Minnesota Department of Health
HEALTH RISK ASSESSMENT UNIT

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MDH Health Risk Assessment Methods:

INCORPORATION OF HUMAN EQUIVALENT DOSE CALCULATIONS INTO DERIVATION OF ORAL REFERENCE DOSES

In 2011, the Minnesota Department of Health (MDH) implemented recommendations from the Environmental Protection Agency (EPA) guidance for human equivalent dose (HED) calculations used in risk assessment (USEPA, 2011). This guidance describes the rationale for HEDs, the methods for calculating HEDs, and the use of HED calculations by MDH in developing drinking water guidance. MDH revised the guidance in 2017 for dogs to better reflect relevant age-adjusted body weights for studies of various durations (see Attachment – DAF Table).

Mammalian animal data often forms the basis for dose-response assessment and extrapolation from laboratory animals to humans is typically required. The most scientifically sound approach by which this may be accomplished is through the use of chemical- and species-specific information to estimate the internal dose at the target tissue(s) of the two species. An HED is a dose that would induce the same magnitude of toxic effects in humans as the experimental animal species dose if the toxic responses of the target tissues are similar in the two species.

Research comparing dosing in species has shown that comparable human doses are related to a mathematical function of animal body weight. The best approximation across species is body weight raised to the ¾ power (body weight scaling). The EPA has compiled body weight data for each species and strain and gender of the animals typically used in toxicity studies. (USEPA, 1988) This information can be used to calculate generic dosimetric adjustment factors (DAFs) that can be used when risk assessors do not have study specific data.

The EPA recommends a hierarchy of approaches for deriving HEDs: 1) physiologically-based pharmacokinetic modeling (PBPK); 2) chemical-specific information; and 3) body weight scaling to $BW^{¾}$ as a default adjustment in the absence of chemical-specific information. EPA finalized guidance for the third approach in 2011: "Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose" (https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose.)

The benefits of the body weight scaling approach include:

- A reduction in uncertainty by using a biologically-based interspecies adjustment factor,
- Harmonization with adjustments that have been widely accepted and used in the derivation of inhalation reference concentrations for many years, and
- Harmonization of risk assessment approaches used for derivation of oral and inhalation cancer potency values that are based on body weight scaling.

PBPK modeling and chemical-specific approaches are information intensive and their application is usually limited to the few chemicals that have sufficient databases. The EPA recommends deriving HEDs from DAFs when PBPK or chemical-specific information is unavailable.

Using HEDs

An HED is the product of the dose administered to the animals in the animal study and the DAF. The HED that is selected as a point of departure (POD) for the study is then adjusted by variability and uncertainty factors, to account for what is not known about a chemical's toxicity to a human population, to yield the Reference Dose (RfD).

The uncertainty regarding using animal toxicity to describe human toxicity (extrapolation from laboratory animal species to humans) is addressed by the interspecies extrapolation uncertainty factor (UF_A). The UF_A (typically a value of 10) is composed of two numerically equal parts: toxicokinetics and toxicodynamics. Toxicokinetics (i.e., pharmacokinetics) refers to the disposition of the chemical within the body (e.g., absorption, distribution, metabolism and elimination). Toxicodynamics refers to the effects the chemical has on the body (e.g., molecular and cellular interactions that disrupt normal cell functions).

The DAF addresses the toxicokinetic differences between species (one-half of the UF_A) and is not an uncertainty factor, but a data-based dose adjustment. However, some uncertainty in the extrapolation from animal to human remains. Since the magnitude of toxicity can also be influenced by species-specific toxicodynamic differences the toxicodynamics portion of the UF_A (typically $10^{0.5}$ or approximately 3) is retained. As a result, when an RfD based on animal studies is calculated, the interspecies uncertainty is typically 3 when an HED is calculated and 10 when unadjusted animal doses are used.

The application of this guidance involves more than a simple DAF adjustment to the POD for the study that, without adjustment, would be considered the critical study. HEDs must be calculated for the various dose levels utilized in the toxicity studies conducted for each chemical. The HEDs, rather than administered doses, will then form the basis for selecting the key (critical and co-critical) studies, point of departure, and health endpoints. The magnitude of the DAFs utilized to calculate HEDs vary depending upon which species have been tested. Additionally, the HED adjusted Lowest Observed Adverse Effect Level (LOAEL), rather than the administered LOAEL will be utilized when identifying health endpoints. Therefore, it is possible that when HEDs are calculated, the critical study, point of departure, and health endpoints may differ than if the toxicity database had been evaluated based on the administered doses.

There are situations for which application of $BW^{¾}$ scaling as a default to estimate HEDs may not be appropriate. These include: 1) when there is sufficient chemical-specific information; 2) when toxicity is a consequence of exposure to a very reactive parent compound or metabolite that is not removed from the site of formation by biological processes but chemically reacts with cellular constituents; and 3) when neonatal animals are dosed directly (differences in

temporal patterns of development as well as endpoint-specific toxicokinetic and toxicodynamic differences need to be considered).

The MDH chemical summary sheets contain a place to record the Human Equivalent Dose calculations (see example below):

Reference Dose/Concentration:	HED/Total UF = 0.15 mg/kg-d (Fischer 344 rats)
Source of toxicity value:	determined by MDH in 2017
Point of Departure (POD):	66.3 mg/kg-d (administered dose NOAEL, Smith et al. 2006)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA 2011)
Human Equivalent Dose (MDH, 2017):	POD x DAF = 66.3 x 0.23 = 15 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty

Evaluating and calculating a study-specific time-weighted average body weight and corresponding DAF for each study is resource intensive. To be resource efficient, MDH will identify key studies for further evaluation by estimating HEDs using generic DAFs. The DAFs are based on the appropriate species, strain, duration and gender specific body weight information contained in EPA's "Recommendations For and Documentation of Biological Values For Use in Risk Assessment (1988)" (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855)

Once key studies have been identified the following hierarchy for identifying the appropriate DAF is recommended:

1. study-specific time-weighted average (TWA) body weight information over the duration of the study, if readily available, and
2. generic body weight information for the appropriate duration, species, strain and gender from EPA 1988.
3. In situations where gender specific doses have not been specified, an average of the male and female DAFs will be used.
4. In situations where the specific strain is not specified within the study information or if information on the specific strain utilized in the critical study is not available in the EPA 1988 document, the duration and gender specific body weight DAF values will be averaged across the various strains for that species.

A compilation of strain, duration (subchronic & chronic) and gender specific body weight information for each laboratory animal species and corresponding DAFs have been summarized in the attached table. Staff will continue to track EPA's implementation of the Body Weight$^{3/4}$ scaling guidance and any relevant information on laboratory animal body weights.

MDH Practice

MDH anticipates that future EPA risk assessments will use HEDs in deriving RfDs. Per EPA recommendations, MDH risk assessors are now incorporating the BW¾ default adjustment in deriving RfDs for chemicals under review. The BW¾ adjustment will also be incorporated into previously derived HRLs, HBVs and RAA when those chemicals are re-evaluated in the future. Therefore, the use of this new guidance will not affect published guidance or the HRLs promulgated in 1993, 1994, 2009, or 2011. All guidance developed after 2011 will include an HED determination as part of the RfD calculations whenever applicable. In cases where the application of body weight scaling to estimate HEDs is not appropriate, MDH will individually evaluate each relevant study.

References

U.S. Environmental Protection Agency - Office of Research and Development (1988). Recommendations for and Documentation of Biological Values for Use in Risk Assessment. (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=34855)

U.S. Environmental Protection Agency - Office of the Science Advisor (2011). Recommended Use of Body Weight¾ as the Default Method in Derivation of the Oral Reference Dose. (https://www.epa.gov/risk/recommended-use-body-weight-34-default-method-derivation-oral-reference-dose)

Attachment – DAF Table

COMPILATION OF STRAIN, DURATION (SUBCHRONIC, CHRONIC) AND GENDER-SPECIFIC BODY WEIGHT INFORMATION AND CALCULATED DOSIMETRIC ADJUSTMENT FACTORS (DAFS)

Species and Duration	Animal TWA BW (kg)		Human BW (kg)	$BW_A^{1/4}$ / $BW_H^{1/4}$ =DAF		Source
	Male	Female		Male	Female	(see footnotes)
MICE						
Subchronic						
A/JCr	0.0243	0.0224	70	0.14	0.13	(b)
AKD2F1	0.0246	0.0209	70	0.14	0.13	(b)
AKR/LwCr	0.0252	0.0222	70	0.14	0.13	(b)
AL/NCr	0.0274	0.0251	70	0.14	0.14	(b)
B6AKF1	0.0234	0.021	70	0.14	0.13	(b)
B6C3F1	0.0316	0.0246	70	0.15	0.14	(a)
BAF1	0.0223	0.0204	70	0.13	0.13	(a)
BALB/cAnCr	0.0218	0.02	70	0.13	0.13	(b)
C3H/HeCr	0.0267	0.0255	70	0.14	0.14	(b)
C3HF/HeCr	0.0205	0.0181	70	0.13	0.13	(b)
C57B1/10ScCr	0.0269	0.0233	70	0.14	0.14	(b)
C57B1/6Cr	0.022	0.0198	70	0.13	0.13	(b)
C57L/Cr	0.0207	0.019	70	0.13	0.13	(b)
CBA/JCr	0.0263	0.0231	70	0.14	0.13	(b)
CBF1	0.0254	0.0218	70	0.14	0.13	(b)
Cr:GP(S).Swiss	0.027	0.0246	70	0.14	0.14	(b)
Cr:MGAPS (SW)	0.0246	0.0222	70	0.14	0.13	(b)
D2AKF1	0.024	0.0209	70	0.14	0.13	(b)
DBA/2Cr	0.0225	0.0214	70	0.13	0.13	(b)
NZB/Cr	0.0286	0.0255	70	0.14	0.14	(b)
NZW/Cr	0.0285	0.0255	70	0.14	0.14	(b)
PRI/PlCr	0.0302	0.0284	70	0.14	0.14	(b)
SJL/JCr	0.0243	0.0206	70	0.14	0.13	(b)

Species and Duration	Animal TWA BW (kg)		Human BW (kg)	$BW_A^{1/4}$ / $BW_H^{1/4}$ =DAF		Source
	Male	Female		Male	Female	(see footnotes)
SM/JCr	0.0182	0.0165	70	0.13	0.12	(b)
Various Inbred	0.024	0.022	70	0.14	0.13	(b)
ZWZBF1	0.0333	0.0235	70	0.15	0.14	(b)
	MOUSE SUBCHRONIC AVERAGE DAF			**0.14**	**0.13**	
			SD	**0.0048**	**0.0040**	
			MIN DAF	**0.13**	**0.12**	
			MAX DAF	**0.15**	**0.14**	
Chronic						
A/JCr	0.0302	0.0263	70	0.14	0.14	(b)
AKD2F1	0.0308	0.0233	70	0.14	0.14	(b)
AKR/LwCr	0.032	0.0259	70	0.15	0.14	(b)
AL/NCr	0.0364	0.0318	70	0.15	0.15	(b)
B6AKF1	0.0283	0.0235	70	0.14	0.14	(b)
B6C3F1	0.0373	0.0353	70	0.15	0.15	(a)
BAF1	0.0261	0.0222	70	0.14	0.13	(a)
BALB/cAnCr	0.0251	0.0214	70	0.14	0.13	(b)
C3H/HeCr	0.035	0.0326	70	0.15	0.15	(b)
C3HF/HeCr	0.0224	0.0176	70	0.13	0.13	(b)
C57B1/10ScCr	0.0354	0.0281	70	0.15	0.14	(b)
C57B1/6Cr	0.0255	0.021	70	0.14	0.13	(b)
C57L/Cr	0.0229	0.0194	70	0.13	0.13	(b)
CBA/JCr	0.0342	0.0277	70	0.15	0.14	(b)
CBF1	0.0324	0.0251	70	0.15	0.14	(b)
Cr:GP(S).Swiss	0.0356	0.0308	70	0.15	0.14	(b)
Cr:MGAPS (SW)	0.0308	0.0259	70	0.14	0.14	(b)
D2AKF1	0.0295	0.0233	70	0.14	0.14	(b)
DBA/2Cr	0.0265	0.0243	70	0.14	0.14	(b)
NZB/Cr	0.0389	0.0326	70	0.15	0.15	(b)
NZW/Cr	0.0387	0.0326	70	0.15	0.15	(b)

Species and Duration	Animal TWA BW (kg)		Human BW (kg)	$BW_A^{1/4}$ / $BW_H^{1/4}$ =DAF		Source
	Male	Female		Male	Female	(see footnotes)
PRI/PlCr	0.0421	0.0385	70	0.16	0.15	(b)
SJL/JCr	0.0302	0.0227	70	0.14	0.13	(b)
SM/JCr	0.0178	0.0143	70	0.13	0.12	(b)
		MOUSE CHRONIC AVERAGE DAF		0.15	0.14	
			SD	0.0078	0.0076	
			MIN DAF	0.13	0.12	
			MAX DAF	0.16	0.15	
RATS						
Subchronic						
ACP 9935/Cr	0.169	0.131	70	0.22	0.21	(c)
Acl 9935/Cr	0.168	0.137	70	0.22	0.21	(c)
ALBANY/Cr	0.24	0.184	70	0.24	0.23	(c)
August 28807/Cr	0.207	0.159	70	0.23	0.22	(c)
BN/Cr	0.21	0.138	70	0.23	0.21	(c)
BUFFALO/Cr	0.229	0.168	70	0.24	0.22	(c)
Copenhaagen/Cr	0.204	0.149	70	0.23	0.21	(c)
Cr:MGAPS (OM)	0.245	0.192	70	0.24	0.23	(c)
CR:RAR(SD)	0.263	0.202	70	0.25	0.23	(c)
Fischer 344	0.18	0.124	70	0.23	0.21	(a)
Long Evans	0.248	0.179	70	0.24	0.22	(a)
Marshall 520/Cr	0.217	0.143	70	0.24	0.21	(c)
NBR/PlCr	0.193	0.14	70	0.23	0.21	(c)
Osborne-Mendel	0.263	0.201	70	0.25	0.23	(a)
SH/Cr	0.205	0.143	70	0.23	0.21	(c)
Sprague-Dawley	0.267	0.204	70	0.25	0.23	(a)
S5B/PlCr	0.21	0.143	70	0.23	0.21	(c)
Wistar/Furth Cr	0.179	0.137	70	0.22	0.21	(c)
Wistar/Lewis Cr	0.289	0.234	70	0.25	0.24	(c)

Species and Duration	Animal TWA BW (kg)		Human BW (kg)	$BW_A^{1/4}$ / $BW_H^{1/4}$ =DAF		Source
	Male	Female		Male	Female	(see footnotes)
Wistar	0.217	0.156	70	0.24	0.22	(a)
Yoshida/Cr	0.271	0.154	70	0.25	0.22	(c)
			RAT SUBCHRONIC AVERAGE DAF	**0.24**	**0.22**	
			SD	**0.0095**	**0.0097**	
			MIN DAF	**0.22**	**0.21**	
			MAX DAF	**0.25**	**0.24**	
Chronic						
ACP 9935/Cr	0.3237	0.2466	70	0.26	0.24	(c)
Acl 9935/Cr	0.3217	0.2588	70	0.26	0.25	(c)
ALBANY/Cr	0.4678	0.3542	70	0.29	0.27	(c)
August 28807/Cr	0.4008	0.3034	70	0.28	0.26	(c)
BN/Cr	0.4069	0.2608	70	0.28	0.25	(c)
BUFFALO/Cr	0.4455	0.3217	70	0.28	0.26	(c)
Copenhaagen/Cr	0.3947	0.2832	70	0.27	0.25	(c)
Cr:MGAPS (OM)	0.4779	0.3704	70	0.29	0.27	(c)
CR:RAR(SD)	0.5144	0.3907	70	0.29	0.27	(c)
Fischer 344	0.38	0.229	70	0.27	0.24	(a)
Long Evans	0.472	0.344	70	0.29	0.26	(a)
Marshall 520/Cr	0.4211	0.271	70	0.28	0.25	(c)
NBR/PlCr	0.3724	0.2649	70	0.27	0.25	(c)
Osborne-Mendel	0.514	0.389	70	0.29	0.27	(a)
SH/Cr	0.3968	0.2771	70	0.27	0.25	(c)
Sprague-Dawley	0.523	0.338	70	0.29	0.26	(a)
S5B/PlCr	0.4069	0.271	70	0.28	0.25	(c)
Wistar/Furth Cr	0.344	0.2588	70	0.26	0.25	(c)
Wistar/Lewis Cr	0.5672	0.4556	70	0.30	0.28	(c)
Wistar	0.462	0.297	70	0.29	0.26	(a)
Yoshida/Cr	0.5307	0.2933	70	0.30	0.25	(c)

Species and Duration	Animal TWA BW (kg)		Human BW (kg)	$BW_A^{1/4}$ / $BW_H^{1/4}$ =DAF		Source
	Male	Female		Male	Female	(see footnotes)
		RAT CHRONIC AVERAGE DAF		0.28	0.26	
			SD	0.0114	0.0116	
			MIN DAF	0.26	0.24	
			MAX DAF	0.30	0.28	
DOGS (more specific values are available in EPA 1988, Chapter 3)						
3-Month Duration Study						
Beagles	6.4	5.4	70	0.55	0.53	(e)
6-Month Duration Study						
Beagles	8.1	6.75	70	0.58	0.56	(e)
1-Year Duration Study						
Beagles	9.6	8.25	70	0.61	0.59	(e)
1.5-Year Duration Study						
Beagles	10.5	9.1	70	0.62	0.60	(e)
2-Year or Longer Duration Study						
Beagles	11.0	10.0	70	0.63	0.61	(e)
RABBITS (more specific values are available in EPA 1988, Chapter 3)						
Subchronic						
New Zealand	2.86	3.1	70	0.45	0.46	(a)
Chronic						
New Zealand	3.76	3.93	70	0.48	0.49	(a)
GUINEA PIGS						
Subchronic						
	0.48	0.39	70	0.29	0.27	(a)
Chronic						
	0.89	0.86	70	0.34	0.33	(a)
HAMSTERS						
Subchronic						
Chinese & Djungarian	0.03	0.025	70	0.14	0.14	(a)

Species and Duration	Animal TWA BW (kg)		Human BW (kg)	$BW_A^{1/4}$ / $BW_H^{1/4}$ =DAF		Source
	Male	Female		Male	Female	(see footnotes)
Golden Syrian	0.097	0.095	70	0.19	0.19	(a)
Chronic						
Chinese & Djungarian	0.041	0.038	70	0.16	0.15	(a)
Golden Syrian	0.134	0.145	70	0.21	0.21	(a)
GERBILS						
Subchronic						
Mongolian	0.048	0.04	70	0.16	0.15	(a)
Chronic						
Mongolian	0.084	0.073	70	0.19	0.18	(a)
CATS						
Subchronic						
	1.72	1.49	70	0.40	0.38	(a)
Chronic						
	3.66	2.96	70	0.48	0.45	(a)
MINK (see EPA 1988 Figure 3-60 & 3-61 Growth Curves)						
Subchronic						
			70			(d)
Chronic						
			70			(d)
PRIMATES						
Chronic						
Rhesus	10.9	8	70	0.63	0.58	(a)
Chimpanzee	19.25	19.25	70	0.72	0.72	(a)

(a) EPA 1988, Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Table 1-2. Reference Body Weights.

(b) EPA 1988, Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Table 3-3. Reference Values for Body Weights of Various Strains of Mice

(c) EPA 1988, Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Table 3-5. Reference Values for Body Weights of Various Strains of Rats

(d) EPA 1988, Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Figure 3-60, Recommended Growth Curve for Male Mink and Figure 3-61, Recommended Growth Curve for Female Mink

(e) EPA 1988, Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Figure 3-46, Recommended Growth Curve for Male Beagle Dogs and Figure 3-47, Recommended Growth Curve for Female Beagle Dogs. Interpolation of time-weighted average body weights considered that dogs were 4 to 6 months old at the study onset, based on widely accepted EPA/OECD dog study protocol guidelines.

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