and the guidance manual was finalized in 2004. Also all interaction profiles and the guidance manual were peer-reviewed – for more information see response to submitter B, comment 1b.

Comment 2 “The Food Quality Protection Act (FQPA) of 1996 does require a consultation between the U.S. Environmental Protection Agency (EPA) and the Department of Health and Human Services (DHHS). However, ATSDR has an improbable stretch to reach a mandate for its mixtures policy based on this clause. DHHS could consult with EPA without finalization of any interaction profiles or the overarching policy hidden in the Guidance Manual. DHHS has not formally delegated the consultation to ATSDR. The factors listed in FQPA for EPA to consider do not restrict the factors that ATSDR might want to take into account in its mixtures approach. FQPA does not cite ATSDR. Thus, CTRAPS does not understand how ATSDR asserts a mandate to develop a mixtures program based on FQPA.

Response See response to submitter A, comment 5.

Comment 3 ATSDR could, but did not, properly use experts’ subjective assessments to decide which mixtures merit empirical assessment.

Response An explanation regarding ATSDR's selection of this mixture was provided in the interaction profile. Experts in the field of chemical mixtures were involved in final decisions.

Comment 4 ATSDR needs a stopping point, beyond which experimental evaluation of a mixture will have no value, or some other way to set priorities on research needs.

The nature, direction and magnitude of a biological interaction, if any, between substances in a mixture will remain uncertain until ATSDR develops an evaluation process based on experimental evidence.

Response The theoretical evaluation of interactions of chemicals has merit for assessing toxicity of mixtures in lieu of experimental data. The analysis performed in interaction profiles helps to identify the data gaps. In developing and implementing their research programs, ATSDR and EPA are directed to coordinate the program with the National Toxicology Program and programs of toxicological testing under the Toxic Substances Control Act and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The purpose of this coordination is to utilize the results, expertise and experience in these programs to accomplish the objectives of the ATSDR research program and avoid duplication of effort. ATSDR submits the identified data gaps to NTP for further research. The slope approach and methods of ATSDR's chemical mixture program was fully coordinated with EPA and NIEHS, who, in part, supported this program financially and through experimental work.

Comment 5 ATSDR's mixtures approach is based on subjective, not objective criteria. This mixtures approach asks ATSDR personnel to assign values to substances in mixtures. These values have structural relationships to substances with known biological activities, not values based on empirical bioassay. Inherently, ATSDR calculates the toxicity of a mixture, using assigned values for the constituents of the mixture. Subjectively assigned values mean that the assessment of "toxicity" in a mixture is a subjective process. In addition, ATSDR's mixtures approach uses numerical values to represent subjective estimates of expected "toxicity" for different substances. Both the numerical values and the mathematical processing of the numerical values, obfuscate ATSDR's mixtures approach. The numerical values and mathematical procedures give a false impression of precision to the approach.

Response See response to submitter 1, comment 9. The alpha-numeric designations assigned in this method are descriptive and are not used quantitatively. The quantitative aspects of the hazard index are empirically based and reflect widely accepted risk assessment methods.

