INTERACTION PROFILE FOR SELECTED METALLIC IONS IDENTIFIED IN WASTE WATER FROM UNCONVENTIONAL OIL AND GAS EXTRACTION ACTIVITIES:

BARIUM, CALCIUM, IRON, MAGNESIUM, MANGANESE, SODIUM, AND STRONTIUM

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

July 2023

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.

To carry out these legislative mandates, ATSDR's Office of Innovation and Analytics, Toxicology Section 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 of 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 the first draft of the profile in 2015. The panel consisted of the following members:

1. Dale Hattis, PhD; The George Perkins Marsh Institute; Center for Toxicology, Environment, and Development; Clark University; Worcester, MA.

2. Robert E. Oswald, PhD; Department of Molecular Medicine; Cornell University; Ithaca, NY.

3. Nicole C. Deziel, PhD.; Yale School of Public Health; Yale University; New Haven, CT.

4. Max Costa, PhD; Department of Environmental Medicine; New York University Medical Center; Nelson Institute of Environmental Medicine; Tuxedo, NY.

A second peer review panel was assembled for the second draft of the profile in 2019. The panel consisted of the following members:

1. David C. Dorman, DVM, PhD, DABT, DABVT, ATS; Professor, Toxicology; North Carolina State University, Raleigh, NC.

2. Professor Pascal Houillier, MD, PhD; Renal and Metabolic Diseases Unit; Georges Pompidou Hospital, Paris Descartes University Cordeliers Research Center; Paris, France.

3. Michael Aschner, PhD; Department of Molecular Pharmacology; Albert Einstein College of Medicine Forchheimer 209; 1300 Morris Park Avenue; Bronx, NY.

4. Thomas Benedict Bartnikas, MD, PhD; Manning Assistant Professor of Pathology and Laboratory Medicine; Brown University; Providence, RI.

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

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 purpose of this profile is to investigate the possible joint toxic actions of elevated groundwater levels of selected metallic ions (barium [Ba], calcium [Ca], iron [Fe], magnesium [Mg], manganese [Mn], sodium [Na], and strontium [Sr]) that may occur near unconventional oil and gas (UOG) extraction activities, and potential impacts on human health. Health hazards associated with excess oral exposure to these cations show variability with respect to the most sensitive toxicity targets associated with repeated oral exposure: barium (kidney effects), calcium (kidney effects), iron (gastrointestinal disturbances), magnesium (gastrointestinal disturbances), manganese (nervous system effects), sodium (blood pressure effects), and strontium (bone development effects in children). The focus of this profile is not intended to minimize the importance of understanding and assessing the potential individual and combined (mixtures) effects from other ions and chemicals that may also be present in groundwater contaminated with UOG waste waters. In assessing the available information on possible interactions among these metallic cations, this profile concludes with recommendations for conducting screening-level assessments of public health impacts from repeated joint exposure to mixtures of these seven metallic cations in potentially contaminated groundwater near UOG extraction activities.

ATSDR recommends a component-based approach assuming dose addition for screening-level, exposure-based assessments of potential hazards to public health from repeated oral exposure to mixtures containing barium, calcium, iron, magnesium, manganese, sodium, and strontium. The recommendations include the estimation of an overall screening-level hazard index for all compounds (with no grouping by common adverse outcomes) for an initial Tier 0 human health assessment. In a subsequent Tier 1 analysis, calculation of separate screening-level hazard indexes is recommended for cardiovascular (hypertensive) effects from barium and sodium, neurological effects from barium and manganese, kidney effects from barium, calcium, and magnesium, and gastrointestinal effects from iron and magnesium. Data regarding potential interactions between members of the 21 pairs of cations were assessed in this document. Evidence for coupling of homeostatic mechanisms at the cellular level was available for all 21 pairs of the selected metallic cations; evidence for coupling at the whole-body level of organization was available for 12 pairs. In contrast to the relative wealth of evidence for homeostatic coupling among the seven metallic cations, limited evidence for how repeated oral co-exposure may influence toxic responses was available for only 11 pairs. The evidence for interactions was adequate to suggest possible influences on the critical-effect toxicity of barium and calcium (kidney effects), manganese (neurotoxic effects), sodium (cardiovascular effects), and strontium (skeletal effects).

Hazard index approaches for exposure to mixtures with the subject metals and utilizing a hazard quotient for manganese should be accompanied with qualitative statements about the likely susceptibility of iron-deficient individuals to manganese neurotoxicity, the possible joint toxic action of excess iron and excess manganese on neurological endpoints, and the possible, but uncertain, protective effects of concurrent exposure to excess calcium or magnesium. Calculation of a neurological target toxicity hazard index with hazard quotients for barium and manganese should be accompanied by qualitative statements that: (1) available interaction data for barium and manganese are inadequate to assess whether the joint action of these metals on neurotoxic endpoints may be dose-additive, greater-than-dose-additive, or less-than-dose-additive and (2) accumulation of iron, manganese, and other metals in the brain may jointly act to produce neurological impairment that may not be accounted for in a neurological hazard index based only on barium and manganese.

A hazard quotient for sodium-induced hypertension should be accompanied with a qualitative statement about the possible, but uncertain, protective actions of concomitant high exposure levels to calcium and magnesium against sodium-induced hypertension. Calculation of a cardiovascular hazard index with hazard quotients for barium and sodium should be accompanied by qualitative statements that available interaction data for barium and sodium are inadequate to assess whether the joint action of these metals to produce cardiovascular effects may be dose-additive, greater-than-dose-additive, or less-than-dose-additive and that possible contributions to effects on blood pressure from excess iron are not accounted for in the hazard index due to the lack of adequate data for toxicity target dose (TTD) development.

A hazard quotient for adverse skeletal effects from strontium should be accompanied by qualitative statements about: (1) the uncertainty that excess calcium may counteract the development of strontium-induced skeletal effects and (2) skeletal effects from excess sodium are also possible, but available data are inadequate for TTD development. A hazard quotient for adverse skeletal effects from strontium should also be accompanied with a qualitative statement about the potential beneficial effects of strontium in inhibiting bone resorption and stimulating bone formation in osteoporotic animals and humans presumably via interactions with the calcium-sensing receptor (CaSR).

A hazard quotient for calcium based on kidney stone formation should be accompanied by qualitative statements of the uncertainties associated with calcium's potential to induce kidney stones in humans and magnesium's potential to protect against kidney stone formation in humans. Calculation of a kidney hazard index with hazard quotients for barium, calcium, and magnesium should be accompanied by qualitative statements that available interaction data are inadequate to assess whether the joint toxic action

may be dose-additive, greater-than-dose-additive, or less-than-dose-additive and that possible contributions to adverse kidney effects from excess iron and excess sodium would not be captured in the hazard index due to inadequate data for kidney TTDs for these metallic cations.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

8OHdG	8-hydroxy-2'-deoxyguanosine
ACGIH	American Conference of Governmental Industrial Hygienists
AI	adequate intake
ATSDR	Agency for Toxic Substances and Disease Registry
Ba	barium
BINWOE	binary weight of evidence
BMDL	benchmark dose limit
Ca	calcium
CaSR	calcium-sensing receptor
CASRN	Chemical Abstracts Service Registry Number
CD	cluster of differentiation-68
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CI	confidence interval
DMT-1	divalent metal transporter 1
DNA	deoxyribonucleic acid
DWEL	drinking water equivalent level
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
FDA	Food and Drug Administration
Fe	iron
GABA	gamma-aminobutyric acid
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
L-NAME	N^G-nitro-L-arginine methyl ester
LOAEL	lowest-observed-adverse-effect level
Mg	magnesium
Mn	manganese
MRL	Minimal Risk Level
mRNA	messenger ribonucleic acid
Na	sodium
NAS	National Academy of Sciences
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PAI-1	plasminogen activator inhibitor 1
PBPK/PD	pharmacokinetic/pharmacodynamic
PEL	permissible exposure limit
PND	postnatal day
POD	point of departure
PRI	Population Reference Intake
PTH	parathyroid hormone
REL	recommended exposure limit
RDA	recommended dietary allowance
RfC	reference concentration
RfD	reference dose

SHRSP	spontaneously hypertensive rats, stroke prone
Sr	strontium
TfR	transferrin receptor
TGF-β	transforming growth factor beta 1
TLV	Threshold Limit Value
TRP	transient receptor potential
TRPC	transient receptor potential channel
TTD	target-organ toxicity
TUNEL	terminal dUTP nick end labeling
TWA	time-weighted average
UL	tolerable upper intake level
INII	Unique Ingredient Identifier
UOG	unconventional oil and gas
U.S.	United States
VSMC	vascular smooth muscle cell
WHO	World Health Organization