3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture

As discussed by ATSDR (1992, 2001a), exposure-based health assessments are used, in conjunction with evaluation of community-specific health outcome data, consideration of community health concerns, and biomedical judgement, to assess the degree of public health hazard presented by mixtures of hazardous substances released into the environment.

Due to the lack of data regarding toxicity of the mixture of jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90, a component-based approach is recommended to assess potential public health effects associated with exposure to this mixture. Because of the extensive overlap of toxic endpoints for the five components of this mixture, the specific recommendation for this mixture is to assume additivity among the mixture components. BINWOE analysis of the joint toxic action of the component pairs was indeterminate for most pairs due to scarcity of data available regarding joint toxic action of the component pairs and insufficient understanding of toxic and pharmacokinetic mechanisms of the individual substances, but did support the assumption of additivity for depression of the central nervous system from exposure to jet fuels and trichloroethylene. Greater-than-additive effects were predicted for the effect of strontium-90 on general arsenic toxicity, due to inhibition of arsenic metabolic detoxification by strontium.

The hazard index is a component-based approach that assumes additivity for noncancer effects (ATSDR 2001a). In this approach, the ratio of exposure level to health guidance value (hazard quotient) for each substance affecting a particular endpoint is summed to provide a measure of hazard for the whole mixture. For cancer effects, the cancer risk for each substance (calculated from the lifetime average daily intake and the potency factor) is summed to provide an estimate of risk due to the whole mixture (ATSDR 2001a). These approaches incorporate the assumptions of dose addition for noncancer effects and response addition for cancer.

Because it assumes dose addition, the hazard index is most appropriately applied to components that cause the same effect by the same mechanism of action. However, the method is frequently applied to components with the same critical target organ or critical effect (effect that is the basis for the MRL, RfD, or other health guideline), without regard to mechanism of action, and may take into consideration other sensitive targets beside the critical target. Use of the dose-additivity assumption is likely to produce

estimates of health hazard that range from appropriate to somewhat conservative, and which are therefore protective of public health (ATSDR 2001a).

Specific recommendations for implementing these approaches for noncancer and cancer effects are presented in the *Guidance Manual for the Assessment of the Joint Toxic Action of Chemical Mixtures* (ATSDR 2001a). Figure 2 of the guidance document shows that hazard indexes are only calculated if two or more of the individual components have hazard quotients equaling or exceeding 0.1. If only one or if none of the components has a hazard quotient that equals or exceeds 0.1, then no further assessment of the joint toxic action is needed, since additivity and/or interactions are unlikely to result in a significant health hazard. Similarly, Figure 3 of the guidance document shows that cancer risks are summed only if estimated risks exceed $1x10^{-6}$ for at least two components.

Suggestive evidence that exposure to the mixture may constitute a hazard is provided when the hazard index for a particular exposure scenario exceeds 1. Although there is no direct quantitative relationship between hazard index and risk, concern for the possibility of a health hazard increases with increasing value of the hazard index above 1. An important point to note for the mixture of jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90, where exposure to some components may be by multiple pathways, is that the route-specific hazard indexes for a given duration and endpoint (or cancer risks) can be summed to account for exposure by multiple pathways (e.g., inhalation hazard index + oral hazard index = overall hazard index).

Critical endpoints for the health guidance values available for jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90 are shown in Table 1 in the Introduction. Other sensitive endpoints for these five substances are shown in Table 3 of the Introduction. In the absence of oral MRLs or RfDs for jet fuels, hydrazines, and strontium-90, oral hazard quotients cannot be calculated for these chemicals. This leaves only arsenic and trichloroethylene contributing to the hazard index for oral exposure to the mixture. Although the critical endpoints for these chemicals differ (neurological and hepatic effects for trichloroethylene, and dermal and gastrointestinal effects for arsenic), Table 3 shows that neurological, renal, and immunological endpoints are sensitive targets for both chemicals. Because these chemicals affect many of the same endpoints, it is recommended to calculate hazard indexes for oral exposure using both chemicals (ATSDR 2001a). Noncancer health guidance values for oral exposure to this mixture are shown in Table 8.

Inhalation MRLs or RfCs are available for all three chemicals for which this route is expected to potentially contribute to exposure to offsite receptors at rocket launch sites: jet fuels and hydrazines based on liver effects, and trichloroethylene based on neurological effects. Table 3 shows that the central nervous system and the liver are sensitive targets for all three chemicals. The immune system is also a sensitive target for jet fuels and trichloroethylene, and based on limited evidence, may also be a target for hydrazines (see Appendix B). Therefore, it is recommended that inhalation hazard indexes be calculated using all three chemicals together. The relevant health guidance values are shown in Table 9.

The target organ toxicity dose (TTD) modification of the hazard index method (ATSDR 2001a, 2001b) is not currently recommended for this mixture, due to weakness of the data and expected limited utility of the results. Lack of health guidance values for oral exposure to jet fuels and hydrazines is a major problem. These substances are known to produce liver and central nervous system effects by oral exposure, as well as inhalation exposure. However, the oral data are insufficient for dose-response assessment (see Appendices A and B). As a result, the hazard index recommended above for oral exposure may significantly under-represent the health hazard associated with oral exposure to the mixture, and especially with regard to potential hepatotoxicity. In light of this major uncertainty, there is little justification for fine-tuning the oral hazard index of arsenic and trichloroethylene by developing TTDs based on endpoints other than liver toxicity (the chronic RfD for trichloroethylene is already based on liver effects and the liver is not a sensitive target for arsenic). Because the oral hazard index and inhalation hazard index are combined into an overall hazard index, and the liver and central nervous system effects of jet fuels and hydrazines by the oral route are not being taken into account in the oral hazard index, it seems reasonable to compensate by employing the most health protective form of the inhalation hazard index, using MRLs/RfCs rather than TTDs.

Cancer assessments available for jet fuels, hydrazines, trichloroethylene, arsenic, and strontium-90 are shown in Table 2 in the Introduction. By inhalation exposure, only hydrazine and trichloroethylene contribute to cancer risk, but by oral exposure, hydrazine, trichloroethylene, arsenic, and strontium-90 all may contribute. The slope factors and unit risks for these substances are presented in Table 10.

Table 8. Noncancer Health Guidance Values for Oral Exposure to Chemicals of Concern (See Appendices A, B, C, D, and E for Details)

Duration	Chemical				
	Trichloroethylene (mg/kg/day)	Arsenic (mg/kg/day)	Jet fuels (mg/kg/day)	Hydrazines (mg/kg/day)	Strontium-90 (mg/kg/day)
Acute	0.2	0.005	—	—	—
Intermediate	—	—	—	—	—
Chronic	$2x10^{-4}$	$3x10^{-4}$	—	—	—

Table 9. Noncancer Health Guidance Values for Inhalation Exposure to Chemicals of Concern (See Appendices A, B, and C for Details)

Duration	Chemical		
	Jet fuels (mg/m^3)	Hydrazines (mg/m^3)	Trichloroethylene (mg/m^3)
Acute	—	—	10
Intermediate	3[a]	0.005[b] $5x10^{-4}$[c]	0.5
Chronic	0.3	—	0.04

[a]assessment for JP-5/JP-8 recommended because (1) kerosene-type JP-5/JP-8 more representative of jet fuels as a group than wide-cut JP-4, and (2) less uncertainty in this assessment than in that for kerosene
[b]hydrazine
[c]1,1-dimethylhydrazine; reasonable default value for other hydrazines

Table 10. Cancer Health Guidance Values for Oral or Inhalation Exposure to Chemicals of Concern (See Appendices B, C, D, and E for Details)

Exposure	Chemical			
	Trichloroethylene	Arsenic	Hydrazines	Strontium-90[a]
Non radiation				
Oral $(mg/kg/day)^{-1}$	0.4[b]	1.5	3.0[c]	—
Inhalation $(\mu g/m^3)^{-1}$	$5x10^{-6}$	$4.3x10^{-3}$	$4.9x10^{-3}$[c]	—
Radiation				
Oral $(pCi)^{-1}$	—	—	—	$5.59x10^{-11}$
Inhalation $(pCi)^{-1}$	—	—	—	$6.93x10^{-11}$

[a]and disintegration products
[b]high end of range of central risk estimates with lowest uncertainty
[c]based on hydrazine; reasonable default value for other hydrazines