APPENDIX B

Route-to-Route Extrapolation of Inhalation Benchmarks

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Introduction

For a number of the contaminants commonly found at Superfund sites, inhalation benchmarks for toxicity are not available from IRIS or HEAST. As pointed out by commenters to the December 1994 *Soil Screening Guidance*, ingestion SSLs tend to be higher than inhalation SSLs for most volatile chemicals with both inhalation and ingestion benchmarks. This suggests that ingestion SSLs may not be adequately protective for inhalation exposure to chemicals that lack inhalation benchmarks.

To address this concern, the Office of Emergency and Remedial Response (OERR) evaluated potential approaches for deriving inhalation benchmarks using route-to-route extrapolation from oral benchmarks (e.g., inhalation reference concentrations [RfCs] from oral reference doses [RfDs]). OERR evaluated Agency initiatives concerning route-to-route extrapolation, including: the potential reactivity of airborne toxicants (e.g., portal-of-entry effects), the pharmacokinetic behavior of toxicants for different routes of exposure (e.g., absorption by the gut versus absorption by the lung), and the significance of physicochemical properties in determining dose (e.g., volatility, speciation). During this process, OERR consulted with staff in the EPA Office of Research and Development (ORD) to identify appropriate techniques and key technical aspects in performing route-to-route extrapolation. The following sections describe OERR's analysis of route-to-route extrapolation and the conclusions reached regarding the use of extrapolated inhalation benchmarks to support inhalation SSLs.

B.1 Extrapolation of Inhalation Benchmarks

The first step taken in considering route-to-route extrapolation of inhalation benchmarks was to compare existing inhalation benchmarks to inhalation benchmarks extrapolated from oral studies. This comparison was important to determine whether a simple route-to-route extrapolation could provide a defensible inhalation benchmark for chemicals lacking appropriate inhalation studies. OERR identified nine chemicals found in IRIS (Integrated Risk Information System) that have verified RfDs and RfCs for noncancer effects, including three chemicals found in the SSL guidance (ethylbenzene, styrene, and toluene). Reference concentrations for inhalation exposure were extrapolated from oral reference doses for adults using the following formula:

$$\text{extrapolated RfC}\ \left(\text{mg}/\text{m}^3\right) = \text{RfD}\ \left(\text{mg}/\text{kg}-\text{d}\right) \times \frac{70\ \text{kg}}{20\ \text{m}^3/\text{d}}\ . \qquad \textbf{(B-1)}$$

It is important to note that dosimetric adjustments were not made to account for respiratory tract deposition efficiency and distribution; physical, biological, and chemical factors; and other aspects of exposure (e.g., discontinuous exposure) that affect uptake and clearance. Consequently, this simple extrapolation method relies on the implicit assumption that the route of administration is irrelevant to the dose delivered to a target organ, an assumption not supported by the principles of dosimetry or pharmacokinetics.

The limited data on noncarcinogens suggest that more volatile constituents tend to have extrapolated RfCs closer to the RfCs developed by EPA (i.e., extrapolated RfC within a factor of 3 of the RfC in IRIS). The less volatile chemicals (e.g., dichlorvos) tend to be below the RfCs developed by EPA workgroups by 1 to 3 orders of magnitude. Although this data set is insufficient to discern trends in extrapolated versus IRIS RfCs, two points are reasonably clear: (1) for some volatile chemicals, route-to-route extrapolation results in inhalation benchmarks reasonably close to the RfC, and (2) as volatility decreases and/or chemical speciation becomes important (e.g., hydrogen sulfide) with respect to environmental chemistry and toxicology, the uncertainty in extrapolated inhalation benchmarks is likely to increase.

For carcinogens, OERR identified 41 chemicals in IRIS for which oral cancer slope factors (CSF_{oral}) and inhalation unit risk factors (URFs) are available, including 23 chemicals covered under the SSL guidance. Unit risk factors for inhalation exposure were extrapolated from oral carcinogenic slope factors for adults using the following formula:

$$\text{URF}\ (\mu g/m^3)^{-1} = \frac{\text{CSF}_{oral}\ (mg/kg-d)^{-1}}{70\ kg} \times 20\ m^3/d \times 10^{-3}\ mg/\mu g \quad . \qquad \textbf{(B-2)}$$

Using the extrapolated URF, risk-specific air concentrations were calculated as a lifetime average exposure concentration as shown in equation B-3:

$$\text{extrapolated air concentration}\ \mu g/m^3 = \frac{\text{target risk}\ 10^{-6}}{\text{URF}\ (\mu g/m^3)^{-1}} \quad . \qquad \textbf{(B-3)}$$

Not surprisingly, the risk-based (i.e., 10^{-6}) air concentrations in IRIS are the same as the air concentrations extrapolated from the CSF_{oral} for 30 of the 41 carcinogenic chemicals evaluated (at one significant figure). Historically, oral and inhalation slope factors have been based on oral studies for chemicals for which pharmacokinetic or portal-of-entry effects were considered insignificant. As a result, route of exposure extrapolations were often included in the development of the carcinogenic slope factors. However, the divergence of extrapolated air concentrations with risk-based (i.e., 10^{-6}) air concentrations in IRIS reflects newer methods in use at EPA that address portal-of-entry effects, dosimetry, and pharmacokinetic behavior. For example, 1,2-dibromomethane has an extrapolated 10^{-6} air concentration that is 2 orders of magnitude below the value in IRIS. This difference is probably attributable to differences in: (1) the endpoint for inhalation exposure (nasal cavity carcinoma) versus oral exposure (squamous cell carcinoma), and/or (2) portal-of-entry effects directly related to deposition physiology and absorption of 1,2-dibromomethane.

B.2 Comparison of Extrapolated Inhalation SSLs with Generic SSLs

Having performed a simple extrapolation of inhalation benchmarks, the next step was to compare the inhalation SSLs (SSL_{inh}) based on extrapolated data to the soil saturation concentrations* (C_{sat}) and generic SSLs for soil ingestion (SSL_{ing}) and ground water ingestion (SSL_{gw}). Table B-1 presents the 50 organic chemicals in the SSL guidance that lack inhalation benchmarks. The table presents oral benchmarks found in IRIS (columns 2 and 3) and extrapolated inhalation benchmarks as

* The derivation of C_{sat} and its significance is discussed in Section 2.4.4 of this Technical Background Document.

described in Equations B-1 and B-2 (columns 4 and 5). In addition, the table presents volatilization-based SSLs and SSLs based on particulate emissions derived from the extrapolated toxicity values. For each column of extrapolated inhalation SSLs in this table, values are truncated at 1,000,000 mg/kg because the soil concentration cannot be greater than 100 percent (i.e., 1,000,000 ppm).

B.2.1 Comparison of Extrapolated SSLs Based on Volatilization

The extrapolated SSL_{inh} for volatilization ($SSL_{inh\text{-}v}$) was calculated with Equation 4 in Section 2.4 using a chemical-specific volatilization factor (VF). In Table B-1, the $SSL_{inh\text{-}v}$ values based on extrapolated inhalation benchmarks (column 6) are compared with the soil saturation concentration (C_{sat}, column 7) and generic migration to ground water SSLs assuming a dilution attenuation factor (DAF) of 20 (SSL_{gw}).

As described in Section 2.4.4, C_{sat} represents the concentration at which soil pore air is saturated with a chemical and maximum volatile emissions are reached. A comparison of the C_{sat} with the extrapolated $SSL_{inh\text{-}v}$ values indicates that, for 36 of the 50 contaminants, $SSL_{inh\text{-}v}$ exceeds the soil saturation concentration, often by several orders of magnitude. Because maximum volatile emissions occur at C_{sat}, these 36 contaminants are not likely to pose significant risks through the inhalation pathway, and therefore the lack of inhalation benchmarks is not likely to underestimate risk through the volatilization pathway.

For the remaining 14 contaminants with extrapolated $SSL_{inh\text{-}v}$ values below C_{sat}, all are above the generic SSL_{gw} values. This analysis suggests that SSLs based on the migration-to-groundwater pathway are likely to be protective of the inhalation pathway as well. However, for sites where groundwater is not of concern, the SSLs based on ingestion may not necessarily be protective of the inhalation pathway. The analysis indicates that the extrapolated inhalation SSLs are below SSLs based on direct ingestion for the following chemicals: acetone, bromodichloromethane, chlorodibromomethane, cis-1,2-dichloroethylene, and *trans*-1,2-dichloroethylene. This analysis supports the **possibility** that the SSLs based on direct ingestion for the listed chemicals may not be adequately protective of inhalation exposures. However, a more rigorous evaluation of the route-to-route extrapolation methods used to derive the toxicity criteria for this analysis is warranted (refer to section B.3).

B.2.2 Comparison of Extrapolated SSLs Based on Particulate Emissions

The extrapolated particulate inhalation SSLs ($SSL_{inh\text{-}p}$) were calculated with Equation 4 in Section 2.4 using the particulate emission factor (PEF) of 1.32×10^9 m^3/kg. Table B-1 compares the $SSL_{inh\text{-}p}$ values based on extrapolated benchmarks (column 10) and generic SSLs based on direct ingestion (SSL_{ing}, Column 9). This comparison indicates that the extrapolated $SSL_{inh\text{-}p}$ values that are based on the PEF are well above the SSLs for soil ingestion. Thus, ingestion SSLs are likely to be protective of inhalation risks from fugitive dusts from surface soils.

B.3 Conclusions and Recommendations

Based on the results presented in this appendix, OERR reached several conclusions regarding route-to-route extrapolation of inhalation benchmarks for the development of generic inhalation SSLs. First, it is reasonable to assume that, for some contaminants, the lack of inhalation benchmarks may underestimate risks due to inhalation exposure. Of the 17 volatile organics for which both the ingestion and inhalation SSLs are based on IRIS benchmarks, all had inhalation SSLs that were below the ingestion SSLs. Nevertheless, generic SSLs for ground water ingestion (DAF of 20) are lower,

often significantly lower, than both extrapolated and IRIS-based inhalation SSLs with the exception of vinyl chloride, which is gaseous at ambient temperatures. Thus, at sites where ground water is of concern, migration to ground water SSLs generally will be protective from the standpoint of inhalation risk. However, if the ground water is not of concern at a site (e.g., if ground water below the site is not potable), the use of SSLs for soil ingestion may not be adequately protective of the inhalation pathway.

Second, the **extrapolated** SSL_{inh} values are not intended to be used as generic SSLs for site investigations; the **extrapolated** inhalation SSLs are useful in determining the potential for inhalation risks but should not be misused as SSLs. Route-to-route extrapolation methods must account for the relationship between physicochemical properties and absorption and distribution of toxicants, the significance of portal-of-entry effects, and the potential differences in metabolic pathways associated with the intensity and duration of inhalation exposure. However, methods required to generate sufficiently rigorous inhalation benchmarks have recently been developed by the ORD. A final guidance document was made available by ORD in November of 1995 that addresses many of the issues critical to the development of inhalation benchmarks described above. The document, entitled *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994), describes the application of inhalation dosimetry to derive inhalation reference concentrations and represents the current state-of-the-science at EPA with respect to inhalation benchmark development. The fundamentals of inhalation dosimetry are presented with respect to toxicokinetics and the physicochemical properties of chemical contaminants.

Thus, at sites where the migration to ground water pathway is not of concern and a site manager determines that the inhalation pathway may be significant for contaminants lacking inhalation benchmarks, route-to-route extrapolation may be performed using EPA-approved methods on a case-by-case basis. Chemical-specific route-to-route extrapolations should be accompanied by a complete discussion of the data, underlying assumptions, and uncertainties identified in the extrapolation process. Extrapolation methods should be consistent with the EPA guidance presented in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*. If a route-to-route extrapolation is found not to be appropriate based on the ORD guidance, the information on extrapolated SSLs may be included as part of the uncertainty analysis of the baseline risk assessment for the site.

Reference

U.S. EPA (Environmental Protection Agency). 1994. *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.* EPA/600/8-90/066F. Office of Research and Development, Washington, DC.

Table B-1. Comparison of Extrapolated Inhalation SSLs (SSL_{inh}) with Soil Concentrations (C_{sat}), and Migration to Ground Water (SSL_{gw})

	IRIS oral benchmarks		Extrapolated inhalation benchmarks		VF-based SSLs (mg/kg)				PEF-based SSLs (mg/kg)
Compound	**RfD (mg/kg-d)**	**CSF $(mg/kg\text{-}d)^{-1}$**	**RfC (mg/m^3)**	**URF $(mg/m^3)^{-1}$**	**Extrapolated volatilization $SSL_{inh\text{-}v}$**	**C_{sat}**	**Generic SSL_{gw} (DAF 20)**	**Generic SSL_{ing}**	**Extrapolated particulate $SSL_{inh\text{-}p}$**
Acenaphthene	6E-02		2.1E-01		48,000	181	570	4,700	>1,000,000
Acetone	1E-01		3.5E-01		**4,600**	**103,747**	**16**	**7,800**	>1,000,000
Anthracene	3E-01		1.1E+00		860,000	8	12,000	23,000	>1,000,000
Benz*(a)* anthracene		7.3 E-01		2.1E-04	110	22	2	0.9	15,000
Benzo*(b)* fluoranthene		7.3 E-01		2.1E-04	54	11	5	0.9	15,000
Benzo*(k)* fluoranthene		7.3 E-02		2.1E-05	4,600	6	49	9	150,000
Benzo*(a)* pyrene		7.3 E+00		2.1E-03	28	10	8	0.09	1,500
Benzoic acid	4E+00		1.4E+01		>1,000,000	363	400	310,000	>1,000,000
Bis(2-ethylhexyl)phthalate		1.4 E-02		4.0E-06	130,000	30,804	3,600	46	800,000
Bromodichloromethane		6.2 E-02		1.8E-05	**1.14**	**2,981**	**0.6**	**10**	180,000
Butanol	1E-01		3.5E-01		14,000	10,477	17	7,800	>1,000,000
Butyl benzyl phthalate	2E-01		7.0E-01		>1,000,000	928	930	16,000	>1,000,000
Carbazole		2.0 E-02		5.7E-06	1,100	153	0.6	32	560,000
p -Chloroaniline	4E-03		1.4E-02		4,100	2,632	0.7	310	>1,000,000
Chlorodibromomethane		8.4 E-02		2.4E-05	**1.5**	**1,260**	**0.4**	**8**	130,000
2-Chlorophenol	5E-03		1.8E-02		550	53,482	4	390	>1,000,000
Chrysene		7.3 E-03		2.1E-06	3,200	4	160	88	>1,000,000
DDD		2.4 E-01		6.9E-05	820	540	16	3	47,000
DDE		3.4 E-01		9.7E-05	620	3,218	54	2	33,000
Dibenz*(a,h)* anthracene		7.3 E+00		2.1E-03	120	57	2	0.09	1,500
Di-*n* -butyl phthalate	1E-01		3.5E-01		>1,000,000	2,279	2,300	7,800	>1,000,000
3,3'-Dichlorobenzidine,		4.5 E-01		1.3E-04	24	14	0	1	25,000
***cis* -1,2-Dichloroethylene**	1E-02		3.5E-02		**110**	**1,205**	**0.4**	**780**	>1,000,000
***trans* -1,2-Dichloroethylene**	2E-02		7.0E-02		**170**	**3,067**	**0.7**	**1,600**	>1,000,000
2,4-Dichlorophenol	3E-03		1.1E-02		2,500	4,419	1	240	>1,000,000
Diethylphthalate	8E-01		2.8E+00		>1,000,000	1,974	470	63,000	>1,000,000
2,4-Dimethylphenol	2E-02		7.0E-02		19,000	10,656	9	1,600	>1,000,000
2,4-Dinitrophenol	2E-03		7.0E-03		1,000	279	0.3	160	>1,000,000
2,4-Dinitrotoluene		6.8E-01		1.9E-04	4	182	0.0008	0.9	17,000
2,6-Dinitrotoluene		6.8E-01		1.9E-04	4	94	0.0007	0.9	17,000
Di-*n* -octyl phthalate	2E-02		7.0E-02		>1,000,000	9,984	10,000	1,600	>1,000,000
Endosulfan	6E-03		2.1E-02		18,000	7	18	470	>1,000,000
Endrin	3E-04		1.1E-03		2,500	18	1	23	>1,000,000
Fluoranthene	4E-02		1.4E-01		450,000	132	4300	3,100	>1,000,000

Table B-1. Comparison of Extrapolated Inhalation SSLs (SSL_{inh}) with Soil Concentrations (C_{sat}), and Migration to Ground Water (SSL_{gw})

Compound	IRIS oral benchmarks		Extrapolated inhalation benchmarks		VF-based SSLs (mg/kg)			Generic SSL_{ing}	PEF-based SSLs (mg/kg)
	RfD (mg/kg-d)	CSF $(mg/kg\text{-}d)^{-1}$	RfC (mg/m^3)	URF $(mg/m^3)^{-1}$	Extrapolated volatilization $SSL_{inh\text{-}v}$	C_{sat}	Generic SSL_{gw} (DAF 20)		Extrapolated particulate $SSL_{inh\text{-}p}$
Fluorene	4E-02		1.4E-01		75,000	164	560	3,100	>1,000,000
γ-Hexachlorocyclohexane		1.3 E+00		3.7E-04	3.1	44	0.009	0.5	8,600
Indeno*(1,2,3-cd)* pyrene		7.3 E-01		2.1E-04	660	0.5	14	0.9	15,000
Isophorone		9.5 E-04		2.7E-07	720	4,570	0.5	670	>1,000,000
Methoxychlor	5E-03		1.8E-02		74,000	26	160	390	>1,000,000
2-Methylphenol	5E-02		1.8E-01		37,000	16,827	15	3,900	>1,000,000
Naphthalene	4E-02		1.4E-01		8,200	375	84	3,100	>1,000,000
N -Nitrosodiphenylamine		4.9 E-03		1.4E-06	1,000	275	1	130	>1,000,000
N-Nitrosodi-*n* -propylamine		7.0 E+00		2.0E-03	0.1	2,413	0.00005	0.09	1,600
Pentachlorophenol		1.2 E-01		3.4E-05	83	7,121	0.03	3	94,000
Phenol	6E-01		2.1E+00		400,000	22,588	100	47,000	>1,000,000
Pyrene	3E-02		1.1E-01		420,000	85	4,200	2,300	>1,000,000
2,4,5-Trichlorophenol	1E-01		3.5E-01		250,000	11,618	270	7,800	>1,000,000
m -Xylene	2E+00		7.0E+00		45,000	418	210	160,000	>1,000,000
o -Xylene	2E+00		7.0E+00		45,000	413	190	160,000	>1,000,000
p -Xylene	2E+00		7.0E+00		41,000	461	200	160,000	>1,000,000

NR = $SSL_{inh\text{-}v}$ is greater than 1,000,000 ppm (= no volatile inhalation risk at any soil concentration)

Bold indicates where extrapolated SSL_{inh} values are less than SSL values based on direct ingestion.