INTERACTION PROFILE FOR:
CESIUM, COBALT, STRONTIUM, POLYCHLORINATED BIPHENYLS, 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.

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PEER REVIEW

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All reviewers were selected in conformity with the conditions for peer review specified in CERCLA Section 104(I)(13).

Scientists from 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

Review of Agency for Toxic Substances and Disease Registry's (ATSDR) documents with site-specific information showed that stable and/or radioactive forms of cesium, cobalt, and strontium were found together at seven sites: Oak Ridge, Hanford Site, Brookhaven National Laboratory, Idaho National Environmental and Engineering Laboratory (INEEL), Nevada Test Site, Savannah River Site, and Lawrence Livermore Laboratory. Trichloroethylene was reported together with the radionuclides of cesium, cobalt, and strontium at Brookhaven National Laboratory and INEEL sites. Polychlorinated biphenyls (PCBs) were reported together with the radionuclides of cesium, cobalt, and strontium at Oak Ridge and INEEL sites. The purposes of this profile are: (1) to evaluate data (if available) on health hazards, and their dose-response relationships, from oral exposure to this five-component mixture; (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.

In the event of exposure, the primary route of exposure of nearby populations to these chemicals in soil is likely to be oral, resulting from contamination of soil and/or groundwater. Available reports of chemical use and prior chemical release concerning the sites of concern indicate that strontium, cobalt, and cesium radionuclides, rather than the stable forms of these metals, are of greatest concern for possible adverse health effects. While data on the effects of ingested strontium radionuclides are available, data on the toxic and/or carcinogenic effects of radiocobalt and radiocesium following oral exposure are lacking. However, as the most sensitive effects of the radionuclides are expected to come from emitted radiation, a reasonable estimate as to potentially sensitive targets for oral exposure to radiocobalt and radiocesium can be made from examining the toxicokinetics of the stable compounds, as well as the tissues that are sensitive to external exposure to cobalt or cesium radiation.

Recent ATSDR toxicological profiles are available for all five components that comprise the mixture (ATSDR 1997, 2000, 2001c, 2001d, 2001e). For the information on the mechanisms and health effects of radiation, the ATSDR Toxicological Profile for Ionizing Radiation (ATSDR 1999) was also consulted.

No studies were located that examined health effects in humans or animals exposed to mixtures exclusively containing strontium, cobalt, cesium, trichloroethylene, and PCBs, and no physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for this mixture have been developed. As such, a component-based approach (ATSDR 2001a, 2001b), wherein the potential effect of individual

components on other components in the mixture is evaluated, was used. The weight-of-evidence analysis indicates no evidence sufficient to support the existence of greater-than-additive or less-than-additive joint actions of the component pairs, where recommendations can be made at all. As data are lacking for the majority of the component pairs, the mechanisms of action for each component pair were also analyzed for evidence of joint toxic actions.

Component-based approaches that assume additive joint toxic action are recommended for exposure-based assessments of possible noncancer or cancer health hazards from oral exposure to strontium, cobalt, cesium, trichloroethylene, and PCBs, because there are no direct data available to characterize health hazards (and dose-response relationships) from the five-component mixture. The weight-of-evidence analysis indicated that data are inadequate to characterize the modes of joint action of the components, but the additivity assumption appears to be suitable in the interest of protecting public health since the components have several shared targets of toxicity (organs or organ systems that are individually affected by the components).

A target-organ toxicity dose (TTD) modification of the hazard index approach is recommended for conducting exposure-based assessments of noncancer health hazards. TTDs for several toxicity targets have been derived for each of the components, including TTDs for hematological, immunological, reproductive, neurodevelopmental, and hepatic effects. For assessment of cancer risks from joint toxic action of the mixture, a similar component-based approach is recommended that involves multiplication of intakes of the components by U.S. Environmental Protection Agency (EPA) cancer slope factors and summation of the resultant risk estimates.

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Ah	aryl hydrocarbon
ALI	annual limit on intake
ARS	acute radiation sickness
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
Bq	Becquerel
CDDs	chlorinated dibenzo-p-dioxins
CDFs	chlorinated dibenzofurans
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
Ci	Curie
Co	cobalt
$CoCl_2$	cobalt chloride
CRS	chronic radiation sickness
Cs	cesium
DCVC	S-(1,2-dichlorovinyl)-L-cysteine
DCVG	S-(1,2-dichlorovinyl)glutathione
DNA	deoxyribonucleic acid
DOE	Department of Energy
DT	Division of Toxicology
EADs	early afterdepolarizations
EDTA	ethylenediaminetetraacetic acid
ED_{50}	median effective dose (produces measured effect in 50% of population)
EPA	Environmental Protection Agency
EROD	ethoxyresourufin-O-deethylase
Gy	Gray
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
INEEL	Idaho National Environmental and Engineering Laboratory
iNOS	inducible nitric oxide synthase
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LOAEL	lowest-observed-adverse-effect level
LSE	levels of significant exposure
mg	milligram
mL	milliliter
MRL	Minimal Risk Level
mRNA	messenger ribonucleic acid
mSv	millisievert
NCRP	National Council on Radiation Protection and Measurements
NOAEL	no-observed-adverse-effect level
NRC	Nuclear Regulatory Commission
NTP	National Toxicology Program
PBPK	physiologically based pharmacokinetic
PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
PCBs	polychlorinated biphenyls
PFC	plaque-forming cell
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PTU	6-propyl-2-thiouracil
RfC	reference concentration
RfD	reference dose
SGOT	serum glutamic-oxaloacetic transaminase
Sr	strontium
$SrCl_2$	strontium chloride
SRBC	sheep red blood cells
Sv	Sievert
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCE	trichloroethylene
TEF	toxicity equivalent factor
TEQ	toxic equivalency
TSH	thyroid stimulating hormone
TTD	target-organ toxicity dose
UDP-GT	uridine-5'-diphosphate glucuronyltransferases
µg	microgram
µmole	micromole
U.S.	United States
VOC	volatile organic compound
VT	ventricular tachyrhythmia
WOE	weight-of-evidence

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to