

1. Introduction

The primary purpose of this *Interaction Profile for Selected Metallic Ions Identified in Waste Water from Unconventional Oil and Gas Extraction Activities* is to evaluate data on the toxicology of the “whole” mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of mixtures of these metals to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern, adequacy of the data as the basis for a mixture health guidance value, and adequacy and relevance of physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence approach is commonly used in these profiles to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although the Agency for Toxic Substances and Disease Registry (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. The profile provides environmental health scientists with ATSDR Office of Innovation and Analytics, Toxicology Section recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios.

ATSDR has received comments from the public expressing concern for possible health effects from exposure to drinking water containing methane, organic chemicals, and metals, potentially from or exacerbated by unconventional oil and gas (UOG) extraction activities in Pennsylvania and West Virginia. In response to these concerns and the rapid expansion of natural gas extraction from shale formations using horizontal drilling and hydraulic fracturing in this and other regions of the United States, ATSDR initially considered the preparation of an Interaction Profile on repeated combined exposure to methane and metallic ions in drinking water but settled on a focus on interactions among metallic cations. Methane, although presenting a flammability and explosive hazard, is generally considered to be inert, and available scientific data are inadequate to establish a specific health hazard of concern for methane (other than as an asphyxiant gas) or evaluate whether co-exposure to metals may affect the expression of methane’s toxicity or whether methane may affect the toxicity of metallic cations, as further explained in the following paragraphs. Cations discussed in this profile are accompanied by anions, which also influence the toxicity of the mixture. For some metals, the anion that accompanies the cation could be of

greater toxicological concern than the cation (e.g., nitrate, nitrite, cyanide, chromate). Anions in the UOG extraction waste water may will influence the toxicity of the soluble mixture. Dietary mineral intakes may confound the impact of barium, calcium, iron, magnesium, manganese, sodium, and strontium from the waste water when these minerals are also present in the conventional daily diet, especially for those minerals that are essential nutrients.

The reader is referred to reports developed by EPA (EPA 2016a, 2016b, 2016c) for more detailed information about potential impacts of UOG extraction activities on groundwater and drinking water and factors that can affect variability in the mineral composition of UOG waste water. Processes by which UOG extraction activities can result in waste water being released into groundwater and surface water are complex and, in general, include the following (EPA 2016 a, 2016b, 2016c):

- Waste water from drilling activities is typically managed via disposal in injection wells or evaporation ponds, application to fields, spreading on roads, and/or treatment and reuse for future oil and gas operations.
- Produced water is often disposed of by injecting it into deep geologic formations via wells that are specifically designed for that purpose. In some cases, produced water can be treated and reused to hydraulically fracture another well.
- The water used for fracking—a mixture of water, sand, and chemicals—is pumped underground at high pressure and wedges rocks apart. The sand stays put in the cracks, creating pathways for oil and gas to travel towards the well. About 40% of the water and chemicals flow back to the surface.

Exposure to drinking water contaminated with methane and metallic ions is possible and can impact water quality, although groundwater contamination can be difficult to attribute to stray gas and metals specifically from natural gas extraction activities. From 2008 through March 2019, the Pennsylvania Department of Environmental Protection (PA DEP 2019) documented 339 cases where the state determined a private water supply was impacted by oil and gas activities in Pennsylvania. These oil and gas activities include “operations associated with both conventional and unconventional drilling activities that either resulted in a water diminution event or an increase in constituents above background conditions.” Another possible hazard associated with methane in drinking water is the initiation of chemical and biological reactions which could result in reductive dissolution of iron and manganese (EPA 2016a).

In studies of Pennsylvania private drinking water wells, elevated levels of methane, ethane, or propane, but not salts, metals, or radioactivity, were found in a subset of drinking water wells within a 1-km radius of shale gas extraction sites (Jackson et al. 2013a; Osborn et al. 2011). Another study identified subsets of drinking water wells in Pennsylvania and Texas (overlying the Marcellus and Barnett Shales, respectively) in which methane, ethane, or propane concentrations were increasing with time (Darrah et al. 2014). Isotope and compositional data for noble and hydrocarbon gases suggested that contamination in these subsets of wells, located <1 km from gas extraction sites, was associated with deficiencies in gas well casings or cements (Darrah et al. 2014). Other studies have hypothesized that natural gas in shallow aquifers occurs naturally from microbial methane production in aquifers or from gas-bearing geological formations of intermediate depth between aquifers and underlying shale formations, and is not related to gas extraction activities (Baldassare et al. 2014; Kornacki and McCaffrey 2011; Molofsky et al. 2013).

Waste fluids from hydraulic fracturing shale gas extraction activities (including drill cuttings, flowback water, and produced water) are known to contain relatively high levels of salinity, metals, and naturally occurring radioactivity, compared with surface streams (Barbot et al. 2013; Brown 2014; EPA 2015; Haluszczak et al. 2013; Jackson et al. 2013b; Lampe and Stolz 2015; Warner et al. 2013). Appendix I Tables I-1, I-2, and I-3 list concentrations of inorganic ions in waste water samples from several shale formation UOG extraction sites in the United States (Barbot et al. 2013; Haluszczak et al. 2013; Jackson et al. 2013b). Metallic cations detected in the waste water samples and listed in approximate order of decreasing average concentrations in mg/L are: sodium (Na, ~5,000–24,000) > calcium (Ca, ~2,000–11,000) > strontium (Sr, ~20–2,300) = barium (Ba, ~1–2,000) > magnesium (Mg, ~75–630) > iron (Fe, ~25–75) > manganese (Mn, ~4–45). These data emphasize the possibility that metals in UOG waste water could contaminate drinking water, if they enter into surface waters or underground aquifers. Confirming empirical data for this possibility, however, are not available.

Disposal options for UOG activities include recycling of waste fluids for shale gas operations, injection into deep disposal wells, and treatment in publicly owned or commercially operated waste water treatment plants before release into surface streams (Warner et al. 2013). Waste water treatment operations can include addition of Na_2SO_4 to remove metals (and salts) as solid precipitates, which are subsequently placed in landfills (Warner et al. 2013). Barium and radium levels in effluent from a western Pennsylvania treatment plant were substantially decreased by about 90%, compared with the waste water, but ^{226}Ra levels in stream sediments at the point of discharge were about 200 times higher than background and upstream sediment levels (Warner et al. 2013). In addition, elevated concentrations of bromide and chloride concentrations were found in stream samples collected >300 m downstream,

compared with upstream and background samples (Warner et al. 2013). Because Pennsylvania geology generally is not compatible with deep injection wells, UOG waste water has been transported to Ohio for deep injection disposal (Brown 2014). Based on Brown (2014), Pennsylvania had 6 deep injection wells, whereas Ohio had 177 and Texas had 50,000. It is unlikely that UOG extraction waste water components will migrate from deep injection wells to shallow aquifers, but casing issues/failures and resulting spill events at gas well sites, at deep injection sites, and during transport are possible ways by which UOG extraction waste water components could enter into surface streams or shallow aquifers.

ATSDR decided that including methane in an Interaction Profile for potential mixtures in waste water generated from gas extraction activities would not be useful, because the human health hazards associated with repeated exposure to methane gas by inhalation or methane gas dissolved in water are not well characterized. Associations between repeated exposure of humans or laboratory animals to methane and specific health hazards have not been established. Thus, even though there is public concern for possible health hazards from methane gas in drinking water, available scientific data are inadequate to establish a specific health hazard of concern or evaluate whether co-exposure to metals may affect the expression of methane's toxicity. Conversely, available scientific data are inadequate to determine whether the presence of methane in groundwater may influence potential toxic effects of metals or water chemistry (e.g., solubility of metals). Methane is considered to be relatively inert (although of high flammability), and its toxic effects are thought to be restricted to its action as an asphyxiant gas. The presence of methane in waste water from UOG extraction activities may alter dissolution and solubility of metals and these changes could affect exposures to those metals (EPA 2016a; Konrad and Lankau et al. 2005; Loomer et al. 2018; Vengosh et al. 2014).

ATSDR decided that preparing an Interaction Profile on repeated combined drinking water exposure to metals potentially elevated in groundwater near UOG extraction activities would be more useful, because: (1) elevated concentrations of metallic cations in UOG waste fluids have been measured in several studies; (2) the toxicities of repeated exposure to several metals identified in UOG extraction waste waters are well characterized; and (3) samples of UOG extraction waste waters from the Marcellus Shale in Pennsylvania were cytotoxic to cultured human BEAS-2B cells and transformed them to carcinogenic cells that produced tumors in mice following subcutaneous injection (Yao et al. 2015). Radioactivity levels were below detection limits (by beta detectors and gamma scintillation counters) in the waste water samples used in the BEAS-2B studies, and the samples were filtered through 0.22 μm polyethersulfone membrane filters to remove possible biotic materials and large organic molecules and allow small particles containing metals to remain in the test mixtures of chemicals. Yao et al. (2015) proposed that

metallic cations present in the test substance filtrates could account for a considerable fraction of the observed *in vitro* toxicity but noted that they could not discern if the “transformation activity was solely from Ba, Sr, or other metals that have been detected in the flow back waters at lower levels.”

For the focus of this Interaction Profile, ATSDR selected the seven metallic cations that have been detected in UOG extraction waste water samples at the highest elevated concentrations: barium, calcium, iron, magnesium, manganese, sodium, and strontium (see Appendix I). Relative toxicity was not considered in the selection of the metallic cations. ATSDR believed that it was important to evaluate evidence for interactions among each of the metallic cations, even though reported concentrations for cations with the highest values (calcium and sodium) were at least an order of magnitude higher than those metallic cations with the lowest concentrations in UOG extraction waste water samples (iron and manganese) (see Appendix I). The toxicities of several of these cations are well characterized (e.g., barium, manganese, sodium, and strontium), and several of these cations are essential elements that are only toxic at very elevated intakes (i.e., calcium, iron, and magnesium). The oral route was selected as the focus, because this would be the primary route of exposure if groundwater or drinking water wells become contaminated from repeated spills or leakage from waste water holding facilities, and oral toxicity values for the relatively toxic metallic cations are available. Thus, the exposure scenario of greatest concern for this mixture and interaction profile is chronic-duration, environmentally relevant oral exposure to contaminated drinking water. Environmentally relevant concentrations of the subject cations in groundwater and drinking water wells are expected to be lower than concentrations detected in UOG extraction waste water samples (see Appendix I), due to dilution and ground filtering. Noncancer effects from these cations were the focus of this profile because none of them have cancer weight-of-evidence determinations or cancer slope factors, which would be used in public health assessments (see Appendices A–G).

ATSDR recognizes that exposure while bathing or showering is possible via the skin or inhaled via respirable droplets, but assumes that such exposure scenarios will be secondary to oral exposure to metallic cations. It is also recognized that any assessment of the possible public health impacts of metallic cations present at elevated levels in UOG extraction waste waters should acknowledge possible toxicity contributions of other components in these fluids; it should not be assumed that the mixture of these five chemicals is representative of the full hydraulic fracturing waste fluid mixture.

As discussed in Appendix J, a literature search was conducted to identify noncancer and cancer toxicity, toxicokinetic, and interaction data from studies of humans and laboratory animals, as well as mechanistic

studies using tissue, cell, or *in vitro* systems. The search targeted studies mentioning two or more of the metals of interest. The toxicologist selected interaction studies with whole-body exposure scenarios with mammals, but did not exclude interaction studies conducted with isolated cell components, cells, or tissues.

Health guidance values for repeated oral exposure were identified by searching ATSDR (<http://www.atsdr.cdc.gov/toxprofiles/index.asp>), U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) (<http://www.epa.gov/iris/index.html>), and the National Academy of Sciences (NAS) (<https://www.nap.edu>) for minimal risk levels (MRL), reference doses/concentrations (RfD/RfC), and tolerable upper intake limits (UL), respectively. None of the subject metallic cations have been assessed for carcinogenicity by the International Agency for Research on Cancer (IARC; <https://monographs.iarc.fr/agents-classified-by-the-iarc/>) or the National Toxicology Program (NTP; <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html>), and no cancer slope factors are available (see Appendices A–G). The EPA IRIS classified barium, manganese, and strontium in cancer Group D, *not classifiable as to human carcinogenicity*, and has not assessed the carcinogenicity of calcium, iron, magnesium, or sodium. Critical endpoints (i.e., the most sensitive effects) forming the basis of ATSDR MRL health guidance values for noncancer toxic effects from repeated oral exposure are tabulated in Table 1. Appropriate ATSDR oral MRL values were not available for some of the metallic cations: calcium, iron, magnesium, manganese, and sodium. For the first four cases of essential metals, health guidance values for repeated oral exposure derived by the NAS (ULs) were used to identify critical effects. For manganese, EPA’s oral RfD was used (see Appendices A–G for additional details). The following critical effects were identified for repeated oral exposure to each metal of concern: barium (kidney effects), iron (gastrointestinal effects), calcium (kidney stones), magnesium (diarrhea)manganese (neurobehavioral effects), sodium (hypertension), and strontium (skeletal effects).

Table 1. Noncancer Health Guidance Values and Critical Endpoints for the Selected Metallic Cations^a

	Inhalation (mg/m ³) ^b			Oral (mg/kg/day) ^b			
	Intermediate MRL	Chronic MRL	RfC	Intermediate MRL	Chronic MRL	RfD	UL ^c
Barium	–	–	–	0.2 (Kidney)	0.2 (Kidney)	0.2 (Kidney)	–
Calcium	–	–	–	–	–	–	36 (Kidney)
Iron	–	–	–	–	–	–	0.6 (GI)

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	Intermediate MRL	Chronic MRL	RfC	Intermediate MRL	Chronic MRL	RfD	UL ^c
Magnesium	–	–	–	–	–	–	5 (GI)
Manganese	–	0.003 (Neuro)	0.0005 (Neuro)	–	–	0.14 (Neuro) ^d	0.16 (Neuro)
Sodium	–	–	–	–	–	–	33 (Cardio)
Strontium	–	–	–	2 (Skeletal)	–	0.6 (Skeletal)	–

^aSee Appendix H for more details.

^bNo acute MRLs were derived for any of the metals of concern.

^cDoses were converted from mg/day to mg/kg/day using an assumed body weight of 70 kg.

^dATSDR did not derive oral MRLs for manganese. The EPA RfD and the NAS UL are similarly based on a lack of adverse neurological effects associated with average manganese intake levels in Western diets (see Appendix E).

Cardio = cardiovascular; GI = gastrointestinal; MRL = Minimal Risk Level; Neuro = neurotoxicity; RfC = reference concentration; RfD = reference dose; UL = tolerable upper intake level

Based on the reviews in the ATSDR or NAS documents deriving the health guidance values, some biological systems are adversely affected by repeated exposure to more than one of the subject metallic cations (see Appendices A–G). Table 2 (prepared from information in Appendices A–G) describes common targets from repeated oral exposure (not necessarily the critical effects) as the cardiovascular system for barium, sodium, and potentially iron, the nervous system for barium, iron, and manganese, the gastrointestinal system for barium, iron, and magnesium, and the kidney for barium, calcium, magnesium, and potentially iron. Additional information on these toxic effects, as well as toxicokinetic and mechanistic considerations, are presented in Appendices A–G. In addition, Toxicity Target Doses (TTDs) for less sensitive effects (i.e., effects occurring at doses higher than those associated with the critical effect for the health guidance value) were derived, if available dose-response data in the review documents were sufficient for derivations. Individuals at risk for primary or secondary iron overload due to altered iron absorption/uptake/excretion because of genetic or disease factors or extremely high oral intakes may develop systemic toxicity involving many organs, particularly the liver and heart, but available dose-response data were insufficient to derive TTDs for these high-dose iron effects (see Appendix C). Information included in the appendices is intended to provide public health assessors with a broad, accurate overview of the toxicity of individual compounds, and is based primarily on existing

Table 2. Noncancer Targets of Subchronic and Chronic Oral Toxicity of Selected Metallic Cations^a

Endpoint	Affected by:						
	Barium	Calcium	Iron	Magnesium	Manganese	Sodium	Strontium
Cardiovascular	Yes	No	With overload ^b	No	No	Yes, <i>CUL</i>^a	No
Neurological	Yes	No	With overload	No	Yes, <i>cRfD</i>, <i>UL</i>^c	No	No
Skeletal	No	No	No	No	No	Limited evidence	Yes, <i>CMRL</i>, <i>RfD</i>
Kidney	Yes, <i>CMRL</i>, <i>RfD</i>	Yes, <i>CUL</i>	With overload	Yes	No	Secondary to cardiovascular	No
Gastrointestinal	No	No	Yes, <i>CUL</i>	Yes, <i>CUL</i>	No	No	No
Respiratory	No	No	No	No	No	Limited evidence	No
Liver	No	No	With overload	No	No	No	No
Reproductive	No	No	With overload	No	Yes	No	No

^aCritical effects for derivation of health guidance values (MRLs, RfDs, or ULs) are bolded and italicized. Additional information on other health effects associated with higher exposures to the subject metallic ions is presented in Appendices A–G. Available data were adequate to derive TTDs for cardiovascular and neurological effects from repeated oral exposure to barium (Appendix A). For iron, data were inadequate to derive a TTD for neurotoxicity. For magnesium, data were adequate to derive a TTD for kidney effects (Appendix D). For manganese, data were adequate to derive a TTD for reproductive effects, but the resultant value was equivalent to the RfD. For the other cations, data were inadequate to derive oral TTDs for less sensitive effects occurring above the critical effect for the MRL, RfD, or UL (see Appendices A–G).

^bIndividuals susceptible to primary or secondary iron overload due to genetic disorder/polymorphism or disease state can develop systemic iron toxicity (cardiovascular, neurological, kidney, liver, or reproductive); limited evidence exists for iron overload symptoms in some populations with unusually high dietary intakes in food or drinking water. Available dose-response data were inadequate to derive TTDs for high-dose effects from iron (Appendix C).

^cATSDR (2012) did not derive a chronic or intermediate-duration oral MRL for manganese. The RfD for manganese (0.14 mg/kg/day) is recommended for ATSDR public health assessments in the absence of a chronic oral MRL. The RfD is similar in value to the NAS UL for manganese (0.16 mg/kg/day) and is similarly based on a lack of adverse effects associated with average manganese intake levels in Western diets (Appendix E).

CMRL = chronic-duration Minimal Risk Level (Agency for Toxic Substances and Disease Registry); cRfD = chronic-duration reference dose (U.S. Environmental Protection Agency); cUL = chronic tolerable upper intake limit (National Academy of Sciences)

ATSDR Toxicological Profiles with supplementation information from other public health, occupational health, or regulatory agency guidance documents (e.g., NAS, European Food Safety Authority [EFSA], IRIS, American Conference of Governmental Industrial Hygienists [ACGIH]). In instances where guidance documents were limited to older NAS documents (sodium, iron) and/or specific information was not included in available public health guidance documents (e.g., mechanisms of toxicity), reviews and meta-analyses from the peer-reviewed literature were included as appropriate. Appendices are not intended to provide a comprehensive review of the primary literature. Primary literature reviewed for this document was limited to studies focusing on possible interactions among the subject metallic cations.