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

Examination of the available joint toxic action data, presented in Section 2.2, reveals that no health effects data are available for the complete mixture, or for ternary or quaternary submixtures. Because suitable data, joint action models, and PBPK models are lacking for the complete mixture, the recommended approach for the exposure-based assessment of joint toxic action of this mixture is to use a hazard index approach with a target-organ toxicity dose (TTD) modification and a qualitative weight-of-evidence (WOE) method. The WOE approach assesses the potential consequences of additive and interactive joint action of the components of the mixture on noncarcinogenic endpoints of concern (ATSDR 2001a). Table 11 presents a matrix of the BINWOE values, where available, for each of the component pairs of the chemicals of concern as discussed in Chapter 2. For each of the chemicals of concern, TTDs for oral exposure scenarios have been derived as described in the Appendices, using the methods recommended by ATSDR (2001a). Table 12 lists numerical values of these TTDs (and MRLs when available) for the endpoints of concern for chronic oral exposure to this mixture: hematological, immunological, reproductive, neurological, developmental, and hepatic effects.

It is recommended that these approaches treat mixtures of PCB congeners (i.e., total PCBs) as a single component of concern. This approach is consistent with ATSDR's approaches to deriving oral MRLs for PCBs, which are based on data linking health effects with exposure to PCB mixtures (Appendix E; ATSDR 2000). The profile does not focus on a representative PCB congener (or congeners) or subclasses of PCBs to discuss interactions with the other components of the subject mixture, because it is likely that: (1) multiple mechanisms are involved in PCB-induced health effects; (2) different PCB congeners may produce effects by different and multiple mechanisms; and (3) humans are exposed to complex mixtures of PCB congeners with differing biological activities.

Because the nature of the potential hazard from exposure to the radionuclides is likely to be different from nonradioactive compounds, an approach following exposure that takes the unique characteristics of exposure to these compounds into account should be utilized. The International Commission on Radiological Protection (ICRP 1979, 1990, 1993, 1996) has developed age-dependent biokinetic models for oral exposure to radionuclides, as well as dose coefficients for the different isotopes of the radionuclides which may be utilized to calculate an effective radiation dose (in Sv) to a given tissue based on

Table 11. Matrix of BINWOE Determinations for Hematological, Immunological, Neurological, (neuro)Developmental, Reproductive, Hepatic, and Carcinogenic Effects of Intermediate or Chronic Simultaneous Oral Exposure to Chemicals of Concern

		ON TOXICITY OF				
		Strontium	Cobalt	Cesium	Trichloroethylene	PCBs
EFFECT OF	Strontium		=IIC (0) r =IIC (0) i =IIC (0) d =IIC (0) c	=IIC (0) r =IIB (0) i =IIC (0) d =IIB (0) c	? (0)	? (0)
	Cobalt	? (0) h =IIC (0) i =IIC (0) c		=IIB (0) r =IIB (0) i =IIB (0) d =IIB (0) c	? (0)	? (0)
	Cesium	=IIB (0) h =IIB (0) i =IIB (0) c	=IIB (0) r =IIB (0) i =IIB (0) d =IIB (0) c		? (0)	? (0)
	Trichloro-ethylene	? (0)	? (0)	? (0)		? (0)
	PCBs	? (0)	? (0)	? (0)	>IIB2 (+0.40) p >IIB2 (+0.40) n	

h = hematological, i = immunological, n = neurological, d = (neuro)developmental, r = reproductive, p = hepatic, c = cancer

The BINWOE determinations were explained in Section 2.3. No pertinent interactions data were available for the pairs of metals classified as indeterminate (?), and mechanistic information appeared inadequate or ambiguous, so indeterminate ratings were assigned to these pairs.

BINWOE scheme (with numerical weights in parentheses) condensed from ATSDR (2001a, 2001b):

DIRECTION: = additive (0); > greater than additive (+1): < less than additive (–1); ? indeterminate (0)

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction (1.0);
II: mechanistic data on related compounds to infer mechanism(s) and likely direction (0.71);
III: mechanistic data do not clearly indicate direction of interaction (0.32).

TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint (1.0);
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals (0.71);
C: toxicologic significance of interaction is unclear (0.32).

MODIFYING FACTORS:
1: anticipated exposure duration and sequence (1.0);
2: different exposure duration or sequence (0.79);
a: *in vivo* data (1.0);
b: *in vitro* data (0.79);
i: anticipated route of exposure (1.0);
ii: different route of exposure (0.79).

Table 12. TTDs and MRLs for Chronic Oral Exposure to Chemicals of Concern (see Appendices A, B, C, D, and E for Details of Derivations)

Endpoint	Chemical				
	Strontium	Cobalt	Cesium	Trichloro-ethylene	PCBs
Hematological	$8x10^{-6}$ Sv/day (dose localized to bone marrow)	$3x10^{-5}$ Sv/day (dose localized to bone marrow)	$8x10^{-6}$ Sv/day (dose localized to bone marrow)	4 mg/kg/day	0.8 µg/kg/day ($8x10^{-4}$ mg/kg/day)
Immunological	$8x10^{-6}$ Sv/day (dose localized to bone marrow)	$2x10^{-3}$ Sv/day (whole body dose)	$8x10^{-6}$ Sv/day (dose localized to bone marrow)	2 mg/kg/day	0.02 µg/kg/day ($2x10^{-5}$ mg/kg/day) (chronic MRL)
Reproductive	ID	$1x10^{-2}$ Sv/day (total body dose)	0.1 Sv/day (total body dose)	ID	0.05 µg/kg/day ($5x10^{-5}$ mg/kg/day
Developmental	ID	0.004 Sv	0.004 Sv	0.1 mg/kg/day	0.03 µg/kg/day ($3x10^{-5}$ mg/kg/day) (intermediate MRL)
Neurological	ID	ID	ID	0.008 mg/kg/day	0.03 µg/kg/day ($3x10^{-5}$ mg/kg/day) (intermediate MRL)
Hepatic	ID	ID	ID	3 mg/kg/day	0.1 µg/kg/day ($1x10^{-4}$ mg/kg/day)

ID = inadequate data to derive a TTD

the ingested activity (in Becquerels, Bq). These coefficients take into account the biological and radioactive half-lives of the isotopes, the energies and intensities of the various radiations emitted, the resulting energy distribution throughout the body, and the biokinetics of the radionuclides once ingested, in the calculation of the effective dose from a given radiation exposure.

A similar approach has been recommended by the National Council on Radiation Protection and Measurements (NCRP 1999) in calculating acceptable limits for surface soil contaminated with radio-nuclides. Rather than calculate a dose from radionuclides in soil, however, the NCRP screening limits

report a level in media that will give a yearly radiation dose equivalent to the NCRP limiting dose (0.25 mSv/year). In the case of exposure to multiple radionuclides, the level of each radionuclide in the media of concern is compared to the screening limit for the radionuclide, and the fractions of all the radionuclides in a given sample are added. The resulting sum should not exceed unity. This approach is similar to a hazard index approach in that it assumes additive joint toxic action.

The Nuclear Regulatory Commission (NRC 2001) recommends a similar approach for dealing with exposure to multiple radionuclides, wherein the sum of the ratios of dose from a nuclide to its annual limit on intake (ALI) value should not exceed unity for internal radiation dose.

For exposure-based assessments of the non-carcinogenic health hazards from multiple radionuclides within the mixture, it is recommended that the ICRP dose coefficients should be used to calculate an effective dose from each radionuclide to the target tissue, based on the measured levels of strontium, cobalt, and/or cesium in the water and/or soil in the areas of concern. The values for the effective dose to the whole body or to the target tissue, as appropriate, from each radionuclide should then be utilized in a hazard index approach, and compared to the TTDs derived for the individual radionuclides. This approach is essentially identical to the sum of fractions approach recommended by the NCRP (1999) and NRC (2001). For example, for assessing the risk of hematological effects following an exposure to only strontium and cesium, the activity of strontium (in Bq) in the medium of concern (i.e., soil or drinking water) should be multiplied by the ICRP dose coefficient for strontium's delivered dose to the bone marrow (listed in ICRP 1996) to attain a target tissue dose (in Sv), then divided by the TTD for hematological effects for strontium. Similarly, a target tissue dose (in Sv) should be calculated for exposure to the cesium radionuclides, and compared to the appropriate TTD.

Proceeding with the TTD modification of the hazard index approach involves calculating endpoint-specific hazard indices for each endpoint of concern, as described in ATSDR (2001b, Section 2.3.2 and Figure 2 with accompanying text). For example, a hazard index for hematological effects of this mixture is calculated as follows:

$$HI_{HEMATO} = \frac{E_{Sr}}{TTD_{Sr\ HEMATO}} + \frac{E_{Co}}{TTD_{Co\ HEMATO}} + \frac{E_{Cs}}{TTD_{Cs\ HEMATO}} + \frac{E_{TCE}}{TTD_{TCE\ HEMATO}} + \frac{E_{PCB}}{TTD_{PCB\ HEMAT}}$$

where HI_{HEMATO} is the hazard index for hematological toxicity, E_{Sr} is the exposure to strontium (as the oral intake in the same units as the corresponding TTD, in this case Sv/day, calculated as described above), E_{TCE} is the exposure to trichloroethylene (as the oral intake in the same units as the corresponding TDD, mg/kg/day), $TTD_{TCE\ HEMATO}$ is the TTD for the hematological toxicity of trichloroethylene, and so forth.

These methods are to be applied only under circumstances involving significant exposure to the mixture, i.e., only if hazard quotients for two or more of the compounds equal or exceed 0.1 (Figure 2 of ATSDR 2001b). Hazard quotients are the ratios of exposure estimates to noncancer health guideline values, such as MRLs. If only one or if none of the compounds have a hazard quotient that equals or exceeds 0.1, then no further assessment of the joint toxic action is needed because additivity and/or interactions are unlikely to result in significant health hazard. As discussed by ATSDR (1992, 2001b), the exposure-based assessment of potential health hazard is used in conjunction with biomedical judgment, community-specific health outcome data, and community health concerns to assess the degree of public health hazard. If one or more of the endpoint-specific hazard indices exceed one, they provide preliminary evidence that the mixture may constitute a health hazard due to the joint toxic action of the components on that endpoint.

Because of the stochastic (nondeterministic) nature of carcinogenesis (i.e., only the incidence of cancer is related to dose, not the severity), a different approach is recommended for assessing the carcinogenic risks from exposure to the mixture. The carcinogenic risk from each component, based on measured concentrations of the component in the media of concern (e.g., soil or groundwater), should be calculated by multiplying lifetime oral exposure estimates for each component by the appropriate U.S. Environmental Protection Agency's (EPA) cancer oral slope factor (an estimate of cancer risk per unit of exposure). Oral cancer slope factors are available for strontium, cobalt, cesium, and PCBs (see Appendices A, B, C and E); evidence of the carcinogenicity of trichloroethylene is equivocal, so no oral cancer slope factor is available. As cited in ATSDR (2000), if two or more of the components have cancer risks equal to or exceeding $1x10^{-6}$, then the component cancer risks are summed to arrive at a cancer risk estimate for the mixture. If only one or if none of the component risks equals or exceeds $1x10^{-6}$, then no further assessment of joint toxic action is needed due to the low likelihood that additivity and/or interactions would result in a significant health hazard.