USEtox® Update Form – Submission	
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(1) Title (update title)

Human toxicity non-cancer effects including uncertainty based on ED10

(2) Summary (1-2 sentences of main update content)

This update proposes a refined way of deriving human toxicity (non-cancer) effect factors based on using a wide range of underlying effect information from regulatory test data and data obtained from stochastic models. This approach is based on a global consensus model developed under the World Heath Organization/International Program on Chemical Safety (WHO/IPCS) and the resulting effect factors can be combined with existing and revised USEtox intake fractions to derive updated human toxicity characterization factors, as recommended in the latest UNEP/SETAC Pellston workshop.

(3) Reason(s) for updating USEtox (need, meaningfulness, added value)
- *a. Is the update meaningful to be considered in practice?*
- *b. What is the improvement from a practical point of view?*
- *c. Does the update entail an additional effort and is it worth it?*

a. The proposed update addresses several concerns of the current approach for deriving human toxicity (non-cancer) effect factors in USEtox. These concerns include a relatively low substance coverage for human toxicity effects, large deviations from the approaches followed for determining human toxicity effects in other assessment fields, using effect metrics that are not in the range of environmentally relevant exposure concentrations, assuming a linear slope up to the ED50, and the absence of uncertainty estimates around effect factors. Aligned with recent global consensus developments in risk assessment under WHO/IPCS, the update builds on a simplified stochastic approach. This approach allows considering a wide range of input data, characterizes uncertainty, and a non-linear extrapolation from ED50 to ED10 as a more environmentally relevant concentration level, which is also aligned with recommendations for ecotoxicity effect factor modeling (Owsianiak et al. 2019, Chapter 7).

b. In integration of this approach into USEtox and publication of related characterization factors will provide the user community with factors that can be readily applied in any LCA. This constitutes a fundamental step for increasing the substance coverage for human toxicity, allows for distinguishing reproductive and developmental from other non-cancer effects, provides an opportunity to address substances with very different effect severities, allows the characterization of uncertainty for each resulting factor, and provides a better alignment with environmentally relevant exposure concentrations.

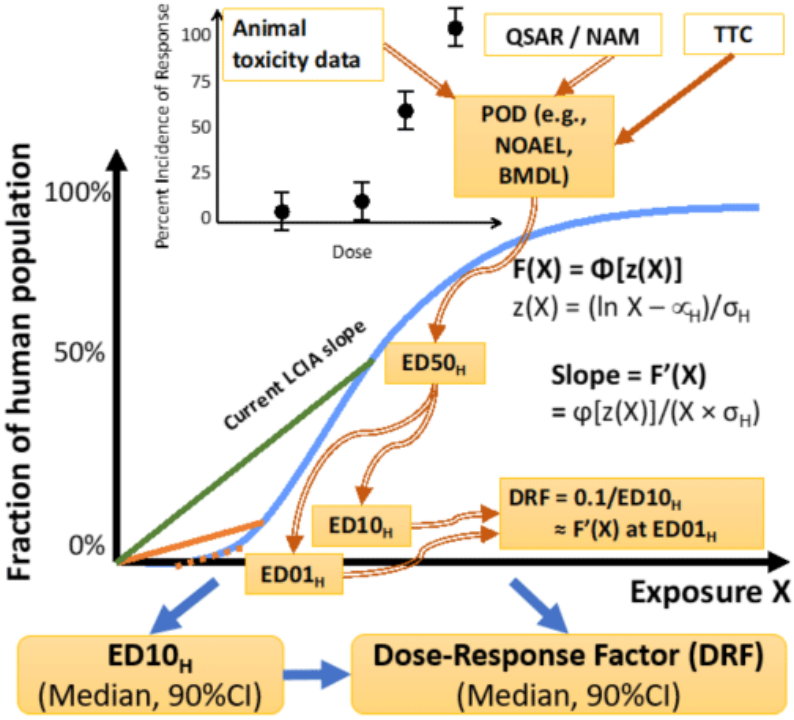
c. After the implementation of this update into USEtox, the user may readily apply the updated factors. For applying the update to new substances that users might wish to introduce into USEtox, there is similar effort required to collect and pre-process effect input data as compared to the currently followed approach.

(4) Method description

a. Explain main proposed USEtox modifications, how to achieve them and basics of scientific methods

b. How does the proposed method deviate from existing/established methods?

a. The update is already implemented in an Excel-based workbook, which can be transferred into the "human toxicity" data sheet of the USEtox model file. The general workflow is illustrated in the following figure:



(Source: Fantke et al. 2019)

- Inputs into the update are related to the underlying test data (e.g. exposure route and duration, effect type, and experimental-animal species) and the effect endpoint (e.g. NOAEL) for the given point of departure (POD).
- Input data are selected according to the following hierarchy:
  a) If regulatory animal toxicity values (e.g. NOAEL, BMDL) are available, select from hierarchy of sources and extract data;
  b) Else, check if other experimental-animal data are available, select or derive POD for each study/effect and extract data;
  c) Else, check if QSAR or other new approach methods (NAM) are available – as reference point, use the approach developed by Chiu et al. 2018, identify what effect/POD NAM is a surrogate for and extract data;
  d) Else, use threshold of toxicological concern (TTC) multiplied by 100 as NOAEL and add a TTC flag.

- For the POD, upper and lower 90% confidence interval bounds are estimated following this approach: Approximate probabilistic analysis combines uncertainties probabilistically assuming independent lognormal distributions, and defines Lower Confidence Limit (LCL) = P05, Upper Confidence Limit (UCL) = P95; given P50 and P95/P50, assumes P05 = P50/(P95/P50); given P05 and P95, assumes P50=SQRT(P05xP95).
- From the POD, a human dose-response factor is derived by first obtaining an $ED50_H$ (mg/kgBW/d) from POD-specific extrapolations according to:

$$ED50_H = \frac{\mathrm{PoD}}{PF_{BMD} \times PF_{BW} \times PF_{TKTD} \times PF_T \times PF_{H,I}} \quad (1)$$

PoD: Point of Departure, could be either BMDL, NOAEL or LOAEL
PF_{BMD}: Probabilistic factor for extrapolation from NOAEL (or LOAEL) to BMDL (if POD = BMDL, UF_{BMD} = 1)
PF_{BW}: Probabilistic factor for interspecies body weight (BW) scaling
PF_{TKTD}: Probabilistic factor for interspecies toxicokinetic (TK) / toxicodynamic (TD) differences
PF_T: Probabilistic factor for duration extrapolation
$PF_{H,I}$: Probabilistic factor for human variability in sensitivity for population incidence

- Next, from $ED50_H$, the effect dose at 10% response level, $ED10_H$ (mg/kgBW/d), is derived using a non-linear probabilistic approach proposed by Chiu and Slob 2015
- Then, to derive an effect metric compatible with USEtox, $ED10_H$ is converted into a lifetime dose, $DLT10_H$ (kg/lifetime) as:

$$DLT10_H = \frac{ED10_H \times BW \times LT \times cf_{d/yr}}{cf_{mg/kg}} \quad (2)$$

$ED10_H$: Effect dose at 10% response level (mg/kgBW/d)
BW: Human average body weight (kg)
LT: Human average lifetime (yr)
$cf_{d/yr}$: Conversion factor days per year (d/yr)
$cf_{mg/kg}$: Conversion factor mg per kg $(\mathrm{mg/kg})$

- Finally, the effect factor, EF (incidence risk/kg), is determined as linear slope to $ED10_{H,LT}$ as:

$$EF = \frac{0.1}{DLT10_H} \quad (3)$$

This central tendency linearly extrapolated slope from $ED10_H$ is also approximately equal to that of the marginal slope at $ED1_H$ (Fantke et al. 2019).

b. The update follows current recommendations for deriving non-linear dose-response estimates based on a stochastic approach that results from a global consensus building effort under WHO/IPCS. The update allows for a broader consideration of effect data and estimation methods, includes a characterization of uncertainty, and provides dose estimates that are more environmentally relevant than previous estimates in USEtox. Further, the update allows for distinguishing reproductive and developmental from other non-cancer effects based on different effect severity.

(5) Documentation and transparency check
- *a. List of scientific publications: What is the main publication and what are related publications?*
- *b. Description of full update content*
- *c. Description of level of detail of documentation*
- *d. What are data sources behind parameterization? (provide original data sources of new/updated data/methods)*
- *e. How has the update content been evaluated?*

a. Main publication:
- United Nations Environment Programme, 2019. Global Guidance on Environmental Life Cycle Impact Assessment Indicators: Volume 2. UNEP/SETAC Life Cycle Initiative, Paris, France. http://lifecycleinitiative.org/training-resources/global-guidance-for-life-cycle-impact-assessment-indicators-volume-2
- Chiu, W.A., Axelrad, D.A., Dalaijamts, C., Dockins, C., Shao, K., Shapiro, A.J., Paoli, G., 2018. Beyond the RfD: Broad application of a probabilistic approach to improve chemical dose-response assessments for noncancer effects. Environmental Health Perspectives 126, 1-14. http://doi.org/10.1289/EHP3368

Related/supporting publications:
- World Health Organization, 2014. Guidance document on evaluating and expressing uncertainty in hazard characterization. World Health Organization, Geneva, Switzerland, p. 191. http://who.int/ipcs/methods/harmonization/areas/hazard_assessment
- Chiu, W.A., Slob, W., 2015. A unified probabilistic framework for dose-response assessment of human health effects. Environmental Health Perspectives 123, 1241-1254. http://doi.org/10.1289/ehp.1409385
- Bokkers, B.G.H., Mengelers, M.J., Bakker, M.I., Chiu, W.A., Slob, W., 2017. APROBA-Plus: A probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances. Food and Chemical Toxicology 110, 408-417. http://doi.org/10.1016/j.fct.2017.10.038

b. A description of the update content is provided in the following documents:
- Fantke, P., Aylward, L., Bare, J., Chiu, W.A., Dodson, R., Dwyer, R., Ernstoff, A., Howard, B., Jantunen, M., Jolliet, O., et al., 2018. Advancements in life cycle human exposure and toxicity characterization. Environmental Health Perspectives 126, 125001. http://doi.org/10.1289/EHP3871

c. A full documentation of the underlying approach is found in above main and related/supporting publications, as well as at https://wchiu.shinyapps.io/APROBAweb

d. Data sources for the update are provided in above related/supporting publications, mainly building on curated animal test data and regulatory values for risk assessment from the US EPA

e. The update content has been checked against the original stochastic approach

(6) Applicability check
- *a. To which substances does the update apply? (all substances, inorganics, metals, etc.)*
- *b. Feasibility and influence in application: Is the update possible to consider in practice?*
- *c. What is foreseen in the future related to the update?*

a. The update provides new human toxicity (non-cancer) effect factors and related characterization factors for all substances in principle that fall within the applicability domain of the underlying stochastic approach.

b. The update is fully considerable in practice in its simplified version. It has been tested in several research projects as well as in several training courses. It serves both LCA and risk assessment needs, and is widely accepted in the risk assessment world.

c. There may be future recommendations regarding specific input data sources and estimation approaches regarding this update, but this is not scheduled in any way. Further, it is foreseen to apply this update to a wider range of organic substances to increase the substances coverage in USEtox.

(7) Level of consistency with USEtox check
a. Parsimony: How is the update parsimonious?
b. Data selection hierarchy (for previously published CFs and databases) as published in the official USEtox papers in IJLCA

a. The underlying model of the proposed approach is fully stochastic (e.g. Chiu et al. 2018). This approach has been simplified using median estimates and standard deviations to obtain uncertainty bounds, which has been identified during a UNEP/SETAC Pellston workshop to be the most parsimonious way to model human non-cancer toxicity effects in LCA based on widely accepted state-of-the-art effect assessment methods.

b. Proposed effect input data selection hierarchy: use regulatory toxicity values (e.g. NOAEL, BMDL) when available, else use experimental animal data (e.g. NOEL, ED50) when available, else use quantitative structure-activity relationships (QSAR) or other new approach methods (NAM) estimates, else use data based on threshold of toxicological concern (TTC) estimates (see Fantke et al., 2019, Figure 4.2). With this data selection hierarchy, we are fully aligned with recommendations in USEtox to start from best available data first (e.g. regulatory/experimental data) and alternatively using estimated data. The update will affect previously published USEtox factors and input data.

(8) Discussion of level of acceptance/consensus
a. Level of scientific acceptance/consensus in the community: Is update already used in published work?

a. The approach underlying this update has been recommended as state-of-the-art approach for use in probabilistic risk assessment by WHO's International Programme on Chemical Safety (IPCS), see IPCS 2014. The underlying approach has been used in a limited number of studies and publications, such as Chiu et al. 2018 to derive 1,464 reference doses across different non-cancer effects. The approach has also been implemented into a web-based version; see Chiu 2018. The update itself has been tested in a LCA case study on rice production and consumption, where non-cancer effects for 135 chemicals have been derived following the parameterized approach that is compatible with USEtox non-cancer effect modelling; see Fantke et al. 2019 (Chapter 4).

(9) Suggested reviewers (propose at least 2 independent reviewers)

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