1. Introduction

The primary purpose of this Interaction Profile for jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90 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 this mixture 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 Minimal Risk Level (MRL), and adequacy and relevance of physiologically-based pharmacokinetic/pharmaco-dynamic models (PBPK/PD) for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence (WOE) 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 Division of Toxicology's (DT) 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.

The mixture of jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90 was chosen to represent potential exposures in the vicinity of sites where past and/or present activities include use and/or release of these materials. Such sites might include rocket testing facilities, air force bases, and similar installations. Activities at such sites might include use of jet fuels and hydrazines as aircraft and rocket fuels and trichloroethylene as a solvent to clean engine components. Such sites sometimes include or are co-located with nuclear research facilities or radioactive waste storage sites, where strontium-90 may be found in spent nuclear fuel rods. Arsenic, although not necessarily used or produced at such sites, is frequently detected at hazardous waste sites and would not be unexpected at any specific site.

The primary route of exposure for offsite receptors (i.e., receptors located beyond the borders of the site where the materials have been used or released) is expected to be oral for all five of these substances, resulting from contamination of soil and/or ground or surface water. Inhalation is also a potential route of exposure for jet fuels, hydrazines, and trichloroethylene, all of which are volatile. However, due to rapid

degradation of hydrazine in air and dispersion of all chemicals during transport offsite, inhalation is expected to be a relatively minor route of exposure for offsite receptors under most conditions. Inhalation exposure may occur when contaminated groundwater is used as household water, resulting in volatilization of the chemicals into indoor air, or when contamination of groundwater and subsurface soil results in migration of these chemicals into basements as soil gas. While inhalation is an important route of exposure to arsenic at industrial facilities that generate arsenic particulates (e.g., smelters), it is not relevant to arsenic at the sites being considered here. Catastrophic accidental release of strontium-90 to the air from nuclear facilities is possible, but is beyond the scope of this document.

Before evaluating the relevance of interactions data for these substances, an understanding of the endpoints of concern for this mixture is needed. The endpoints of concern include the critical effects that are the bases for MRLs, as well as other sensitive endpoints of the individual substances. Endpoints in common to multiple substances that may become significant due to additivity or interactions are also considered.

Jet fuels are complex mixtures of hydrocarbons produced by distillation of petroleum crude oil. Most jet fuels (e.g., JP-5, JP-7, JP-8) are middle distillates similar in composition to kerosene, although some (e.g., JP-4) also include lower boiling naphtha streams, like those used to produce gasoline. For jet fuels and related substances, intermediate and chronic inhalation MRLs are available based on liver effects (hepatocellular fatty change, hepatic inflammation) in animal studies (ATSDR 1995a, 1995b, 1998). Liver effects were also reported after oral exposure to jet fuels, although the oral data were insufficient to support derivation of MRLs. Other endpoints of concern for jet fuels are central nervous system depression, which is a well-known effect of jet fuels in humans exposed by any route of exposure, and immunosuppression. While jet fuels have been shown to produce hyaline droplet nephropathy in male rats, this effect is not predictive of renal effects in humans and is, therefore, not considered in this analysis. Jet fuels are not genotoxic and have not been demonstrated to be carcinogenic. See Appendix A for more information.

The hydrazines considered in this document are hydrazine and 1,1-dimethylhydrazine, which have both been used as rocket fuel. Both of these compounds have intermediate inhalation MRLs based on liver effects (ATSDR 1997a). Oral data confirm that the liver is a target by this route as well, but the data are too limited to support MRL derivation. The central nervous system is a prominent target of hydrazines in humans and animals by any route of exposure. Other targets of concern for hydrazines include the respiratory tissues (following inhalation exposure), the blood (anemia), and the reproductive organs of

both males and females (ovarian and testicular atrophy). Both hydrazine and 1,1-dimethylhydrazine have been demonstrated to be genotoxic and have been shown to produce multiple tumor types in rodents by inhalation, oral, and parenteral exposure. The U.S. Environmental Protection Agency (EPA) has derived an oral slope factor and inhalation unit risk for hydrazine (IRIS 2001). Further details regarding hydrazines can be found in Appendix B.

The most sensitive targets for trichloroethylene are the central nervous system (central nervous system depression, neurobehavioral deficits, hearing loss) and the liver (changes in serum cholesterol and bile acids, liver enlargement, and cellular hypertrophy). Trichloroethylene has acute and intermediate inhalation MRLs and a draft chronic reference concentration (RfC) based on central nervous system effects, and an acute oral MRL based on neurological effects and draft chronic oral reference dose (RfD) based on liver effects (ATSDR 1997b; EPA 2001). Other sensitive targets for trichloroethylene are the kidneys (increased kidney weights and cytomegaly and karyomegaly in renal tubular epithelial cells), endocrine system (altered hormone levels), immune system (depressed immune function, autoimmune disease), male reproductive system (decreases in sperm count and motility), and developing fetus (cardiac and eye malformations, neurobehavioral alterations). Recent analyses have concluded that trichloro-ethylene is probably carcinogenic to humans (EPA 2001; IARC 1995; NTP 2001), and EPA (2001) has derived draft oral slope factors and inhalation unit risks for the chemical. Appendix C contains additional information regarding trichloroethylene.

For this mixture, exposure to arsenic is assumed to be entirely by the oral route, as discussed above. Chronic oral exposure to arsenic produces characteristic dermal lesions in humans that are the basis for the chronic oral MRL (ATSDR 2000) and EPA's chronic oral RfD (IRIS 2001). A provisional acute oral MRL was based on facial (periorbital) edema and gastrointestinal irritation in humans (ATSDR 2000). Other endpoints of concern for ingested arsenic are vascular disease, peripheral and central neuropathy, anemia, leukopenia, and renal effects, all of which have been observed in humans. Arsenic is a known human carcinogen, and EPA has derived an oral slope factor for this chemical (IRIS 2001). A point of interest is that there appears to be no good animal model for arsenic toxicity in humans. No other species has been found to develop the arsenic effect of greatest concern, cancer in the skin and other organs. Nor have the studied species of animals been found to develop the noncancer skin lesions seen in humans exposed to arsenic. The species most often used in interactions studies, the rat, is significantly different from humans in terms of arsenic metabolism, distribution, and health effects. For more information on arsenic, see Appendix D.

As discussed previously, exposure to strontium-90 for this mixture is assumed to be entirely by the oral route. ATSDR (2001c) did not derive oral MRLs for strontium-90, and EPA has not derived an RfD (IRIS 2001). Since radiostrontium is preferentially retained in bone, and therefore has a long biological half-life, internal exposures of any duration will lead to chronic internal exposure to ionizing radiation. Consequently, the most significant effects of exposure to absorbed radioactive strontium are necrosis and cancers of bone, bone marrow, and tissues adjacent to bone. Noncancer effects include dystrophic and osteolytic lesions in bone, anemia, and immunosuppression. Radioactive strontium is a known human carcinogen. EPA (1997) has calculated oral slope factors (lifetime risk per picocurie [pCi]) for ingested strontium-90 (4.09×10^{-11} for ^{90}Sr and 5.59×10^{-11} for ^{90}Sr plus disintegration products). For more details, see Appendix E.

Information on the toxicity of the individual substances in the jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90 mixture is summarized in Tables 1–3. Table 1 shows the availability of MRLs and RfDs/RfCs for the individual substances. The availability of cancer assessments is shown in Table 2. Table 3 displays the endpoints of concern for each substance. Additional information about the individual substances can be found in Appendices A–E.

Table 1. Critical Endpoints for Noncancer Health Guidance Values for the Mixture of Jet Fuels, Hydrazines, Trichloroethylene, Arsenic, and Strontium-90

	Inhalation				Oral			
	Acute MRL	Intermediate MRL	Chronic MRL	RfC	Acute MRL	Intermediate MRL	Chronic MRL	RfD
Jet fuels								
JP-4	—	Liver	—	—	—	—	—	—
JP-5	—	Liver	—	—	—	—	—	—
JP-7	—	—	Liver	—	—	—	—	—
JP-8	—	Liver	—	—	—	—	—	—
Kerosene	—	Liver	—	—	—	—	—	—
Hydrazines								
Hydrazine	—	Liver	—	—	—	—	—	—
1,1-Dimethyl-hydrazine	—	Liver	—	—	—	—	—	—
Trichloroethylene	Neuro	Neuro	—	Neuro	Neuro	—	—	Liver
Arsenic[a]					Dermal/ gastro[b]	—	Dermal	Dermal
Strontium-90[a]					—	—	—	—

[a]Inhalation exposure is not relevant for these chemicals under the assumed conditions.
[b]Provisional value

MRL = Minimal Risk Level; RfC = reference concentration; RfD = reference dose

Table 2. Cancer Assessments for the Mixture of Jet Fuels, Hydrazines, Trichloroethylene, Arsenic, and Strontium-90

	Weight-of-evidence category			Basis for quantitative assessment		
	IARC[a]	NTP[b]	EPA[c]	Inhalation unit risk	Oral slope factor	Genotoxicity
Jet fuels	3	—	—	—	—	Negative
JP-4						
JP-5						
JP-7						
JP-8						
Kerosene						
Hydrazines						
Hydrazine	2B	R	B2	Nasal tumors	Liver tumors	Positive
1,1-Dimethyl-hydrazine	2B	R	—	—	—	Positive
Trichloroethylene	2A	R	B1	Kidney tumors	Liver and kidney tumors, lymphoma	Weak positive
Arsenic[d]	1	K	A		Dermal tumors	Mixed: weak mutagen, but clastogenic
Strontium-90[d]	1	—	A		Internal tumors	Positive

[a]1 = carcinogenic to humans; 2A = probably carcinogenic to humans; 2B = possibly carcinogenic to humans; 3 = not classifiable as to carcinogenicity in humans; 4 = probably not carcinogenic to humans

[b]K = known to be a human carcinogen; R = reasonably anticipated to be a human carcinogen

[c]A = human carcinogen; B = probable human carcinogen (B1 based on human data, B2 based on animal data); C = possible human carcinogen; D = not classifiable as to human carcinogenicity; E = evidence of non-carcinogenicity for humans

[d]Inhalation exposure not relevant for these chemicals under the assumed conditions.

EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; NTP = National Toxicology Program

Table 3. Potential Health Effects of Concern for Mixtures of Jet Fuels, Hydrazines, Trichloroethylene, Arsenic, and Strontium-90

Jet fuels	Hydrazines	Trichloroethylene	Arsenic	Strontium-90
Hepatic[a]	**Hepatic**[a]	**Neurological**[a]	**Dermal**[a]	Hematological
Neurological	Respiratory	**Hepatic**[a]	**Gastrointestinal**[a]	Musculoskeletal
Immunological	Hematological	Renal	Cardiovascular	Immunological
	Neurological	Endocrine	Hematological	Cancer
	Reproductive	Immunological	Renal	
	Cancer	Reproductive	Neurological	
		Developmental	Immunological	
		Cancer	Cancer	

[a]basis for MRL/RfC/RfD

MRL = Minimal Risk Level; RfC = reference concentration; RfD = reference dose