INTERACTION PROFILE FOR: ARSENIC, HYDRAZINES, JET FUELS, STRONTIUM-90, and TRICHLOROETHYLENE

U.S. Department of Health and Human Services
Public Health Service
Agency for Toxic Substances and Disease Registry

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PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology (DT) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these 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. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur.

CONTRIBUTORS

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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

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All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be addressed in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this mixture. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

SUMMARY

The mixture of jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90 was chosen to represent potential exposures in the vicinity of sites where past and/or present activities include use and/or release of these materials. Such sites might 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 frequently detected at hazardous waste sites and would not be unexpected at any specific site. The purposes of this profile are: (1) to evaluate data (if available) on the health hazards and corresponding dose-response relationships associated with exposure to this five-component mixture as a whole; (2) to evaluate data on the joint toxic actions of components of this mixture; and (3) to make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

The primary route of exposure for offsite receptors (i.e., receptors located beyond the borders of the site where the materials have been used or released) is expected to be oral for all five of these substances, resulting from contamination of soil and/or ground or surface water. Inhalation is also a potential route of exposure for jet fuels, hydrazines, and trichloroethylene, all of which are volatile. However, due to rapid degradation of hydrazine in air and dispersion of all chemicals during transport offsite, inhalation is expected to be a relatively minor route of exposure for offsite receptors under most conditions. Potential exceptions may occur when contaminated groundwater is used as household water, resulting in volatilization of the chemicals into indoor air, or when contamination of groundwater and subsurface soil results in migration of these chemicals into basements as soil gas. While inhalation is an important route of exposure to arsenic at industrial facilities that generate arsenic particulates (e.g., smelters), it is not relevant to arsenic at the sites being considered here. Catastrophic accidental release of strontium-90 to the air from nuclear facilities is possible, but is beyond the scope of this document.

No studies were located that examined health effects in humans or research animals exposed to mixtures containing jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90, and no physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for this mixture have been developed. Binary weight-of-evidence (BINWOE) analysis of the joint toxic action of the component pairs was indeterminate for most pairs due to scarcity of data regarding joint toxic action of the component pairs

and insufficient understanding of toxic and pharmacokinetic mechanisms of the individual substances, but did predict additivity for depression of the central nervous system from exposure to jet fuels and trichloroethylene and a greater-than-additive effect of strontium on arsenic toxicity due to inhibition by strontium of arsenic metabolism.

Although the BINWOEs were indeterminate for all of the remaining pairs due to insufficient data, the extensive overlap of toxic endpoints for the five mixture components suggests that there is a potential for joint toxic action among these substances. Therefore, it is reasonable to be cautious when evaluating public health concerns for this mixture by assuming additivity.

The hazard index approach is recommended as an additive component-based method for assessing possible health hazards from noncancer effects for mixtures of jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90. The hazard index approach allows for summing across routes of exposure to account for multiple pathways of exposure, which may be important for this mixture. For oral exposure, the lack of health guidance values is problematic and leaves only arsenic and trichloroethylene contributing to the hazard index for oral exposure to the mixture. Because these chemicals affect many of the same sensitive endpoints (neurological, renal, and immunological targets), it is recommended to calculate hazard indexes for oral exposure using both chemicals. For inhalation exposure, intermediate Minimal Risk Levels (MRLs) are available for all three chemicals for which this route is expected to potentially contribute to exposure to offsite receptors at rocket launch sites: jet fuels and hydrazines based on liver effects and trichloroethylene based on neurological effects. Because the central nervous system and the liver are sensitive targets for all three chemicals, it is recommended that inhalation hazard indexes be calculated using all three chemicals together. Application of the target-organ toxicity dose (TTD) modification of the hazard index method is not justified by the existing data set.

For cancer effects, the cancer risk for each substance (calculated from the lifetime average daily intake and the potency factor) is summed to provide an estimate of risk due to the whole mixture. Risk can be summed across routes to account for multiple pathways of exposure.

Additive approaches to assessment for this mixture are only needed when there is reason to believe that two or more chemicals in the mixture contribute significantly to the public health assessment. Therefore, hazard indexes are only calculated if two or more of the individual components have hazard quotients equaling or exceeding 0.1, and cancer risks are summed only if estimated risks exceed $1x10^{-6}$ for at least two components.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
As	arsenic
As_2O_3	arsenic trioxide
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
BrdU	bromo-deoxyuridine
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
CI	confidence interval
DNA	deoxyribonucleic acid
DMA	dimethylarsinic acid
DT	Division of Toxicology
EDTA	ethylenediaminetetraacetic acid
EPA	Environmental Protection Agency
FQPA	Food Quality Protection Act
gastro	gastrointestinal
GST-P	glutathione S-transferase-placental
HEAST	Health Effects Assessment Summary Tables
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LOAEL	lowest-observed-adverse-effect level
m^3	cubic meter
MeV	millions of electron volts
mg	milligram
MMA	monomethylarsonic acid
MRL	Minimal Risk Level
neuro	neurological
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
PBPK	physiologically based pharmacokinetic
PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
pCi	picocurie
ppm	parts per million
RfC	Reference Concentration
RfD	Reference Dose
RR	relative risk
Sr	strontium
$SrCl_2$	strontium chloride
$t_{1/2}$	half-life
TPH	total petroleum hydrocarbons
TTD	target-organ toxicity dose
TUNEL	TdT-mediated dUTP digoxigenin nick end labeling
µg	microgram
µM	micromolar
U.S.	United States
WOE	weight-of-evidence
Y	Yttrium
Zn	Zinc
Zr	Zirconium
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to