

**INTERACTION PROFILE FOR:
CYANIDE, FLUORIDE, NITRATE, AND URANIUM**

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

May 2004

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 (NTP), 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 (EPA) 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 (WOE) 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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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 included 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 compound. 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

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 U.S. Department of Energy (DOE) facilities, and continues to be used today. In addition, cyanide has been reported with great frequency as a contaminant at NPL sites. Review of ATSDR's documents with site-specific information showed that uranium, fluoride, cyanide, and nitrate were reported at one site (Pantax Plant site), while three-component submixtures were reported at eight additional sites: Eastern Michaud Flats, Monticello Mill, Alcoa/Lavaca Bay, Depue/New Jersey Zinc/Mobil Chemical, Hipps Road Landfill, Riverbank Army Ammunition Plant, Savanna Army Depot, and Santa Susana Field Laboratory. The purposes of this profile are to: (1) evaluate data (if available) on health hazards, and their dose-response relationships, from oral exposure to this four-component mixture; (2) evaluate data on the joint toxic actions of components of this mixture; and (3) make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

Evaluation of the available environmental fate data for the components of the mixture suggests that in the event of exposure, the primary route of exposure of nearby populations to mixtures of these chemicals in soil is likely to be oral, resulting from contamination of soil and/or groundwater. ATSDR toxicological profiles are available for cyanide, uranium, and fluoride (ATSDR 1997, 1999b, 2001d, respectively); these documents are the primary sources of information presented in the Appendices concerning the toxicokinetics, health effects, mechanisms of action, and health guidelines for these chemicals. Neither a toxicological profile nor Minimal Risk Levels (MRLs) are available for nitrate; however, U.S. EPA (IRIS 2002) has derived an oral reference dose (RfD) for nitrate.

No studies were located that examined health effects in humans or animals exposed to mixtures exclusively containing uranium, fluoride, cyanide, and nitrate, and no physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for this mixture have been developed. A component-based approach (ATSDR 2001b, 2001c) was applied, wherein the potential influence of individual components on the toxicity of other components in the mixture is evaluated. For the purposes of component analysis, the toxicity from uranium radiation was considered as a separate element from the chemical toxicity of uranium. As joint action data are lacking for the majority of the component pairs, the mechanisms of action for each component pair were also analyzed for evidence of potential joint toxic actions. The weight-of-evidence analysis suggests greater-than-additive joint actions for one component pair (fluoride and cyanide, in both directions), and less-than-additive joint actions for two of the

component pairs (cyanide's effect on the toxicity of uranium radiation and nitrate's effect on cyanide toxicity).

Component-based approaches that assume endpoint-specific additive joint toxic action are recommended for exposure-based assessments of possible noncancer or cancer health hazards from oral exposure to uranium, fluoride, cyanide, and nitrate, because there are no direct data available to characterize health hazards (and dose-response relationships) from the four-component mixture. The weight-of-evidence analysis indicated that data are inadequate to characterize the modes of joint action of the majority of the components, but the additivity assumption appears to be suitable in the interest of protecting public health.

A target-organ toxicity dose (TTD) modification of the hazard index approach is recommended for conducting exposure-based assessments of noncancer health hazards. Where data are available, TTDs for several toxicity targets have been recommended for each of the components, including TTDs for renal, reproductive, and neurological effects.

TABLE OF CONTENTS

PREFACE	iii
CONTRIBUTORS	v
PEER REVIEW	vii
SUMMARY	ix
TABLE OF CONTENTS	xi
LIST OF FIGURES	xiii
LIST OF TABLES	xiii
LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS	xv
1. Introduction	1
2. Joint Toxic Action Data for the Mixture of Concern and Component Mixtures	3
2.1 Mixture of Concern	3
2.2 Component Mixtures	3
2.2.1 Uranium and Fluoride	3
2.2.2 Uranium Radiation and Fluoride	4
2.2.3 Uranium and Cyanide	6
2.2.4 Uranium Radiation and Cyanide	6
2.2.5 Uranium and Nitrate	7
2.2.6 Uranium Radiation and Nitrate	7
2.2.7 Fluoride and Cyanide	8
2.2.8 Fluoride and Nitrate	8
2.2.9 Cyanide and Nitrate	9
2.3 Relevance of the Joint Toxic Action Data and Approaches to Public Health	10
2.4 Recommendations for Data Needs	20
3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture	21
4. Conclusions	27
5. List of References	29
Appendix A. Background Information for Uranium	33
A.1 Toxicokinetics	33
A.2 Health Effects	33
A.3 Mechanisms of Action	35
A.4 Health Guidelines	36
A.5 Derivation of Target-Organ Toxicity Dose (TTD) Values	37
A.6 References	37

Appendix B. Background Information for Fluoride	41
B.1 Toxicokinetics	41
B.2 Health Effects	43
B.3 Mechanisms of Action	45
B.4 Health Guidelines	47
B.5 Derivation of Target-Organ Toxicity Dose (TTD) Values	48
B.6 References	50
Appendix C. Background Information for Cyanide	53
C.1 Toxicokinetics	53
C.2 Health Effects	54
C.3 Mechanisms of Action	56
C.4 Health Guidelines	57
C.5 Derivation of Target-Organ Toxicity Dose (TTD) Values	58
C.6 References	60
Appendix D. Background Information for Nitrate	63
D.1 Toxicokinetics	63
D.2 Health Effects	64
D.3 Mechanisms of Action	65
D.4 Health Guidelines	65
D.5 Derivation of Target-Organ Toxicity Dose (TTD) Values	66
D.6 References	66

LIST OF FIGURES

Figure 1. Binary Weight-of-Evidence Scheme for the Assessment of Chemical Interactions	13
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LIST OF TABLES

Table 1. Data from 2001 CERCLA Priority List of Hazardous Substances	1
Table 2. Potential Health Effects of Concern for Intermediate and Chronic Oral Exposure to the Mixture Uranium, Fluoride, Cyanide, and Nitrate	2
Table 3. Health Effects Forming the Basis of ATSDR Oral MRLs for Chemicals of Concern	11
Table 4. Effect of Uranium Radiation on Cyanide	14
Table 5. Effect of Cyanide on Uranium Radiation	15
Table 6. Effect of Fluoride on Cyanide	16
Table 7. Effect of Cyanide on Fluoride	17
Table 8. Effect of Cyanide on Nitrate	18
Table 9. Effect of Nitrate on Cyanide	19
Table 10. Matrix of BINWOE Determinations for Neurological, Developmental, Reproductive, Renal, and Carcinogenic Effects of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern	22
Table 11. Target Organ Toxicity Doses (TTDs) and MRLs for Chronic Oral Exposure to Chemicals of Concern	23

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ATSDR	Agency for Toxic Substances and Disease Registry	NPL	National Priorities List
ATP/ADP	adenosine triphosphate/adenosine diphosphate	NTP	National Toxicology Program
BINWOE	binary weight-of-evidence	PBPK	physiologically based pharmacokinetic
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act	PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
DNA	deoxyribonucleic acid	ppm	parts per million
DOE	Department of Energy	RfC	reference concentration
DT	Division of Toxicology	RfD	reference dose
EPA	Environmental Protection Agency	TTD	target-organ toxicity dose
Fe	iron	μmol	micromole
FQPA	Food Quality Protection Act of 1996	UO_2F_2	uranyl fluoride
IARC	International Agency for Research on Cancer	U.S.	United States
ICRP	International Commission on Radiological Protection	WOE	weight-of-evidence
IRIS	Integrated Risk Information System	>	greater than
kg	kilogram	\geq	greater than or equal to
L	liter	=	equal to
LC_{50}	50% lethal concentration	<	less than
LD_{50}	50% lethal dose	\leq	less than or equal to
LOAEL	lowest-observed-adverse-effect level		
mg	milligram		
MRL	Minimal Risk Level		
NADH	nicotinamide adenine dinucleotide phosphate (reduced form)		
NADPH	nicotinamide adenine dinucleotide phosphate (oxidized form)		
NOAEL	no-observed-adverse-effect level		