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I. Default "Uncertainty Factors" for noncancer endpoints

UF: Used to ensure human health protection when there is a data gap

Table 1: Types of uncertainty factors

	DPR	OEHHA[a]	USEPA[c]
1. Duration extrapolation (when only NOEL for shorter duration is available)			
Acute to Chronic	10	10	
Subchronic to Chronic/Lifetime[b]		1 (study >12% est. lifetime) $10^{0.5}$ (8-12% of est. lifetime) 10 (<8% est. lifetime)	≤10
2. Dose extrapolation (when there is no experimentally derived NOEL, BMD not used)			
LOEL to estimated NOEL	10	6 (mild effect) 10 (severe or any effect)	≤10
3. Interspecies extrapolation (lab animal data to address human health)			
Oral			
PK and PD	10		
Inhalation			
PK and PD	10	$10^{0.5}$ (nonhuman primate) 10 (non-primate)	
PK		2 (USEPA RfC-HEC, incomplete DAF)	1 (USEPA RfC-HEC)
	$10^{0.5}$	$10^{0.5}$ (no data)	NA
PD	$10^{0.5}$	2 (some data available) $10^{0.5}$ (no data)	$10^{0.5}$
Dermal Skin irritation (PK,PD)	1		
4. Intraspecies extrapolation (interindividual variations in the human population)			
Systemic effects PK	10	$10^{0.5}$ (some PK data) 10 (no data)	10
PD		$10^{0.5}$ (human adult studies, no ↑ susceptibility of children) 10 (↑ susceptibility of children, eg. asthma, NT)	
Dermal effects acute skin irritation	10		
5. Additional Concerns			
Increased sensitivity of infants and children	10	(10, already in #4 for PD)	≤ 10 (food use only)
Database deficiency		$10^{0.5}$	

a/ From Table 4.4.1. of OEHHA Technical Support Document For the Derivation of Noncancer Reference Exposure Levels, June 18, 2008. (OEHHA, 2008)

b/ The NOEL from a 13-week subchronic study (13% of a 2-year rat lifetime) would be adjusted with a UF of $10^{0.5}$, when used to derived the chronic REL, which is for lifetime and annual average exposures.

c/ (Dourson *et al.*, 1996).

Abbreviations: DAF=dosimetric adjustment factor, HEC=human equivalent concentration (with PK considered), PK=pharmacokinetic, PD=pharmacodynamic, NT=neurotoxicity

Table 2: Examples from RCDs on use of UFs

	DPR	Examples	USEPA or OEHHA
1. Duration extrapolation (when only NOEL for shorter duration is available)			
Acute to Chronic	10	**EDS**: 10x (21 day subchronic NOEL to get chronic ENEL)	USEPA: chronic exposure not expected
2. Dose extrapolation (when there is no experimentally derived NOEL, BMD not used)			
LOEL to estimated NOEL	10	**IMP**: 10x (LOEL for DNT-↓ dimensions of brain structures)	OEHHA: concurred, BMD as alternative
		OPP: 10x (LOEL for cardiac degeneration/ fibrosis)	USEPA: set LOEL as NOEL
		MeBr: 10x (LOEL for neurotoxicity for subchronic)	USEPA: set LOEL as NOEL
		MeBr: 10 x(LOEL for nasal epithelial hyperplasia and degeneration for chronic)	3x for chronic (effect not severe)
		MTT: 1x (90-day NOEL for acute NOEL (instead of acute LOEL/10, which is <90-day NOEL for the same endpoint-brain AChE inhibition)	USEPA: same 90-day NOEL for acute
3. Interspecies extrapolation (lab animal data to address human health)			
Oral			
PK and PD	10		
Inhalation			
PK	$10^{0.5}$	**CPC**: 1x (direct irritation of trigeminal nerve endings in the respiratory and ocular mucosa, no PK involved, and human study)	USEPA: 1x
PD	$10^{0.5}$		
Dermal Skin irritation (PK,PD)	1	**MTS**: 10x (local irritation, NOEL from rabbit dermal study)	USEPA: did not evaluate route
4. Intraspecies extrapolation (interindividual variations in the human population)			
Systemic effects PK and PD	10	**CPC**: 10x (see item#5)	OEHHA: 30x (see item#5)
Dermal effects acute skin irritation	10		

5. Additional Concerns			
Sensitivity of infants and children Database deficiency	**10**	**MTS**: 1x (acute NOEL based on resorption)	USEPA: not considered, no food use
		OPP:1x (↑resorption NOEL lower than maternal NOEL; calculate 10X in risk appraisal)	USEPA: 1x
		PPG:1x (pup NOEL=parental NOEL)	USEPA: 1x
		EDS: 1x (dose for endocrine disruption > critical endpoints)	USEPA: 1x OEHHA: 3x (repro effect)
		MeBr: 1x (RCD recommended 10x for DNT, but NAS considered NOEL conservative, thus not needed)	USEPA: 1x (DNT submitted, after DPR completed RCD)
		MeI: 10x (endocrine, DNT not studied)	USEPA: 1x (NOEL for thyroid effect will protect against DNT)
		SF: 10x (brain vacuoles, no DNT study)	USEPA: 10x (no DNT study)
		CPC: recommended additional UF, but did not quantify ("neonates could be more sensitive...due to a higher breathing rate or the immaturity of their respiratory system, immune system and/or metabolic enzymes.)	OEHHA: 3x (or total of intraspecies UF of 30x- 3x PK, 10x PD- children ↑sensitivity to respiratory effects: bronchietectasis, inflammation of nasal epithelium)
		MTT: no UF applied, but concerns about 1) potential ↑ infants and children sensitivity, 2) no tox or exposure data for MTT-oxon 3) cumulative OP exposures	USEPA: 1x (no data gap concerns for MTT)

<u>RCDs reviewed:</u>

CPC=chloropicrin (DPR, 2012) (USEPA, 2008a)
EDS=endosulfan (DPR, 2008)
IMP=imidacloprid (DPR, 2006a)
MeBr=methyl bromide (DPR, 2002); (USEPA, 2008b)
MeI=methyl iodide (DPR, 2010); (USEPA, 2006a)
MTS=metam sodium (DPR, 2004a)
MTT=methidathion ((DPR, 2007a)
OPP=o-phenylphenol (DPR, 2007b)
PPG=propargite (DPR, 2004b)
SF=sulfuryl fluoride (DPR, 2006b)

II. Calculation of NOEL and RfC for inhalation toxicity

1. DPR Default values

(a) Breathing rate- may be referred to as inhalation rate, or ventilation rate

$$\text{BR} = \text{Minute volume} \times \frac{\text{minutes}}{\text{day}} \times \frac{1}{\text{body weight}} = \text{m}^3/\text{kg/day}$$

(b) Human breathing rates (DPR, 2000)

* 0.28 m^3/kg/day (adult) and 0.59 m^3/kg/day (infants)

(c) Animal breathing rates (Zielhuis and van der Kreek, 1979) (1000 L=1 m^3)

* 0.96 m^3/kg/day (rats), 1.8 m^3/kg/day (mice),
* 0.39 m^3/kg/day (dogs), 0.54 m^3/kg/day (rabbits)

(d) Use of values

* mean values and uncertainty
* use experimentally measured rate, if available
* continually track literature on need for revision

2. Comparison of NOELs in laboratory animal studies to find the lowest critical NOEL

The dose, in ppm or µg/ml, should be converted to an amortized dose (mg/kg/day) to account for: species different breathing rate and different duration of exposure:

$$\text{ppm} \times \frac{\text{molecular weight}}{\text{molar volume}} \times \text{animal breathing rate} \times \frac{\text{hours exposed}}{\text{24 hours}} \times \frac{\text{days exposed}}{\text{7 days}}$$

(e.g., molar volume= 24.45 L/mole at 25ºC)

The term for number of days exposed /7 days is used in the calculation only for subchronic or chronic NOELs when the animals were dosed for < 7 days per week. Add absorption factor if human exposure is expressed as absorbed dose.

Example: Acute NOEL of 300 ppm in rats after 6 hours of exposure with 1 ppm = 4.17 mg/m^3:

$$300\,ppm \times 4.17\,mg/m^3 \times \frac{0.96\,m^3}{kg-24hr\ day} \times \frac{6\ hours\ \ exposed}{24\ hours} = 300\,mg/kg/day$$

3. Calculation of human equivalent NOEL for use in MOE calculation

After the selection of the critical NOEL from the animal study, the NOEL in ppm or µg/ml may need to be converted to human equivalent NOEL to account for:

(a) Exposure duration difference

If the animal exposure is of shorter duration (e.g. 1 hour) than human exposure (e.g. 8 hours), then the NOEL is reduced because it is reasonable to assume toxicity would occur at a lower level when the exposure duration is increased. The default is to assume equal dependency of toxicity on concentration and duration of exposure using Haber's Law (C^n x t = k, with n=1), or

$$C_1 \times t_1 = C_2 \times t_2$$

However, the NOEL should not be increased if it is from a study of longer duration (e.g. 8 hours) than that expected for human exposure (e.g. 1 hour), when there are no other data to determine the time-dose relationship. For acute exposure, do not amortize the number of days exposed.

(b) Breathing rate differences

The breathing rate adjustment accounts only for the intake of the pesticide based on the breathing rate differences. This is analogous to consumption rate difference for oral exposures.

$$\text{ppm} \times \frac{\text{animal BR}}{\text{human BR}} \times \frac{\text{animal hours exposed}}{\text{human hours exposed}} \times \frac{\text{animal days/week exposed}}{\text{human days/week exposed}} = \text{human eq. NOEL}$$

<u>Example of human equivalent NOEL calculation</u>: For an acute NOEL of 0.208 μg/L from a rat 4-hour study, and the need to address the 8-hour and 24-hour human exposure durations, the human equivalent NOELs are:

Adult human equivalent NOEL (8-hour worker exposure):

$$0.208\, ug/L \; x \; \frac{960\, L/kg/day}{280\, L/kg/day} \; x \; \frac{4hrs}{8hrs} = 0.36\, ug/L$$

Infant human equivalent NOEL (24-hour infant bystander exposure):

$$0.208\, ug/L \; x \; \frac{960\, L/kg/day}{590\, L/kg/day} \; x \; \frac{4hrs}{8hrs} = 0.06\, ug/L$$

<u>4. Calculation of reference concentration</u>

The reference concentration is based on the human equivalent NOEL calculation with the addition of uncertainty factors to account for interspecies extrapolation and intraspecies variation. The default is a factor of 10 for each (total of 100).

$$\text{ppm} \times \frac{\text{animal BR}}{\text{human BR}} \times \frac{\text{animal hours exposed}}{\text{human hours exposed}} \times \frac{\text{animal days/week exposed}}{\text{human days/week exposed}} \times \frac{1}{\text{UFs}} = \text{RfC}$$

<u>Example</u>: Child 24 hour-RfC for acute NOEL of 300 ppm, 6 hour exposure in rats, UF of 100:

$$300\, ppm \; x \; \frac{0.96}{0.59} \; x \; \frac{6hours}{24hours} \; x \; \frac{1}{100} = 1.22\, ppm$$

Example: Worker 8 hour-RfC for acute NOEL of 300 ppm, 6 hour exposure in rats, UF of 100:

$$300\,ppm\ x\ \frac{0.96}{0.28}\ x\ \frac{6hours}{8hours}\ x\ \frac{1}{100} = 7.71\,ppm$$

5. Comparison with USEPA calculation of reference concentration[1]

The DPR's **human equivalent NOEL** is not the same as the USEPA HEC (**human equivalent concentration**). The HEC from the USEPA RfC methodology includes a calculated "pharmacokinetic" factor. In the following equations: PK (pharmacokinetic) and PD (pharmacodynamic) interspecies UF, 10_{human}=intraspecies variation UF.

(a) DPR RfC calculation equation for both gas and particulates:

$$\text{ppm}\ \text{x}\ \frac{\text{animal BR}}{\text{human BR}}\ \text{x}\ \frac{\text{animal hours exposed}}{\text{human hours exposed}}\ \text{x}\ \frac{\text{animal days/week exposed}}{\text{human days/week exposed}}\ \text{x}\ \frac{1}{10_{\text{PK and PD}}\ \text{x}\ 10_{\text{human}}} = \text{RfC}$$

Human Equivalent NOEL or Concentration →

(b) USEPA RfC calculation equation:

$$\text{ppm}\ \text{x}\ \frac{\text{animal hours exposed}}{\text{human hours exposed}}\ \text{x}\ \frac{\text{animal days/week exposed}}{\text{human days/week exposed}}\ \text{x}\ \text{PK}_{\text{RGDR or RDDR}}\ \text{x}\ \frac{1}{\sqrt{10}_{\text{PD}}\ \text{x}10_{\text{human}}} = \text{RfC}$$

Human Equivalent Concentration →

The PK factor is a RGDR or RDDR[2] (gas *vs* particulates, respiratory *vs* systemic effect). These ratios are calculated using USEPA software.

(a) Gas and respiratory effect:

$$RGDR = \frac{MV_A}{MV_H}\ x\ \frac{SA_H}{SA_A}$$

(b) Gas and systemic effect: (when no data, or calculated RGDR is >1, a factor of 1 is used)

$$RGDR = \frac{Animal\ H_{b/g}}{Human\ H_{b/g}}$$

[1] The rationale for HAS not using the USEPA RfC methodology is has been discussed previously (see Attachment I Boiler Plate RGDR Discussion and USEPA (1994).

[2] A=animal, BW=body weight, H b/g=blood gas partition coefficient, FR=fractional deposition in the region, H=human, MV=minute volume, RGDR=regional gas dose ratio, RDDR=regional deposited dose ratio, SA=surface area

(c) Particulates and respiratory effect:

$$RDDR = \frac{C_A x SA_H x MV_A x FR_A}{C_H x SA_A x MV_H x FR_H}$$

(d) Particulates and systemic effect: (assume 100% of deposited dose is available for uptake)

$$RDDR = \frac{C_A x BW_H x MV_A x FR_A}{C_H x BW_A x MV_H x FR_H}$$

Example of DPR RfC and USEPA RfC values for adult using a NOEL for a gas/systemic effect. The impact of different BR for species is shown using rabbit and rat BRs.

	NOEL	Duration adjustment	Intake adjustment	Interspecies		HEC	intra-species	RfC
				PK	PD		UF	
Rabbit study and adult human								
DPR	40 ppm	$\frac{6 \text{ hours}}{24 \text{ hours}}$	$\frac{0.54 \text{ m}^3 / \text{kg} / \text{day}}{0.28 \text{ m}^3 / \text{kg} / \text{day}} = 2$	10		1.9 ppm	10	0.19 ppm
USEPA	40 ppm	$\frac{6 \text{ hours}}{24 \text{ hours}}$	None	RGDR =1	3	3.3 ppm	10	0.33 ppm
Rat study and adult human								
DPR	40 ppm	$\frac{6 \text{ hours}}{24 \text{ hours}}$	$\frac{0.96 \text{ m}^3 / \text{kg} / \text{day}}{0.28 \text{ m}^3 / \text{kg} / \text{day}} = 3.4$	10		3.4 ppm	10	0.34 ppm
USEPA	40 ppm	$\frac{6 \text{ hours}}{24 \text{ hours}}$	None	RGDR =1	3	3.3 ppm	10	0.33 ppm

6. Current status on breathing rates and uncertainty

Default breathing rates were used by DPR to estimate the exposures for different age groups. These values are average values based on activity pattern from survey data, breathing rate per activity, and default body weights (DPR, 2000). They are consistent with values established by the USEPA in the Exposure Factors Handbook (USEPA, 1997; USEPA, 2011). The use of these average values could underestimate exposures when higher inhalation rates would be expected, such as during acute or short-term high activity level. USEPA also described a revised methodology to calculate the breathing rate using more current databases (USEPA, 2006b) and reported in (Foos *et al.*, 2008). The results showed higher children and lower adult breathing rates than those in the (USEPA, 1997) two USEPA handbooks (USEPA, 1997; USEPA, 2011) and those used by DPR. However, comments submitted to USEPA indicated that there were uncertainties associated with these values, and they included: linking parameters from multiple datasets (i.e. applying body weight data from 1999-2000 NHANES to 1992-1994 NHAPS activity database), no validation, and no consideration of recent trend toward obesity

and sedentary lifestyle. The latter lifestyle change would result in increased body weight and thus lower breathing rate.

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IV. Attachment 1

DPR vs. USEPA RGDR in RfC Methodology for gases

Under Review for Risk Appraisal Discussion

I. Extra-Respiratory (ER) effects; Systemic effects USEPA RfC methodology employs the Regional Gas Dose Ratio (RGDR) for interspecies dose extrapolation. This approach is an approximation of physiologically based pharmacokinetic (PBPK) modeling that is designed to estimate the steady state concentration in the arterial blood after reaching periodicity of exposure (USEPA, 1992). The interspecies scaling factor RGDR is the ratio of blood-gas partition (Hblood/gas) between laboratory animals and humans, or (Hb/g)A/(Hb/g)H.

One major uncertainty in the use of RGDR as an approximation approach for PBPK modeling is the general lack of data on the Hblood/gas for both animals and humans. This uncertainty raises two associated issues. One issue is, when data are not available, the current RfC methodology default for the scaling factor is one. The second issue is, the subsequent use of an interspecies uncertainty factor (UF) of 3 instead of 10. These two issues are further discussed below.

Many factors could affect the blood-gas partition. These include factors that are specific to the species (e.g., red blood cell surface protein, binding sites and capacity, ventilation and tissue perfusion rates) and chemical (e.g., lipophilicity) (Wiester *et al.*, 2002). Biotransformation at the site of contact and en route to the target site could also be an important factor. Under the current RfC methodology, the RGDR default to one when no Hb/g data are available or when the estimated RGDR exceeds one (i.e., animals have higher Hb/g). The latter default is problematic. For example, the rat-to-human (Hb/g)A/(Hb/g)H are often shown to be greater than one for volatile organic chemicals (e.g.,(Gargas *et al.*, 1989), (Wiester *et al.*, 2002)). As much as this default RGDR of one is intended to be more "conservative", without data to indicate how it may realistically model the interspecies differences, its use can introduce additional uncertainties instead of being a tool to refine the interspecies difference as it is intended for.

With the above default scaling factor of 1, the subsequent use of a UF of 3 instead of the common default interspecies UF of 10 may further compound the uncertainties in the RfC methodology. Two factors are included in the common interspecies UF of 10, the pharmacokinetic (PK) and pharmacodynamic (PD) factors. In the RfD methodology, the UF of 3 is to account for the PD differences since the interspecies PK differences have presumably been included in the RGDR, as it is an approximation of the PBPK model. However, in the case of a default RGDR of one, no quantitative adjustment from animals to humans has been made. This is a practical issue because of the lack of data, the default RGDR of one would be applied to most cases for pesticides. While it is not known whether any and what quantitative adjustment is needed for interspecies PK differences, the use of interspecies UF of 3 implies that a PK adjustment has been made.

Alternatively, DPR's methodology seeks to make interspecies exposure adjustment only for the "intake" portion of the exposure scheme (Figure 2-1 in the USEPA 1992 Guidelines for

Exposure Assessment, (USEPA, 1992)), and not the "uptake" to the target site. For this approach, DPR calculates the exposure based on the breathing rate (air "intake") on a per body weight basis (as is the common expression for exposure or dose). This calculation is similar to the estimation of exposure through the diet while the "intake" is the amount of food consumed instead of the air breathed in. DPR recognizes that sufficient data and experience are not yet available for a subsequent adjustment down to the "uptake" portion of the dose estimation that would enable an adequate account for the PK aspect of the interspecies difference in a simple dosimetric equation. Thus, the common interspecies UF of 10 for both the PK and PD factors is then applied to the estimated "intake" dose, or exposure. DPR recognizes the inherent uncertainties in is and any other default approach. For refining the interspecies extrapolation, DPR encourages the exploration of valid PBPK model when credible data are available.