Human effects modelling in USETox™

Stig Irving Olsen
Quantitative Sustainability Assessment
DTU Management Engineering
siol@man.dtu.dk

Partly based on presentation by
Olivier JOLLIET
Center for Risk science and communication
Department of Environmental health Science
SPH, University of Michigan
ojolliet@umich.edu

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

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.
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

<table>
<thead>
<tr>
<th>D, mg/kg-d</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>NOAEL</td>
<td>ED10</td>
<td>ED50</td>
<td>TD50</td>
</tr>
</tbody>
</table>

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

Effect dose and its 95% confidence limit

- Effet 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

USETox simplistic approach

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

Example human effect factor: TCDD

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 TCE

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

\[
ED_{50,h} \text{ inh} = \min \left( \frac{ED_{50,inh}}{4.1}, \frac{ED_{50,inh}}{7.3} \right) \\
ED_{50,hg} = \min \left( \frac{ED_{50,hg}}{4.1}, \frac{ED_{50,hg}}{7.3} \right) \\
ED_{50,life} = 365 \cdot \text{LT} \cdot \text{BW} \cdot ED_{50,h} = \\
\text{EF}_{\text{inh, inh}} = 0.5 \cdot \frac{ED_{50,inh}}{3.7} \cdot \frac{ED_{50,h}}{1.4} \cdot \frac{ED_{50,life}}{\text{inh}} = \text{EF}_{\text{inh, life}} = 0.5 \cdot \frac{ED_{50,life}}{3.7} \cdot \frac{ED_{50,h}}{1.4} \cdot \frac{ED_{50,life}}{\text{life}}
\]

### USEtox framework

**Characterization Factors:** from emission to damage

Damage \quad Mass in environment \quad Intake dose \quad Risk

Mass emitted \quad Mass emitted \quad Env. mass \quad Intake dose \quad Risk

Characterization – Fatality Exposure – Dose response Severity

### Cancers severity from WHO, Murray & Lopez

Due to difficulty to determine human endpoint, taken the average for all cancers: 11.8 DALY/case

<table>
<thead>
<tr>
<th>Disease type</th>
<th>YLL (Years of Life Lost)</th>
<th>YLD (Years of Life lived Disabled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>24.4</td>
<td>21.6</td>
</tr>
<tr>
<td>Breast</td>
<td>14.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Brain</td>
<td>8.6</td>
<td>6.8</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>15.8</td>
<td>13.5</td>
</tr>
<tr>
<td>Cervix corpus</td>
<td>15.8</td>
<td>13.5</td>
</tr>
<tr>
<td>Colon</td>
<td>13.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Esophagus</td>
<td>17.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Liver</td>
<td>21.6</td>
<td>18.3</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Lung</td>
<td>13.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>12.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Mucosa</td>
<td>5.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Nervous system</td>
<td>6.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Nephroblastoma</td>
<td>7.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Ovary</td>
<td>13.8</td>
<td>11.4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>15.8</td>
<td>13.5</td>
</tr>
<tr>
<td>Prostate</td>
<td>17.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Rectum</td>
<td>13.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>3.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Testis</td>
<td>11.3</td>
<td>9.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>14.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Uterus</td>
<td>15.8</td>
<td>13.5</td>
</tr>
</tbody>
</table>

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

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

INERIS (France)

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


