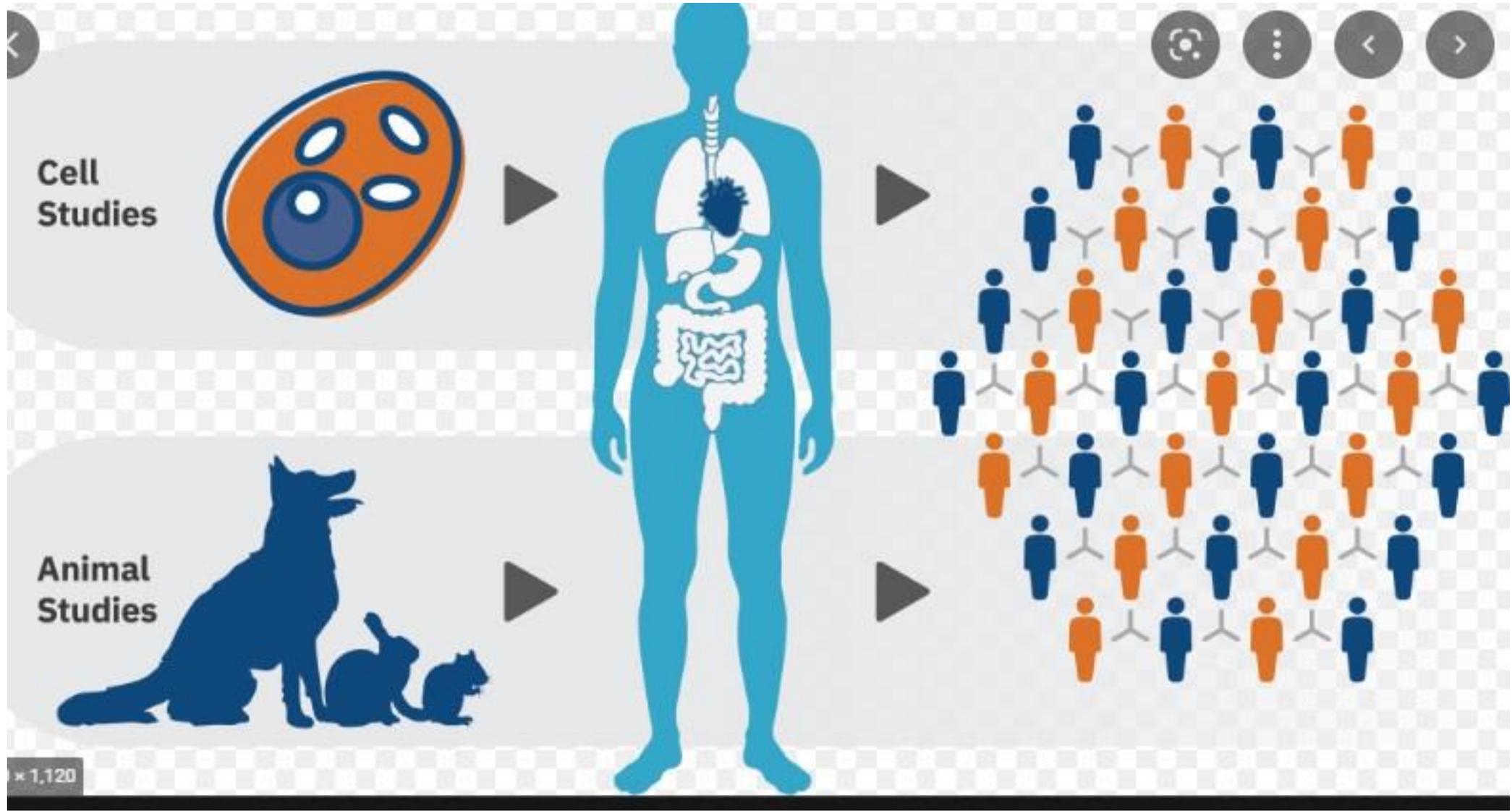# แนวทางระบุขนาดของยาที่ได้จากการทดสอบในสัตว์ทดลอง

Dose escalation from pre-clinical testing in laboratory animal

มาสเกียรติ บุญยฤทธิ์

กลุ่มสัตว์ทดลอง

สถาบันวิจัยวิทยาศาสตร์สาธารณสุข

Cell Studies

Animal Studies

× 1,120

Dose escalation

Meaning

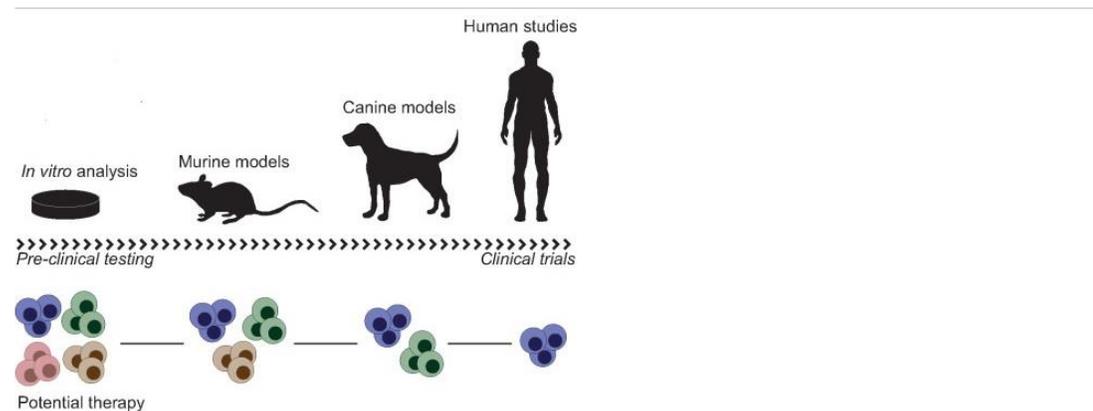A study that *determines the best dose of a new drug* or treatment

Figure 1 Naturally occurring cancers in dogs can facilitate the development of CAR T-cell therapies for cancer. Evaluating cell therapies (Potential Therapy) not only *in vitro* and murine models, but also in canines holds the promise to improve our ability to select the optimal cell product prior to performing clinical studies in humans.

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(16)45327-X

Dose escalation

Dose translation between laboratory animals and human in preclinical and clinical phases of drug development

Appropriate translation and determination of the <u>maximum recommended starting dose</u> in human is a vital task in new drug development and research
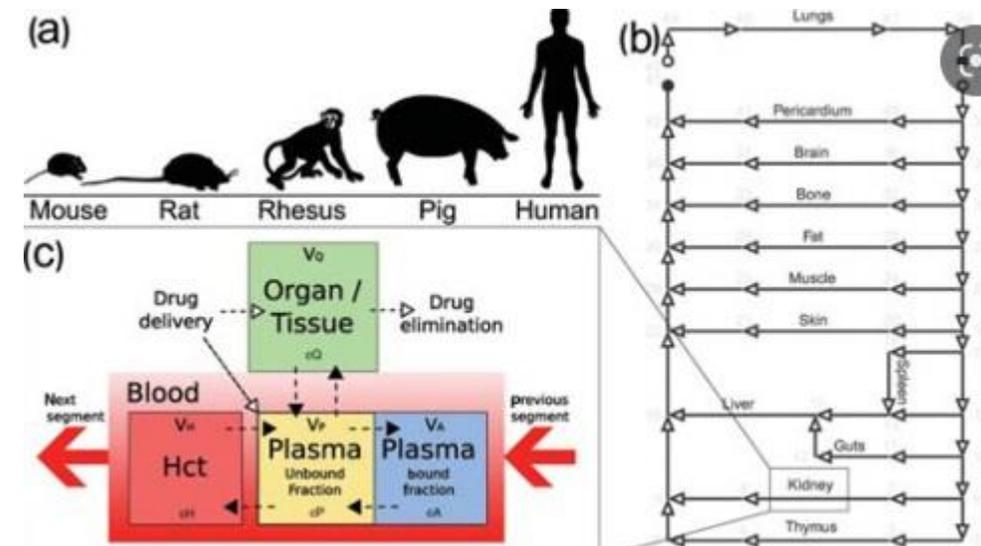
Dose escalation

The animal dose *should not be extrapolated to humans by a simple conversion* method based only <u>on body weight</u>, because many studies suggest the normalization method is based mainly on <u>body surface area</u> (BSA)
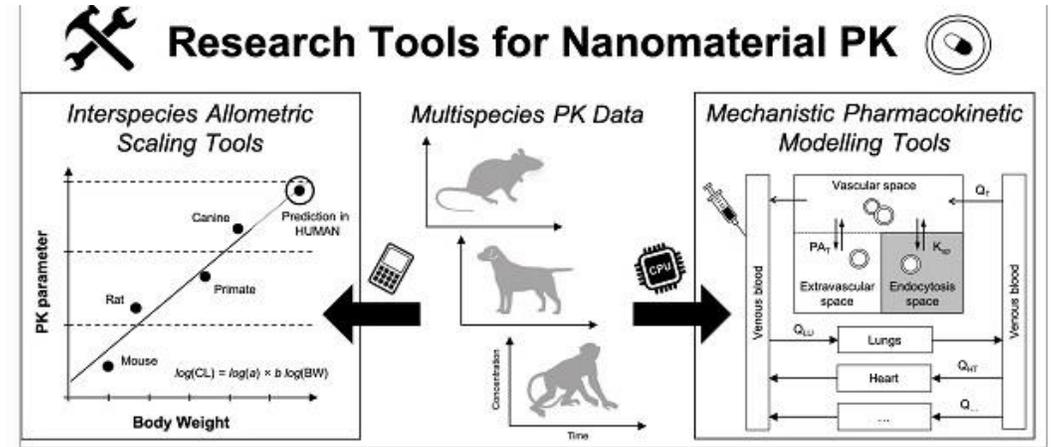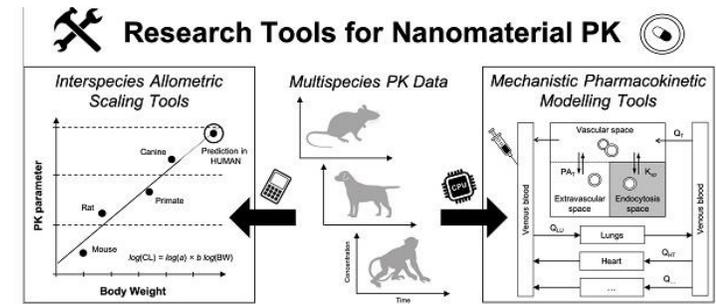
Dose escalation

In general, the body surface area seems to have good correlation among species with several parameters including oxygen utilization, caloric expenditure, basal metabolism, blood volume and circulating plasma protein

Dose escalation

A safety factor should be taken into consideration when deciding high dose in animal toxicology study

In cross-species extrapolation, various factors including pharmacological, physiological, and anatomical factors, metabolic function, receptor, life span, size, and so on should be considered

Research Tools for Nanomaterial PK

Interspecies Allometric Scaling Tools

Multispecies PK Data

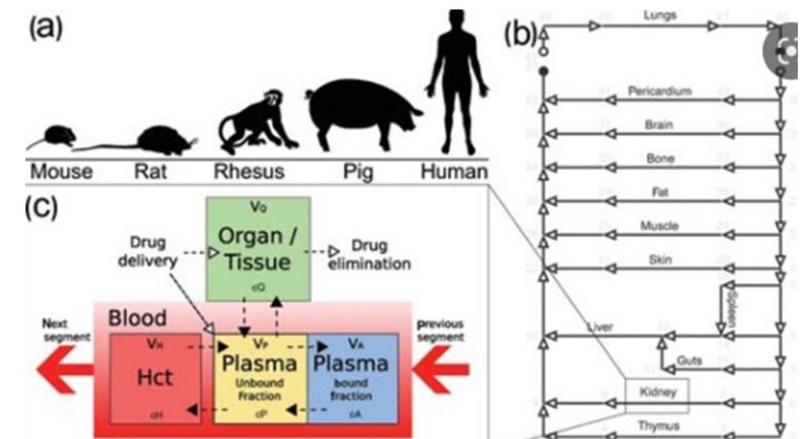Mechanistic Pharmacokinetic Modelling Tools

Dose escalation

Body size is important in the rate of distribution of compounds

For example, the mouse turns its blood volume every minute whereas in humans the cardiac output per minute is only 1/20 of blood volume

Therefore the mouse turns over its blood volume 20 times faster than the human

Dose escalation

Small animals *excrete compounds more rapidly* than larger animals in a rather systematic manner

Among various factors, body weight and body surface area are considered as two major approaches to scaling for general toxicity

Dose escalation

The ratio of blood volume in rabbits, guinea pigs and mice decreases with increasing body weight, while the relationship between blood volume to BSA is constant

Table 2. Total blood and sample volumes for species with specific body weight (i.e. volume estimates are based on the example body weight)

Species	Total blood volume (mL/kg)*	Example animal weight	Total blood volume	7.5%	10% (max. single sample)	15%	20%
Mouse	72	25 g	1.8 mL	0.14 mL	0.18 mL	0.27 mL	0.36 mL
Rat	64	250 g	16 mL	1.2 mL	1.6 mL	2.4 mL	3.2 mL
Guinea Pig	60	1 kg	60 mL	4.5 mL	6.0 mL	9 mL	12 mL
Rabbit	56	3 kg	168 mL	12.6 mL	16.8 mL	25.2 mL	33.6 mL
Cat	57	3 kg	171 mL	12.8 mL	17.1 mL	25.7 mL	34.2 mL
Dog	85	22 kg	1.87 L	140 mL	187 mL	281 mL	374 mL
Swine	65	45 kg	2.93 L	220 mL	293 mL	440 mL	585 mL
Sheep	60	80 kg	4.8 L	360 mL	480 mL	720 mL	960 mL

*For mature, healthy animals with an adequate plane of nutrition.

https://research.umn.edu/units/rar/guidelines/blood-collection

Dose escalation

Smaller animals have **relatively larger surface area** than larger animals

BSA is useful to estimate normal blood volume

Animal	Surface Area	Volume	SVR
	10	2	5
	1128	2016	0.56

Dose escalation

The impact of the *allometric exponent* on the conversion of an animal dose to human equivalent dose (HED) have emphasized that the use of BSA for dose calculation increases clinical trial safety

The approach of converting animal doses to an HED based on BSA is standard for estimating starting doses for initial study in health volunteers

Allometric scaling

DEFINITION

- **Allometry** is the study of the relationship of body size to shape, anatomy, physiology and finally behaviour.

- First outlined by **Otto Snell** in 1892 & Huxley, 1932.

- Allometric scaling is any change that deviates from Isometry.
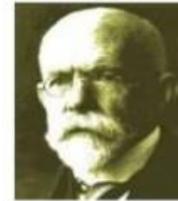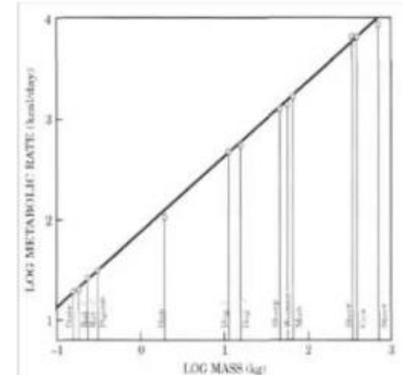
Christopher G. (1996)

Allometric scaling

ALLOMETRIC RELATIONSHIP:
BODY WEIGHT & BMR

- BMR = k$BM^{3/4}$ Cal/day .
  - Surface law* (Negative Allometry).
    - *Basal Metabolic rate per unit surface area of large and small animals is the same or is independent of body size (body Weight)*.

- $B \propto M^{3/4}$
  - *B - Metabolic rate*
  - *M - body mass*
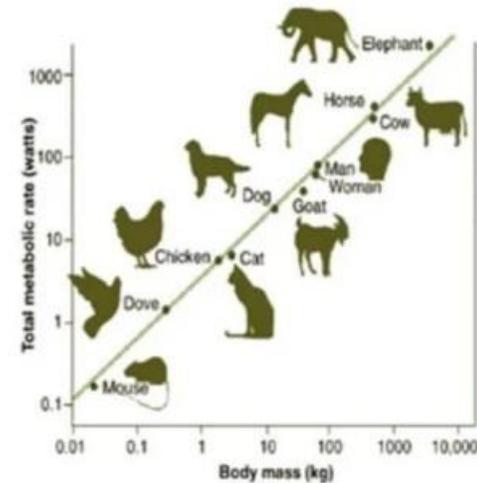 - $b \approx 3/4$ - Metabolic exponent

*(Rubner 1883)

Allometric scaling

CONT..

- This means that larger-bodied species (e.g., elephants) have lower Weight specific metabolic rates and lower heart rates, as compared with smaller-bodied species (e.g., mice).

- This straight line is known as the "mouse to elephant curve".

Brody et al. (1945)

Dose escalation

The Food and Drug Administration has also suggested that the extrapolation of animal dose to human dose is correctly performed only through normalization to BSA

Guidance for Industry and Reviewers

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.
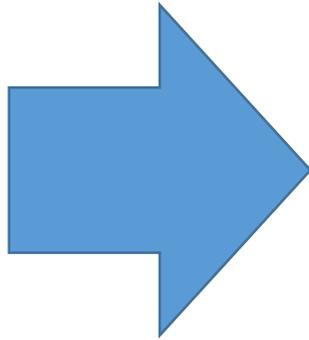
For questions regarding this draft document contact (CDER) Robert Osterberg, 301-594-5476 or (CBER) Martin Green 301-827-5349.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
December 2002
Pharmacology and Toxicology

Dose escalation

Table of Contents

Dose escalation

Table 1: Conversion of Animal Doses to Human Equivalent Doses (HED) Based on Body Surface Area		
Species	To convert animal dose in mg/kg to dose in mg/m², multiply by km below:	To convert animal dose in mg/kg to HED[a] in mg/kg, either:
		Divide animal dose by:	Multiply Animal dose by:

Draft — Not for Implementation

Species	km	Divide	Multiply
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54

Human equivalent dose calculation based on body surface area

Surface area has generally been calculated in formulae for converting doses as mg/m^2
= km × mg/kg

The **km factor** is not constant for any species, but **increases** as **body weight increases**

Human equivalent dose calculation based on body surface area

The km factor was calculated for a range of body weight using km=$100/K \times W^{0.33}$ where K is a value unique to each species

The HED calculated using the standard km value as shown in table 1 will not vary more than ± 20 percent from the HED calculated using a km value

Human equivalent dose calculation based on body surface area

Table 1. Conversion of Human Doses to Animal Doses Based on BSA.

Species	Body Weight (kg)	Working Weight Range (kg)	Body Surface Area (m²)	km Factor	Conversion Factor
Human					
Adult	60	-	1.6	37	1.00
Child	20	-	0.8	25	1.48
Baboon	12	7-23	0.6	20	1.85
Dog	10	5-17	0.5	20	1.85
Monkey	3	1.4-4.9	0.24	12	3.08
Rabbit	1.8	0.9-3.0	0.15	12	3.08
Guinea pig	0.4	0.208-0.700	0.05	8	4.63
Rat	0.15	0.080-0.270	0.025	6	6.17
Hamster	0.08	0.047-0.157	0.02	5	7.40
Mouse	0.02	0.011-0.034	0.007	3	12.33

Human equivalent dose calculation based on body surface area

HED can be calculated from the following formula:

$$\text{HED} \, (\text{mg/kg}) = \text{Animal dose} \, (\text{mg/kg}) \frac{\text{Animal } Km}{\text{Human } Km}$$

Human equivalent dose calculation based on body surface area

For example, suppose effective dose in mice is 1,000 mg/kg

HED (mg/kg) = 1,000 mg/kg × (3/37) = 81.1 mg/kg (4.866 g/day) in humans

$$HED\,(mg/kg) = Animal\ dose\,(mg/kg)\frac{Animal\ Km}{Human\ Km}$$

Human equivalent dose calculation based on body surface area

Controversy, suppose clinical effective dose is 200 mg/kg. Animal dose (mg/kg) = 200 mg/kg × (37/6) = 1,233 mg/kg in rats

$$HED(mg/kg) = Animal\ dose(mg/kg)\frac{Animal\ Km}{Human\ Km}$$

Human equivalent dose calculation based on body surface area

This can be calculated simply using the conversion factor in Table 1

Animal dose (mg/kg) =

$$\text{HED (mg/kg)} \times \text{Conversion factor}$$

HED (mg/kg) =

$$\text{Aimal dose (mg/kg)} \div \text{Conversion factor}$$

Human equivalent dose calculation based on body surface area

For example, suppose effective dose in mice is 1,000 mg/kg

HED (mg/kg) = (1,000 mg/kg) / 12.33 = 81.1 mg/kg (4.866 g/day) in humans

Animal dose (mg/kg) =

$\quad$ HED (mg/kg) × Conversion factor

HED (mg/kg) =

$\quad$ Aimal dose (mg/kg) ÷ Conversion factor

Discussion and Comment