Human effects modelling in USETox™

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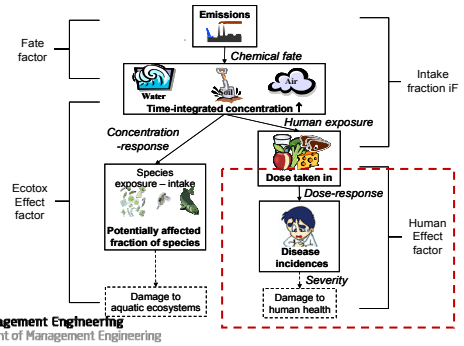
Objectives

- Introduce framework and definitions for human effects modelling in USETox™
  - What is a human health effect and how is it modelled
  - What is dose-response relationship
  - What is severity
- How the USETox™ apply the framework and what are the assumptions
- Illustrate through exercise how effect factors are calculated

USEtox framework



Characterization Factors: from emission to damage

$$\frac{\text{Damage}}{\text{Mass emitted}} = \frac{\text{Mass in environment}}{\text{Mass emitted}} \cdot \frac{\text{Intake dose}}{\text{Env. mass}} \cdot \frac{\text{Risk}}{\text{Intake dose}} \cdot \frac{\text{Damage}}{\text{Risk}}$$

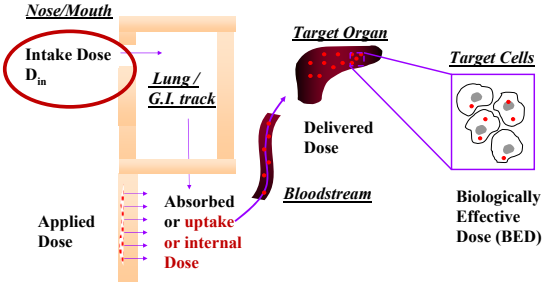
$$\text{Characterization factor} = \text{Fate} \cdot \text{Exposure} \cdot \text{Dose response} \cdot \text{Severity}$$

Definition: Dose-response

Dose-response Assessment:

Dose-response Assessment is the process that defines the quantitative relationship between the dose of a chemical received and the incidence of adverse health effects in the exposed population.

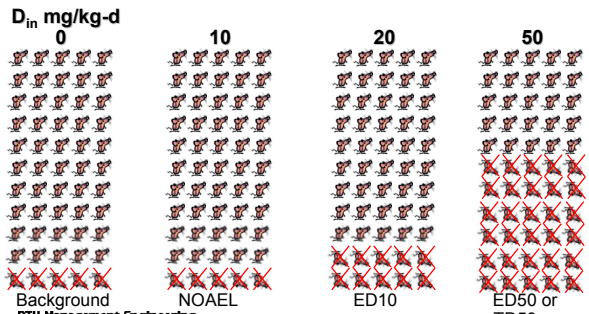
Definition: Dose Concepts and Terms

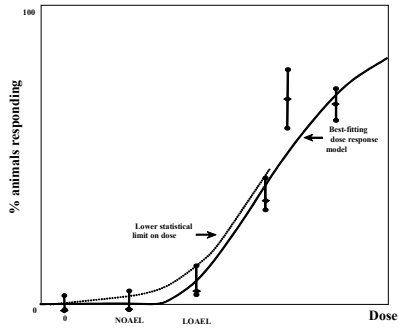


Target organs and types of adverse effects tested

- Target organs (examples)
  - Brain
  - Liver
  - Kidney
  - Thymus
- Types of adverse effects (examples)
  - Cancer
  - Neurotoxicity
  - Reproductive toxicity /developmental toxicity
  - Organ toxicity
  - Systemic toxicity
  - Allergy

Effect or toxic doses: example

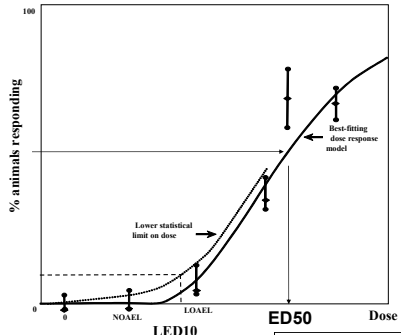




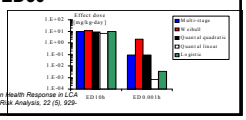
Effect dose and its 95% confidence limit

– Effect dose x: ED_x
(lifetime) dose generating an additional risk of x% over background
e.g 10% over background for an ED_{10}
e.g 50% over background for an ED_{50}

LED_x: Lower 95% confidence limit on ED_x

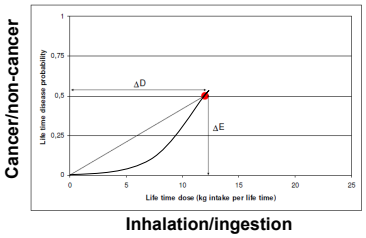


Below 10% effect, the answer depends only on the model retained !
Impossible to predict
(non-) linearity on the basis of bioassays !
→ mode of action is crucial



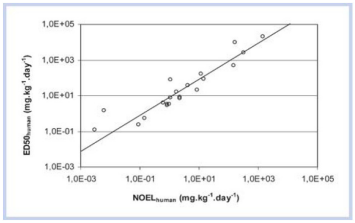
Crettaz, P. et al. 2002. Assessing Human Health Response in LCA using ED10s and DALYs: Carcinogens. Risk Analysis, 22 (5), 929-944. Non-cancer, 22 (5), 945-967.

USETox simplistic approach



Four effect factors are calculated:
- Cancer inhalation
- Cancer ingestion
- Non-cancer inhalation
- Non-cancer ingestion

From NOAEL and LOAEL to ED50



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Conversion factor NOEL to ED50: 9
Conversion factor LOEL to ED50: 2.25

Animal to human extrapolation

ED50h = ED50 animal/allometric factor
→ then select the smallest ED50 across species

Extrapolationfactors for interspecies variation (CFi)

Type	CF interspecies (-	Average bodyweight (k	Source
human	1	70	Vermeire et al., 2001
pig	1.1	48	Baird, 1996
dog	1.5	15	Vermeire et al., 2001
monkey	1.9	5	Vermeire et al., 2001
cat	1.9	5	first assumption
rabbit	2.4	2	Vermeire et al., 2001
hen	2.6	1.6	Baird, 1996
mink	2.9	1	first assumption
guinea pig	3.1	0.75	Vermeire et al., 2001
rat	4.1	0.25	Vermeire et al., 2001
hamster	4.9	0.125	Baird, 1996
gerbil	5.5	0.075	first assumption
mouse	7.3	0.025	Vermeire et al., 2001

Human effect factor (cancer/non cancer)

$$\text{Incremental Risk} = \text{Intake Dose} \cdot \frac{0.5}{\text{Life time dose generating 50\% additional risks}}$$

$$\text{Effect factor}: EF = \frac{0.5}{365 \cdot LT \cdot BW \cdot ED_{50h}} \cdot \text{Severity} = \frac{0.5}{ED_{50h}^{\text{lifetime}}} \cdot 10^6 \frac{mg}{kg} \left[\frac{cases}{kg_{in}} \right]$$

ED_{50h} Effect Dose inducing a response over background of 50% for humans (h) [mg/kg-day]
0.5 Response level corresponding to the ED_{50h} [Individual lifetime risk of cancer]
EF_i Effect factor of substance i [yr lost / mg intake]
$0.5/ED_{50}$ Slope factor of substance i [risk per mg/kg - day]
BW Body weight [kg/person]; 70 kg/person
LT_h Lifetime of humans [yr/lifetime]; 70 years
N_{365} Number of days per year [days/yr]

Example human effect factor

Chemical name	CAS	Rat oral TD50	Rat oral note	Rat oral tissues	Mouse oral TD50	Mouse oral note	Mouse oral tissues
		mg/kg-day			mg/kg-day		
2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN	1746016	0.0000235	mv	liv lun orc thy	0.000156	m	liv thy

1. Calculate the ED50h for dioxin from the ED50 animal

2. Calculate the lifetime ED50h,

3. Determine the cancer cases per kg dioxin ingested, that is the effect factor

Example human effect factor TCDD

$$ED_{50h} = \min\left(\frac{ED_{50rat}}{4.1}, \frac{ED_{50mouse}}{7.3}\right) = \min\left(\frac{0.0000235}{4.1}, \frac{0.000156}{7.3}\right)$$

$$= \min(0.0000057, 0.000022) = 0.0000057 \frac{\text{mg}}{\text{kg} \cdot \text{day}}$$

$$ED_{50h}^{\text{lifetime}} = 365 \cdot LT \cdot BW \cdot ED_{50h} =$$

$$365 \cdot 70 \cdot 70 \cdot 0.0000057 = 10 \left[\frac{mg}{lifetime} \right]$$

$$\text{Effect factor}: EF = \frac{0.5}{ED_{50h}^{\text{lifetime}}} = \frac{0.5}{10} = 0.05 \left[\frac{cases}{mg_{in}} \right] = 5 * 10^4 \left[\frac{cases}{kg_{in}} \right]$$

Exercise human effect factor: TCE

Chemical name	CAS	Rat oral TD_{50} mg/kg-day	Rat oral tissues	Rat inh TD_{50} mg/kg-day	Rat inh tissues
TRICHLOROETHYLENE	79016	-		668	m, tes
		Mouse oral TD_{50}	Mouse oral tissues	Mouse inh TD_{50}	Mouse inh tissues
TRICHLOROETHYLENE	79016	691	m, liv	4400	m, liv lun

1. Calculate the ED50h for inhalation and oral intake for TCE from the ED50 animal

2. Calculate the lifetime ED50h for inhalation and oral intake,

3. Determine the effect factor by inhalation and oral intake

Exercise human effect factor TCE

$$ED_{50h}\,inh = \min\left(\frac{ED_{50rat}}{4.1}, \frac{ED_{50mouse}}{7.3}\right) =$$

$$ED_{50h}\,ing = \min\left(\frac{ED_{50rat}}{4.1}, \frac{ED_{50mouse}}{7.3}\right) =$$

$$ED^{lifetime}_{50h,\,inh} = 365 \cdot LT \cdot BW \cdot ED_{50h} =$$

$$ED^{lifetime}_{50h,\,ing} = 365 \cdot LT \cdot BW \cdot ED_{50h} =$$

$$EF_{carc,inh} = \frac{0.5}{ED^{lifetime}_{50h}} = \qquad EF_{carc,ing} = \frac{0.5}{ED^{lifetime}_{50h}} =$$

Exercise human effect factor TCE

$$ED_{50h}\,inh = \min\left(\frac{ED_{50rat}}{4.1}, \frac{ED_{50mouse}}{7.3}\right) = 162.9\left[\frac{mg}{kg\,d}\right]$$

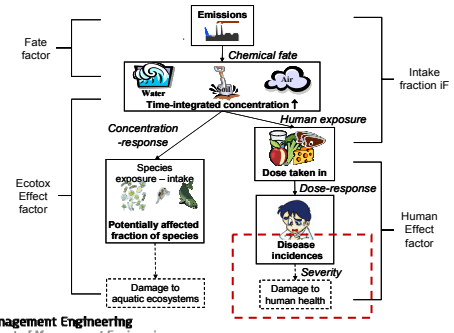
$$ED_{50h}\,orl = \min\left(\frac{ED_{50rat}}{4.1}, \frac{ED_{50mouse}}{7.3}\right) = 94.7\left[\frac{mg}{kg\,d}\right]$$

$$ED^{lifetime}_{50h,\,inh} = 365 \cdot LT \cdot BW \cdot ED_{50h} = 2.91 * 10^{8}\,\frac{mg}{lifetime}$$

$$ED^{lifetime}_{50h,\,orl} = 365 \cdot LT \cdot BW \cdot ED_{50h} = 1.69 * 10^{8}\,\frac{mg}{lifetime}$$

$$EF_{carc,inh} = \frac{0.5}{ED^{lifetime}_{50h}} = 1.72 * 10^{-3}\left[\frac{cases}{kg}\right] \qquad EF_{carc,orl} = \frac{0.5}{ED^{lifetime}_{50h}} = 2.95 * 10^{-3}\left[\frac{cases}{kg}\right]$$

USEtox framework

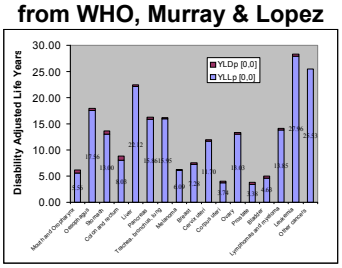


Characterization Factors: from emission to damage

$$\frac{Damage}{Mass\ emitted} = \frac{Mass\ in\ environment}{Mass\ emitted} \cdot \frac{Intake\ dose}{Env.\ mass} \cdot \frac{Risk}{Intake\ dose} \cdot \frac{Damage}{Risk}$$

$$Characterization\ factor = Fate \cdot Exposure \cdot Dose\ response \cdot Severity$$

Cancers severity from WHO, Murray & Lopez



Due to difficulty to determine human endpoint, taken the average for all cancers: 11.5 DALY/case

Carcinogens tumors severity: DALY, (as used by Hofstetter, 1998)

Disability Adjusted Life Years concept of Murray and Lopez [1996].

Disease type	YLL_e (y)	YLD_e (y)	$DALY_e$ (y)
Cancer			
Mouth and oropharynx cancer	5.7	0.5	6.2
Oesophagus cancer	17.6	0.4	17.9
Stomach cancer	13	0.6	13.6
Colon and rectum cancer	8	0.8	8.8
Liver cancer	22.1	0.4	22.5
Pancreas cancer	15.9	0.3	16.2
Trachea, bronchus and lung cancer	16.2	0.3	16.5
Melanoma and other skin cancer	6.1	0.2	6.3
Breast cancer	7.2	0.3	7.6
Cervix uteri cancer	11.7	0.3	12.0
Corpus uteri cancer	3.7	0.4	4.0
Ovary cancer	13	0.3	13.3
Prostate cancer	3.3	0.5	3.9
Bladder cancer	4.6	0.4	5.0
Lymphomas and multiple myeloma	13.9	0.3	14.2
Leukemia	28	0.3	28.3
Cancer average	11.0	0.5	11.5

YLL = Years of Life Lost

YLD = Years of Life lived Disabled

Disease type	YLL_e (y)	YLD_e (y)	$DALY_e$ (y)
Sense-organ diseases			
Glaucoma	0.3	5.6	5.9
Cataract	0.1	1.0	1.1
Cardiovascular diseases			
Rheumatic heart disease	19.2	1.3	20.5
Ischemic heart disease	8.5	0.7	9.2
Cerebrovascular heart disease	11	1.3	12.2
Inflammatory heart disease	5	0.5	5.5
Respiratory diseases			
Chronic obstructive pulmonary disease	5	3.2	8.2
Asthma	0.1	0.4	0.6
Congenital anomalies[a]			
Abdominal wall defect	45	0	45
Anencephaly	80	0	80
Anorectal atresia	16	0.2	16.2
Cleft lip	2.6	3.6	6.2
Cleft palate	5.8	7.8	13.6
Oesophageal atresia	80	0	80
Renal agenesis	80	0	80

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Severity: main challenges

Dose-response endpoint for animal → human endpoints: No direct relationship!!

For non-cancer diseases how to relate a toxicological endpoint to the disease?

Disability weights must be established by recognised body eg. WHO

→ so far equal severity in USEtox,

No severity = (Implicit) weighting in LCA, when summing up across substances assume equal severity !! Not ISO compatible

Available databases: Toxicity Data source

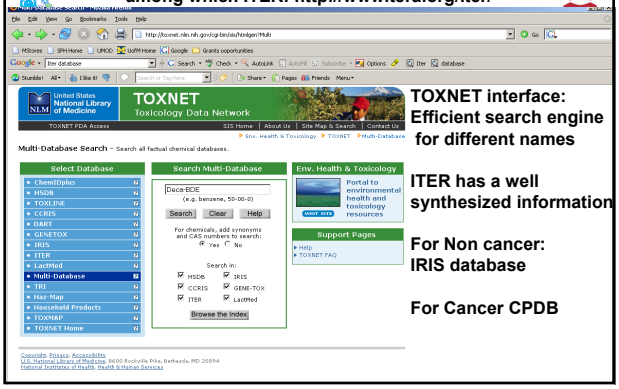
EPA Integrated Risk Information System (IRIS)
http://www.epa.gov/iris/

TOXNET → ITER (well synthesized)
http://toxnet.nlm.nih.gov/

The Carcinogenic Potency Database (CPDB)
http://potency.berkeley.edu/
60% of tested chemicals are positive for carcinogenicity!

INERIS (France)
http://chimie.ineris.fr/en/lien/basededonnees/toxicologie/recherche.php

Additional databases: http://toxnet.nlm.nih.gov/ among which ITER: http://www.tera.org/iter/

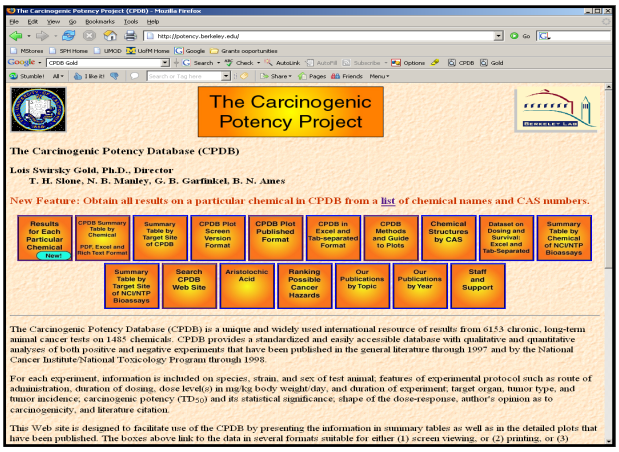


TOXNET interface: Efficient search engine for different names

ITER has a well synthesized information

For Non cancer: IRIS database

For Cancer CPDB



References

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