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.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS:

Mike Fay, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Mark Osier, Ph.D.
Syracuse Research Corporation, Syracuse, NY

Joan Colman, Ph.D.
Syracuse Research Corporation, Syracuse, NY

PEER REVIEW

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

Dr. Christopher Borgert
Applied Pharmacology and Toxicology, Inc.
238 Turkey Creek
10514 Palmetto Boulevard
Alachua, FL 32615
USA

Dr. Kannan Krishnan
Department of Occupational and Environmental Health
University of Montreal
2375 Cote Ste Catherine, Office 4105
Montreal, Quebec H3T 1A8
Canada

Dr. Richard Leggett
Biosystems Modeling Group
Oak Ridge National Laboratory
P.O. Box 2008, 1060 Commerce Park, MS-6480
Oak Ridge, TN 37831-6480

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

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ATSDR	Agency for Toxic Substances and Disease Registry
ATP/ADP	adenosine triphosphate/adenosine diphosphate
BINWOE	binary weight-of-evidence
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
DNA	deoxyribonucleic acid
DOE	Department of Energy
DT	Division of Toxicology
EPA	Environmental Protection Agency
Fe	iron
FQPA	Food Quality Protection Act of 1996
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LC_{50}	50% lethal concentration
LD_{50}	50% lethal dose
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
NPL	National Priorities List
NTP	National Toxicology Program
PBPK	physiologically based pharmacokinetic
PBPK/PD	physiologically-based pharmacokinetic/pharmacodynamic
ppm	parts per million
RfC	reference concentration
RfD	reference dose
TTD	target-organ toxicity dose
µmol	micromole
UO_2F_2	uranyl fluoride
U.S.	United States
WOE	weight-of-evidence
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to