Interaction profiles for simple mixtures: mixtures with radioactive chemicals

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Abstract

The Agency for Toxic Substances and Disease Registry (ATSDR) program for chemical mixtures risk assessment has prepared a guidance document (Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures) that instructs how to conduct health risk assessment for chemical mixtures. ATSDR also develops documents called “interaction profiles” to assess risks associated with exposure to specific chemical mixtures. The assessment method has been applied in practice during consultations in communities around hazardous waste sites.

Interaction profiles are written for mixtures of concern that are on ATSDR’s priority list of mixtures at hazardous waste sites, such as mixtures of VOCs most often found in water and mixtures of metals most often found in contaminated soils. Similarly, interaction profiles on persistent lipophilic chemicals found in fish and breast milk provide information on risk associated with exposures in everyday life. In support of the US Geological Survey (USGS), ATSDR has developed an interaction profile for a mixture of pesticides found in well water. In addition, interaction profiles have been developed for Department of Energy (DOE) and National Aeronautics and Space Administration (NASA) sites. These interaction profiles were unique in evaluating risk associated with exposures to radioactive and non-radioactive chemicals. Weight-of-evidence methodology was used to assess the joint toxic action for most of the mixtures. For most mixtures profiled so far, a target-organ toxicity dose modification of the hazard index approach was utilized for conducting exposure-based assessments of noncancer health hazards.

Keywords: chemical mixtures, risk assessment, radioactive chemicals, additivity, joint toxic action.
1 Introduction

ATSDR’s documents related to the risk assessment of chemical mixtures are available on ATSDR’s web site at www.atsdr.cdc.gov. The documents underwent a rigorous regimen of peer-review and public review. The risk assessment methodology employed is widely accepted and endorsed by other scientists. An overview of the methodology was published previously (Wilbur et al. [19]). Similarly, risk assessment evaluations for specific mixtures of concern including mixtures of VOCs, metals, or persistent chemicals have been published (Pohl et al. [11,13]; Roney and Colman [14]). This paper intends to familiarize the readers with evaluations of mixtures of radioactive and non-radioactive chemicals. ATSDR has evaluated three such mixtures.

Stable or radioactive forms of cesium, cobalt, and strontium were found together at several Department of Energy (DOE) sites. In addition, other non-radioactive chemicals, such as volatile organic compounds (VOCs), semi-volatile compounds, and heavy metals were found at these sites. Trichloroethylene and polychlorinated biphenyls (PCBs) were frequently reported together with radioactive elements at these sites. The sites are not likely a public threat due to limited access by the public and different aquifers for public water supplies; however, ATSDR concluded that some sites were hazardous to the on-site workers and those involved with environmental restoration and management.

Another mixture of interest related to DOE sites consists of cyanide, fluoride, nitrate, and uranium. Uranium and fluoride are used in conjunction with nitrate when separating isotopes of uranium via the gaseous diffusion process. This process has been used at several DOE facilities, and continues to be used today. In addition, cyanide is frequently reported as a contaminant at hazardous waste sites.

The mixture of jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90 was chosen to represent potential exposures in the vicinity of National Aeronautics and Space Administration (NASA) sites where past and/or present activities include release of these materials. Such sites include rocket testing facilities, Air Force bases, and similar installations. Activities at such sites might include use of jet fuels and hydrazines as aircraft and rocket fuels and trichloroethylene as a solvent to clean engine components. Such sites sometimes include or are co-located with nuclear research facilities or radioactive waste storage sites, where strontium-90 may be found in spent nuclear fuel rods. Arsenic, although not necessarily used or produced at such sites, is the most frequently detected chemical at hazardous waste sites and might be expected at the sites.

2 Methods

2.1 Literature review

Searches of scientific literature yielded no toxicity information on featured mixtures as whole entities (all compounds together). Some human and animal
data were available on subgroups of components. This underscores the need for
decision-support assessment methods in the absence of directly applicable
toxicological data.

2.2 Weight-of-evidence evaluation method

Component-based approaches are most useful when augmented with a weight-
of-evidence (WOE) evaluation of the potential for nonadditive interactions
among the components in the mixture. The WOE method used by ATSDR was
proposed by Mumtaz and Durkin [10]. 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. The BINWOE
determination is an end-point-specific 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 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 (ATSDR [1]).
The combined WOE score for a mixture is a sum of all BINWOE scores for the
binary pairs in the mixture. A combined WOE score close to 0 indicates no
deviation from additivity. In contrast, combined WOE scores that are
considerably different from 0 indicate that a component-based analysis may
underestimate, when >0, or overestimate, when <0, the actual hazard presented
by the exposure scenario. For a TTD analysis, a combined WOE score is
computed for each effect of concern for the mixture.

2.3 Hazard index and target-organ toxicity dose methods

For most mixtures, component-based approaches such the Hazard Index (HI) and
the Target-organ Toxicity Dose (TTD) approaches are recommended. The HI
approach uses, as a default, the assumption of dose additivity to assess the
noncancer health effects of a mixture from the data on the components. The TTD
method, which is a refinement of the HI method, was introduced to
accommodate the assessment of mixtures whose components do not all have the
same critical effect (ATSDR [1]). TTDs are derived similarly to other health
based guidance values such as Minimal Risk Levels (MRLs) (Pohl and Abadin
[12]).

3 Results and discussion

Evaluation of the three mixtures involving radioactive elements presented a real
challenge. No toxicity information was found on any of the mixtures as a single
entity. No physiologically based pharmacokinetic (PBPK) models exist for these
mixtures. Therefore, a component-based approach was proposed to first evaluate
the binary combinations of chemicals in the mixtures. It was further decided that if environmental exposure of the surrounding general population were to occur at these hazardous waste sites, the route of exposure would be mainly oral via contaminated soil and groundwater.

Regarding the first mixture, available reports of chemical use and prior chemical release at the sites of concern indicated that strontium, cobalt, and cesium radionuclides, rather than the stable forms of these metals, are of greatest concern for possible adverse health effects, due primarily to the expectation that the radiation-related effects of exposure to the radionuclides will occur at lower exposure levels of the component than the majority of chemical effects (ATSDR [2]). Cobalt is distributed throughout the body with a relatively short effective clearance half-life (<10 days) while cesium is distributed throughout the body with a longer half-life (~70 days). Both cobalt and cesium emit beta and gamma radiation. The latter is expected to be primarily associated with the health effects induced by these radionuclides (e.g., testicular degeneration, hematological, immunological and neurodevelopmental effects), mainly due to the higher penetration ability as compared to beta radiation. Because the mechanism of action for the two radionuclides is similar, additivity in their joint toxic action is expected. In contrast, strontium preferentially accumulates in bone with a long (18 years) effective half-life and emits primarily beta radiation. Because radioactive strontium affects blood cells (decreased erythrocytes, lymphocytes, neutrocytes), additivity of hematological and immunological effects is expected with cesium and cobalt.

It was further decided that mixtures of PCB congeners would be treated as a single component of concern in the whole mixture, according to the approach used to derive health-based guidance values for PCBs (ATSDR [5]). Information on PCBs and trichloroethylene interaction was obtained from the Moslen et al. [9] study. Pretreatment of rats with Aroclor 1254 by gavage daily for 7 days resulted in a longer mean recovery time after TCE-induced anesthesia compared to rats exposed to TCE alone, with significant increases in trichlorinated urinary metabolites, hepatic serum glutamic-oxaloacetic transaminase (SGOT) and cytochrome P450 activity, and hepatic sodium, potassium, and calcium levels. Anesthesia recovery time was positively correlated with mean SGOT levels. Animals pretreated with Aroclor 1254 showed necrotic bands of pyknotic hepatocytes, with calcium-rich necrotic cells in corresponding regions. No examination of effects of Aroclor 1254 alone was reported. However, Carlson [6] did not report hepatic toxicity as a result of exposure to 25 mg/kg Aroclor 1254 for 6 days in male rats. Thus, it appears that the effect of PCB pretreatment on TCE toxicity is greater than additive. The increase in cytochrome P450 activity induced by Aroclor 1254 is possibly responsible for the increased hepatotoxicity and increased neurotoxicity of TCE.

In summary, additivity is assumed for the effects of radionuclides, and greater than additive for the effect of PCBs on toxicity of TCE. However, no decisions on joint toxic action of other binary combinations of chemicals in the mixture were made because of a lack of relevant information.
Similarly, no information is available on the toxicity of a complete mixture of cyanide, fluoride, nitrate, and uranium. WOE analysis of joint toxic action of the binary combinations indicated that data are lacking for most of the pairs (ATSDR [3]).

A less-than-additive effect of nitrate on the toxicity of cyanide is anticipated, based on high-dose acute data on nitrite injection in humans in combination with the observation that small amounts (~5-10%) of oral nitrate are metabolized to nitrite by bacteria in the gastrointestinal tract. Nitrite-induced formation of methemoglobin, either alone or in combination with other agents, has been used for many years as an antidote to acute cyanide toxicity in humans. Methemoglobin competes with cytochrome c oxidase for cyanide, resulting in diminished inhibition of respiratory function as a result of cyanide exposure. Re-establishment of brain levels of cytochrome oxidase enzyme levels has been demonstrated in acute in vivo studies (Isom and Way [8]; Tadic [18]).

A greater-than-additive effect of cyanide on the toxicity of fluoride is anticipated. Both cyanide and fluoride ions have been demonstrated to affect cellular energy metabolism, with fluoride primarily resulting in decreased glycosylation reactions, while cyanide is an inhibitor of oxidative phosphorylation. These chemicals appear to act independently on different sites of energy metabolism. Szabo et al. [17] demonstrated that fluoride and cyanide have opposite effects on cellular glucose metabolism, with fluoride treatment resulting in a decrease in cellular glucose uptake in cultured cells, while cyanide treatment resulted in increased uptake; the increased glucose uptake resulting from cyanide exposure is thought to represent an increased use of the glycolytic pathways subsequent to inhibition of oxidative metabolism. Co-exposure of the cells to the same concentrations of both fluoride and cyanide resulted in decreased glucose uptake, but not to the same extent as fluoride alone.

A less-than-additive effect of cyanide on the toxicity of uranium radiation was reported. The mechanism by which cyanide reduces the susceptibility to ionizing radiation is not fully understood. Cyanide must be actively inhibiting cytochrome c oxidase to be radioprotective, as demonstrated by Schubert [15], who reported that injection of mice with KCN 2 minutes prior to irradiation with an otherwise 100% lethal dose of gamma radiation resulted in complete protection (100% survival), unless thiosulfate, a cyanide antagonist, was given 5 minutes prior to irradiation, in which case survival was 0%. The protective effect of cyanide was also reported for radiation-induced chromosomal damage in vivo (Schubert et al. [16]. While these studies were performed using isotopes that were not alpha emitters, the mechanism of action for alpha and gamma radiation (ionization events leading to cellular damage) is expected to be similar. Therefore, the mechanisms resulting in a protective effect of cyanide against gamma and X-irradiation are expected to function against ionizations caused by alpha radiation, such as that emitted by uranium isotopes. However, because of the different average path lengths of the types of radiation, the distribution of the emissions from uranium will likely be quite different from a whole-body gamma radiation exposure.
The last mixture is related to a NASA site (ATSDR [4]). As before, the major problem was a lack of relevant data for evaluation of interactions in binary combinations of constituent chemicals. For most pairs, no BINWOEs were derived. Interestingly, one combination showed joint toxic action. It is plausible that strontium-90 will increase the toxic effects of arsenic. There is evidence that strontium inhibits methylation of arsenic in vitro (De Kimp et al. [7]). Because methylation of inorganic arsenic is generally considered to be a detoxification reaction, inhibition of methylation may reasonably be expected to produce a general increase in arsenic toxicity at targets throughout the body.

Mechanistic understanding of the effect of strontium on arsenic is limited. The only relevant study (De Kimp et al. [7]) was conducted in freshly-isolated liver cytosol from adult male Flemish giant rabbits. This species has been shown to be an appropriate model for metabolism of arsenic in humans, and the liver is the primary site of arsenic methylation. While strontium was found to inhibit methylation of arsenic in this test system, so were many other inorganic ions and organic compounds. It was found that certain inorganic cations (most notably Zn^{2+}) stimulated methylation. The authors presented evidence suggesting that zinc may be an essential co-factor for arsenic methylation, and hypothesized that competitive inhibition between strontium (or other divalent cations) and zinc could be responsible for the observed inhibition of methylation in this test system. However, it is not clear that strontium would be present in liver cells in sufficient quantity to have an effect in a complete organism. Although low concentrations of strontium can be found in soft tissues, approximately 99% of the total body burden is contained in the skeleton. No studies have been done to investigate whether strontium would inhibit arsenic methylation in a whole animal model.

Another prediction was made for jet fuels and trichloroethylene. These two are expected to produce additive effects on neurological endpoints. Jet fuels and trichloroethylene both produce neurological, hepatic, and immunological effects. Both jet fuels and trichloroethylene are believed to inhibit neuronal function by their physical presence in neuronal membranes, and as such, are expected to produce additive effects on the central nervous system. However, data directly corroborating this prediction are not available. Both trichloroethylene and jet fuels are believed to elicit hepatic and immunological effects as a result of metabolism to reactive products, possibly involving reactive oxidative species. However, understanding of these mechanisms is insufficient to reliably predict the influence, which might involve competitive inhibition and induction of various cytochrome P-450 isozymes, of exposure to trichloroethylene on the hepatic or immunological effects of jet fuels.

4 Recommendations

As discussed above, information on the joint toxic action of chemicals in featured mixtures was scarce. In the absence of an adequate evaluation, the default assumption of additivity is recommended. These methods are to be applied only if hazard quotients for two or more of the compounds equal or
exceed 0.1 (ATSDR [1]; Wilbur [19]). Hazard quotients are the ratios of exposure estimates to noncancer health guideline values, such as MRLs. If only one or if none of the compounds have a hazard quotient that equals or exceeds 0.1, then no further assessment of the joint toxic action is needed because additivity and/or interactions are unlikely to result in significant health hazard. If one or more of the endpoint-specific hazard indices exceed 1, they provide preliminary evidence that the mixture may constitute a health hazard due to the joint toxic action of the components on that endpoint. As discussed by ATSDR (2004a), the exposure-based assessment of potential health hazard is used in conjunction with biomedical judgment, community specific health outcome data, and community health concerns to assess the degree of public health hazard.

In summary, evaluations of mixtures containing both radioactive and nonradioactive chemicals indicated that joint toxic action is plausible (see interactions of cyanide with uranium and arsenic with strontium). This finding underlines the necessity for further research to fill the data gaps that we have encountered during our evaluation.

References


