InLCA: Selected Papers

Current Issues in the Characterisation of Toxicological Impacts

David W. Pennington

Life Cycle Group for Sustainable Development, GECOS, Dept. Génie Rural, Ecole Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, EPFL, Switzerland; e-mail: david.pennington@epfl.ch

Abstract. Fate, exposure and effect measures provide a basis for the calculation of characterisation factors in Life Cycle Assessment (LCA). Such characterisation factors provide insights into the relative concern of chemical emissions within and across life cycle inventories, in the context of toxicological stress to humans and to ecosystems. A brief overview is presented in this paper of the available options for toxicological characterisation and of associated issues that will need to be addressed in future consensus-building initiatives. An introduction is provided to issues such as: (1) the benefit of measures calculated at midpoints versus at endpoints in the toxicological cause-effect chains (sometimes termed environmental mechanisms); (2) the need to use multimedia models with spatial resolution; (3) the political consequences of accounting for variations in population density; (4) uncertainties in the toxicological potency measures; and (5) the different options for the toxicological endpoint measure(s). These issues are addressed under the headings of Fate and Exposure, Human Health and (aquatic) Ecosystem Health.

Keywords: Characterization factors; ecotoxicological, ecosystems; human health; InLCA; LCIA; Life Cycle Impact Assessment (LCIA); toxicological impacts

1 Introduction

Emissions data in a life cycle inventory (LCI) are multiplied by characterisation factors (also termed equivalency factors) to help estimate their relative importance within a given environmental impact category. A large number of characterisation methodologies have been proposed in the context of toxicological stress to humans and ecosystems. (Pennington and Yue 2000) These approaches range in complexity (data intensity, knowledge requirements), comprehensiveness (breadth or scope of representation), sophistication (relevance to and depth of representation of the environmental mechanisms) and accuracy (uncertainty inherent to the model and associated with input data) (Bare et al. 1999, Bare et al. 2000). The resultant uncertainties[1] can be high, sometimes preventing meaningful distinctions in LCA. However, in addition to addressing uncertainties associated with inventory data, commendable efforts to help identify the state-of-the-art in the chemical fate, exposure and effect components of the characterisation factors are underway by groups such as SETAC-Europe's Impact Assessment Initiative (Udo de Haes et al. 1999a, 1999b, Hauschild and Pennington 2001, Hertwich et al. 2001, Krewitt et al. 2001).

The international efforts of SETAC Europe will now continue under the broader umbrella of a global SETAC-UNEP initiative (Letter of intent 2000). Some of the current issues being faced by the LCA community, that were raised in the Virginia conference and that such international consensus building initiatives will need to address, are outlined in the following four sections of this paper (Midpoints versus Endpoints; Fate and exposure; Human health; Ecosystem health). These issues include the need to use multimedia models with spatial resolution; the implications of individual versus population risks in LCA; the uncertainties of available toxicological measures; and which toxicological endpoint measure to select, if indeed an endpoint measure is desirable.

2 Midpoint versus Endpoint

As a common midpoint in the cause-effect chain (or environmental mechanism; see **Fig. 1**) does not exist at the fate or exposure stage to fully describe the differences between chemicals in the context of toxicological impacts, available characterisation factors in Life Cycle Assessment account for all steps to an endpoint; namely fate, exposure, and toxicological effect (Guinee et al. 1996, Hertwich et al. 1998, Huijbregts 1999, Goedkoop and Spriensma 1999, Crettaz 2000):

$$\frac{\text{Effect}}{\text{Emission}} = \frac{\text{Fate}}{\text{Emission}} \cdot \frac{\text{Exposure}}{\text{Fate}} \cdot \frac{\text{Effect}}{\text{Exposure}}$$

So-called midpoint indicators (Bare et al. 2000) may not in themselves provide the basis for toxicological characterisation factors in LCIA, but some straightforward indicators of implicit concern can be useful for double-checking the

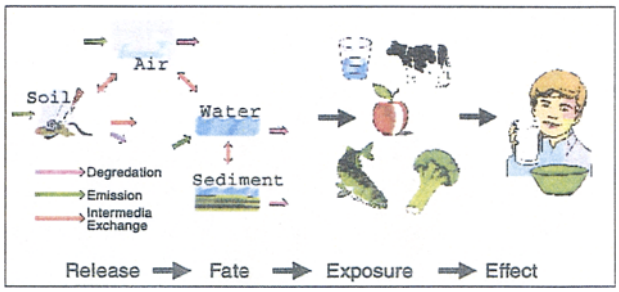

Fig. 1: Cause and effect chain (or web) for ecosystem and human health

[1] Model uncertainty: the accuracy and comprehensiveness of the model determined through evaluation studies. Scenario uncertainty: the relevance of the modelled scenario to the situation being considered. Parameter uncertainty: the uncertainty associated with the input data, as commonly determined using Monte-Carlo analysis.

results of approaches that attempt to more precisely represent environmental mechanisms (Pennington and Bare 2001) or as parallel precautionary indices (Hofstetter 1998, Hofstetter et al. 2000). Examples of midpoint measures adopted in chemical screening include overall persistence[2], bioaccumulation and toxic potency scores. For example:

1) The limited representation of aquatic food webs in a multimedia multi-pathway model in one case study resulted in misleadingly low characterization factors for some chemicals (Pennington and Bare 2001). The error, due to the missing link between contaminants in sediment and the aquatic food web, was spotted through a crosscheck with straightforward indicators of persistence, bioaccumulation and toxicity (so-called PBT indicators).
2) Chemicals can be compared in terms of their overall persistence alone, as many of the effects of chemicals with long environmental residence times may still be unknown. (Scheringer 1999) DDT, a substance that was originally considered a benign answer to many problems and continues to be used today, is one historic illustration of where such precautionary indices could have proved beneficial at an early stage.

3 Fate and Exposure

Multimedia fate and exposure models are commonly adopted in LCA to help estimate toxicological characterisation factors.[3] Their fundamental principles are well established, although models can differ in terms of scope and comprehensiveness. Historically, however, the adoption of multimedia models has been hampered by a perceived lack of available degradation half-life data (for air, water, soil and sediment) and by a lack of transparency. These beliefs are now somewhat changing, particularly given the emerging development of data prediction tools, guideline-based approaches to predetermine which degradation data will be required (Pennington 2000a) and the simplification of models using modular approaches (Jolliet and Crettaz 2000). Focus is now starting to turn to issues such as spatial resolution and associated uncertainties.

Based on the solutions of simultaneous differential equations, multimedia models account for competing degradation, intermedia transport and advective transport processes. Spatial variation within each environmental medium of a modelled region is not commonly taken into account in current practice. With few exceptions, the concentration of a chemical in each environmental medium is considered to be uniform (i.e. air is assumed well mixed; surface waters are well mixed together; etc.). Although extensively used in LCA to-date, in most cases, such single-region models were only designed to provide preliminary insights into the principle fate processes of chemicals. As many available multimedia multi-pathway models do not account for spatial variation, the importance of factors such as population density variation, watershed boundaries (hydrologically-defined geographic boundaries) and wind patterns are ignored. The ability of single-region multimedia models to provide realistic estimates of average concentrations and human exposure doses across a region for use in comparative applications like LCA is therefore questioned.[4]

Some practitioners prefer single medium models (models that do not account for intermedia transport but focus on the fate of a chemical in one environmental medium). Such models often have spatial resolution capabilities but their use is only applicable if risks to ecosystems and humans are primarily associated with the medium of release (e.g. in the context of primary air pollutants (Nigge 2000, Potting 2000). This is not, however, the case for many chemicals. The principle route of human exposure to benzene released to surface waters is still inhalation. A multimedia solution with spatial resolution is therefore still required.

Research is ongoing to determine a best-available practice (Hertwich et al. 2001) and the extent to which next-generation models provide additional information, hence further distinction amongst characterization factors in LCIA. Both location-specific and 'generic' characterisation factors can be developed using multi-region multimedia multi-pathway models (US EPA 1999, Mackay et al. 2000, Pennington 2001). Generic factors can be used with LCA inventory (emissions) data in the common absence of release location information. An estimate of the uncertainty associated with the lack of release location information is provided. The need for generic, as well as location-specific, characterisation factors is discussed in the next section (4) under the subheading 'population basis'.

4 Human Health

In the context of human health, two toxicological characterisation approaches are identifiable in the LCA literature that differ primarily in terms of their effect endpoint (Krewitt et al. 2001):

(1) Guinee et al. (1996), Hertwich et al. (1998), Huijbregts (1999), and others, provide indicators in the context of non-carcinogenic and carcinogenic effects. Population density and the severity of the effect are not considered (all severities are implicitly assumed equal[5] – "an effect is an effect" – and population density does not vary).
(2) Hofstetter (1998), Goedkoop and Spriensma (2000), Crettaz (2000), and others, proposed an alternative; some-

[2] The overall persistence of a chemical is defined as a chemical's tendency to remain in the environment unless removed by irreversible degradation to another chemical species. Overall persistence is often estimated using multimedia models and is represented by the chemical's residence time or half-life in the environment. This is a measure that relates to the fate of chemicals. (Pennington 2000a)

[3] Steady state, first order differential approaches are usually adopted, to help take into account the full time-integrated impacts associated with a given mass of a chemical emitted (the basis of inventory data). The use and relevance of dynamic approaches in LCA, except to calculate the time-integrated exposure, requires further discussion – particularly if spatial resolution is to be taken into account.

[4] Studies to-date have primarily focused on the variation of geographic and climatic parameters within single-region models, often demonstrating significant variation exists. Differences in degradation rates are commonly ignored in such studies and the suitability of assumptions associated with single-region models have not been assessed.

[5] Hertwich et al. (1998) presented separate factors for carcinogenic and non-carcinogenic effects.

times termed the 'damage' or severity-based approach. Population density and differences in toxicological severity are taken into account. Results are presented in terms of Disability Adjusted Life Years (DALYs)[6] experienced by a given population, for example.

Uncertainties and differences between the effect endpoints in these two approaches are outlined in the next three subsections.

Population Basis: The population-basis issue has significant implications when considering production in different regions and across international boundaries. This issue is not new in risk assessment (e.g. individual risk versus risk to a population) and, despite only limited discussion, exists in LCA.

Using severity-based LCIA approaches, an emission in a sparsely populated country can have a lower influence on an LCA result than the same emission in a densely populated country. Analogously, even if the process is identical, a product made in one region may be of lesser importance than the same product made in a more densely populated region. However, the risk to an individual can be equal in both of these cases. The significance of the differences, hence between the two types of LCIA approaches above, is dependent on the location of the emissions and the long-range transport characteristics of the associated chemicals. Location and transport can be taken into account using fate models with a spatial dimension.

The use of spatially explicit characterisation factors that can account for differences in population distributions introduces complexities and value-judgements into LCA, some with significant political consequences that need to be addressed in international forums such as the UNEP-SETAC initiative (Letter of intent 2000). However, even if severity-based approaches are widely considered appropriate in LCA and other beyond-compliance initiatives, the location of many of the emissions in a product's inventory may remain unknown. A need therefore remains to avoid sole reliance on spatially explicit factors. One option is to provide generic equivalency factors for human health with uncertainty distributions that account for the implications of omitting spatial distinction (such as the median and the associated spread of factors calculated using models with spatial capabilities). Although preliminary insights are emerging (Hofstetter 1998, Nigge 2000, Crettaz 2001, Pennington 2001), the significance of this issue needs to be further clarified.[7]

Effect Potency[8]: The basis, hence relevance, of available toxicological potency measures varies tremendously. Screening measures attempt to provide a conservative basis, derived using deterministic extrapolation factors[9], but the associated degree of conservatism is often unknown and chemical specific. If adopted blindly in a relative comparison context, a practice in many LCAs, this introduces uncertainty and bias that are not quantified.

In recent years, risk assessors and risk rankers have increasingly been moving away from deterministic screening approaches to more probabilistic methodologies (Jager et al. 1997). These methodologies can help describe plausible variation (e.g. natural variation in body weights in a population) and uncertainty (e.g. ignorance about the actual value or range of a given parameter) in LCA through the use of probabilistic distributions. The distributions are determined from empirical studies of available data for each extrapolation that is required to derive a relevant measure (e.g. extrapolations from rat acute to rat chronic to human chronic data), as summarized in Pennington (2000b). Such probability-based approaches facilitate greater consistency in comparisons (e.g. using median estimates as the basis of the potency measure), as well as providing an indication of uncertainty. The distributions can also be compared to determine if a statistically significant distinction exists between emissions in a given LCA inventory and between different products. As some decision-makers are uncomfortable with answers in the form of probabilistic distributions, results can be presented in the form of summary statistics (e.g. median, 5th and 95th percentiles).[10] A need therefore exists to advance current practice in LCA and embrace such probabilistic approaches.

Effect Severity[11]: Toxicological impacts differ in terms of severity and such differences can be described qualitatively. Approaches such as DALYs (Disability Adjusted Life Years) and QALYs (Quality Adjusted Life Years) are adopted in some LCIA (damage) approaches to help quantitatively take effect severity into account. QALYs and DALYs are gaining popularity but criticism is also increasing:

1) Similar to potency, the severity of the effect(s) of an emission in the human population can be highly uncertain and often unknown.[12]
2) Unlike the potency of a chemical and qualitative classification of effects by type, the quantification of severity is dependent on an individual's or a societal perspective.

Ongoing research is necessary to determine if effects in human populations exposed to complex chemical mixtures can be readily predicted from available data for specific substances (concordance between the effects in species), how to best represent the implications of differences amongst ef-

[6] Disability Adjusted Life Years and Quality Adjusted Life Years (QALYs) are examples of measures used to account for perceived differences in the severity of a toxicological effect. See Hofstetter (1998) for further discussions.

[7] Some releases in a life cycle occur at multiple locations, particularly when considering multiple suppliers/producers. As the number of locations increases, the need for location-specific characterisation factors or the uncertainty associated with the use of generic factors may decrease; a parallel issue also requiring consideration.

[8] Distinguished here as the quantity of a chemical required to cause a given effect, usually reported in terms of a dose or concentration.

[9] For example, animal (rats and mice) No Observed Effect levels (NOELs) can be divided by a factor of 100 to predict reference doses (RFDs) for humans. In many cases, but not all, these doses will be conservative. An RfD is defined as the daily dose of a chemical (mg/kg body weight) that is unlikely to cause an adverse health effect during a human lifetime.

[10] Caution is required to account for covariant uncertainties when comparing alternatives. There are implications associated with the choice of the summary statistic and defining what is statistically differentiable is a value judgement.

[11] Distinguished here as the consequences or outcome associated with a given effect.

[12] The severity of an emission on humans exposed to complex chemical mixtures cannot be easily determined from chemicals tested in isolation on laboratory animals, or predicted. Many even suggest extreme caution when trying to estimate potency, advocating concern when going beyond but, at the same time, noting that potency and severity are strongly related. Epidemiological data can be of help in some cases to describe the expected type of effect, hence severity, although correlations found in some of these studies do not necessarily imply cause and the number of chemicals studied remains small.

fects (e.g. quantitative vs. qualitative), and the utility/defensibility of epidemiological data in LCA.

5 Ecosystem Health

The fate component of characterisation factors for human health and ecosystems is usually identical. Available characterisation methodologies for ecotoxicological impacts differ primarily in terms of the effect endpoint measure (Hauschild et al. 2001. Available potency measures, their relevance in the context of environmental mixtures and the choice of endpoint are briefly summarized in the following sections to provide an indication of challenges being faced by LCIA researchers.

Biomagnification: As in human health, the food chain plays an important role in the exposure of higher trophic level species (e.g. predators) to chemicals. However, particularly for aquatic species, exposure is commonly considered in LCA in terms of uptake via respiration and dermal contact alone (termed bioconcentration). Ingestion uptake and potential increases in exposure due to the build-up of chemicals in food webs (termed biomagnification), which can result in 'secondary poisoning', often remain ignored. A need therefore exists to establish the importance of biomagnification in the context of the endpoint measure(s) adopted.

Ecotoxicological Potency: A wide variety of effect measures have been proposed to help characterise ecotoxicological impacts in LCA, ranging from toxicological potencies for individual, or important, species like Daphnia or Salmon to measures for entire ecosystems. Potency measures for entire ecosystems are sometimes considered more relevant in LCA and include: the Hazardous Concentration at the 5th percentile (HC_5) on a species sensitivity distribution (SSD, as described in Posthuma & Suter 2000 and illustrated in Fig. 2); the Predicted No-Effect Concentration (PNEC) (the concentration below which a specified percentage of species in an ecosystem are expected to be protected (5% is commonly chosen, i.e. the HC_5); the assumption of a secant gradient (gradient between the origin and the concentration at a given effect level on the SSD, e.g. $0.05/HC_5$); and the tangential gradient (tangent at a given point or background condition on an SSD curve).[13] The two gradient-based measures are illustrated in Fig. 2 and facilitate estimation of the change in effect associated with a change in exposure concentration for an ecosystem (sometimes termed the marginal approach in LCA).

Only a limited quantity and quality of ecotoxicological data, usually acute (from short-term exposure tests), are available for individual species. To compare emissions and chemicals in the context of long-term exposures (chronic) and effects on the species in entire ecosystems, such acute toxicological data require extrapolation to more relevant measures. Calculation of the PNEC measure, for example, often involves extrapolations using 'assessment factors' (sometimes termed safety, uncertainty, or application factors).[14] Assessment factors are often policy-based and, in general, help to ensure that PNECs provide conservative estimates of values like the HC_5 in screening applications. However, as such, the degree of conservatism is not usually specified, nor consistent, and 'extrapolated PNECs' are not suitable for use in comparative tools like LCA. Alternative approaches are therefore required in LCA, such as the probabilistic methods adopted in the derivation of benchmarks like the US Ambient Water Quality Criteria and the Great Lakes Water Quality Criteria. (The basis of such probabilistic approaches was described in the previous human health section and a compiled summary of extrapolation distributions is presented in Pennington and Payet 2001a, for example.)

[13] Limitations of species sensitivity distribution (SSD) curves and measures like the HC_5 are not addressed in this paper, nor are they typically considered in current practice. Such limitations can include the assumption of a mathematical form of the distribution, use of NOECs rather than measures like EC_{10}s (concentration at which 10% of the species are predicted to be affected), the lack of consideration of species co-dependence in food-webs or biomagnification (increased exposure at higher trophic levels in the food-web due to consumption) and the site-specific nature of ecosystems.

[14] For example, the PNEC for an aquatic ecosystem is commonly derived from the lowest LC_{50} (Lethal Concentration in a short-term exposure test at which 50% of a given species are killed) divided by a factor of 1000. This factor accounts for differences with the desired measure or scenario in terms of exposure duration (short to long term), effect endpoint (50% mortality to no morbidity effects) and the number of species represented (sample size).

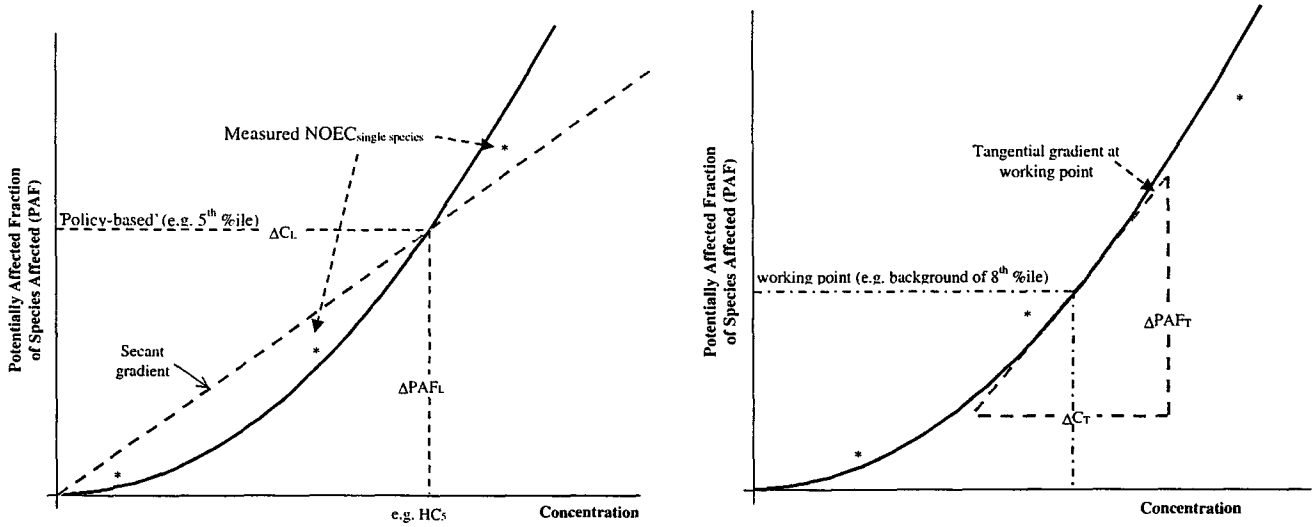

Fig. 2: Species sensitivity distribution (SSD) and potency measures

Mixtures: The existence of thresholds (levels below which effects do not occur) and how to treat them remain ongoing topics of discussion. However, exposures occur in the environment in the presence of complex mixtures and thresholds associated with chemicals tested in isolation may prove irrelevant. The assessment of exposure to a chemical in isolation may result in the conclusion that it poses no significant risk or threat. If background mixtures are then taken into account and these mixtures contain other substances that are toxicologically similar, for example, exposure to the overall mixture can result in unacceptable concern. These issues are pertinent in both the earlier discussions of human health as well as in the context of ecotoxicological impacts, hence require further investigation and discussion. Some insights are briefly presented below.

If chemicals do not interact[15] then their contributions to the effect of mixtures in the environment can be either dose-additive or response-additive. If their modes-of-toxic-action are similar (sometimes relaxed to similar target organs) dose-additive is assumed. If the chemicals act independently then response-additive is assumed.

In the case of dose addition, the doses of the components are scaled by their potency and then added together (assuming parallel dose-response curves and similar modes-of-toxic-action; i.e. the chemicals act as clones). A single SSD curve for a reference chemical can then be used to estimate the response of the entire mixture. Assuming response addition, which is common in the context of carcinogenic risk to humans or for impacts with no thresholds, the responses are first determined for each component (or sub-group of similarly acting components) and then the individual responses are added together.[16] The consequences of these differences are illustrated in Fig. 3.

In a recent effort to take mixtures into account, Goedkoop and Spriensma (2000) adopted a tangential gradient of $\Delta\text{combi-PAF}/\Delta C_T = 0.4/HC_{50}$ for all chemicals based on background combi-PAF estimates between 10 to 50% (the combi-PAF is the overall Potentially Affect Fraction of species (PAF) associated with a mixture of chemicals). This particular value is not highly sensitive to modification of the distribution model for the SSD (log-linear, log-triangular, log-logistic) nor to the background combi-PAF within the reported range. However, it is important to note that the applicability of the underlying assumptions of this approach are undergoing further evaluation and may only be appropriate in the unlikely case of all chemicals in the environmental background mixture considered being dose-additive (Pennington and Payet 2001b, Hauschild and Pennington 2001).

A secant gradient approach can be adopted as an alternative to the assumption of a single tangential gradient. It can be assumed that the number of species that experience an increase in stress due to a specific chemical emission (or cluster of emissions with similar modes-of-action) will be less than 5%. If the effect were greater than 5% then, based on common risk assessment practice, regulatory action would be warranted. That is not to say that the combined response-additive effects of the overall mixture of chemicals will be less than 5% or that risk assessment is infallible. It can be demonstrated that the gradient on the SSD of a chemical (or

[15] If chemicals interact (toxicokinetically and/or toxicodynamically) then the interactions are commonly described as antagonistic (less than additive) or synergistic (greater than additive). However, it can be assumed in LCA that interactions at low dose levels either do not occur at all or are small enough to be insignificant in most cases.

[16] Independent risks can be combined using the statistical law of independence (e.g. total risk = $1-(1-r_1)(1-r_2)$; one minus the product of the probabilities of not responding to any of the chemicals; analogously combi-PAF = $1-(1-PAF_1)\cdot(1-PAF_2)$). However, for small risks, the statistical law of independence can be simplified (e.g. total risk = $r_1 + r_2$). Hence, whether the additive effects on an ecosystem are treated as probabilities (combi-PAF = $1-(1-PAF_1)\cdot(1-PAF_2)$) or, more plausibly, they are added (combi-PAF = $PAF_1 + PAF_2$) will be of little theoretical consequence.

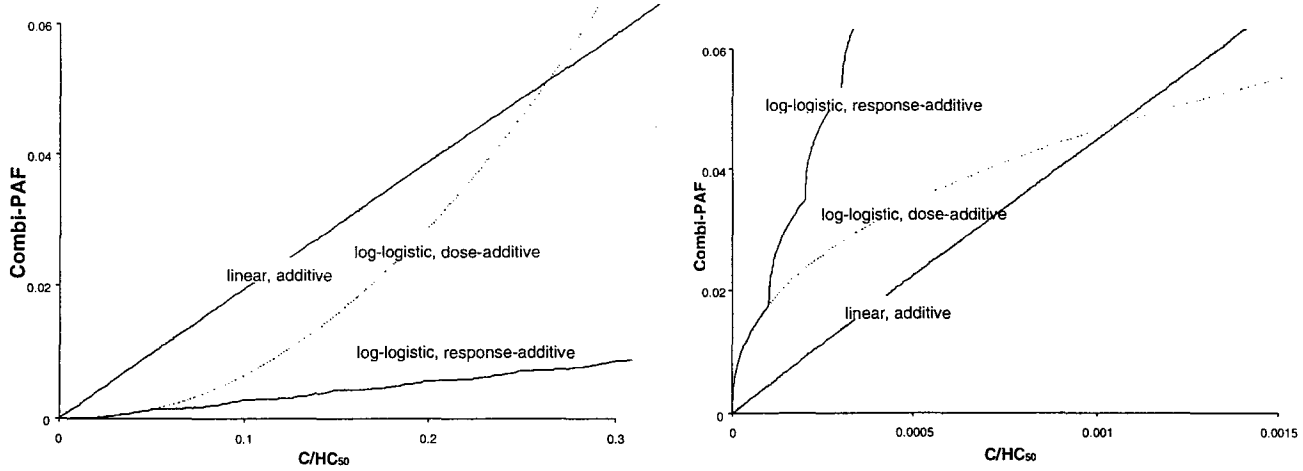

Fig. 3: Comparison of dose-additive and response-additive curves for two mixtures of similar chemicals assuming linear and log-logistic dose-response curves. Each chemical in the left hand plot is at an illustrative concentration of $C_i = 0.05/HC_{50,i}$. The curve shape is represented by $\beta = 0.2$ (or log SD = 0.36, terminology commonly adopted for other types of distribution) for all chemicals. (right hand plot: $\beta = 1$, or log SD = 1.8, and $C_i = 0.0001/HC_{50}$). Note that the concentrations are normalized by HC50, leaving variance as the only degree of freedom to describe the position of a chemical's SSD.

cluster of chemicals) below a PAF of 5% is highly dependent on the distribution model selected (linear, log-logistic, log-triangular, log-normal, etc.). Hence, the selection of a gradient for use as the potency measure in LCA in the absence of a mechanistic justification introduces significant uncertainty. In the absence of alternative insights, the linear gradient (e.g. $0.05/HC_5$) therefore provides a basis to estimate ΔCombi-PAF/ΔConcentration at a justifiable level of complexity.[17] It is interesting to note, however, that this may often yield similar results to the single tangential gradient of $0.4/HC_{50}$ adopted by Goedkoop and Spriensma (2000).

Model and scenario uncertainty can be high when adopting the secant or tangential gradient approach but the secant approach is analogous to the widely accepted use of secant gradient slope factors for carcinogens in human health risk assessment – a factor that may be important when trying to achieve international consensus. The uncertainty of the secant gradient is dependent on the true shape of the dose response curve at low exposure concentrations, how many similar chemicals in the mixture can be treated as dose-additive, whether thresholds exist even for complex mixtures and the extent to which the exposure concentration of the chemical will be changed. In some cases the actual contribution of a chemical to the stress on an ecosystem may be as low as zero, for example if a threshold exists or if the chemical affects an already stressed group of species.

Endpoint: One comparison basis for ecosystem potency measures in current practice is the number, percentage, or fraction of species stressed (termed Potentially Affect Fraction – PAF) above their No Observed Effect Concentration (NOEC), as described by Species Sensitivity Distribution (SSD) curves (see earlier sections and Fig. 2). However, the degree of stress on species exposed beyond their NOEC and the associated extent of species loss (Potentially Disappeared Fraction – PDF) are not reflected by such PAF-based measures. For example, the emission of a chemical can result in an increase in stress on a particular group of species but may not result in an increase in the overall number of species stressed. In this case the change in overall or combi-PAF would be zero but some of the species that are already stressed may become extinct (PDF would increase but combi-PAF would remain constant).

As an alternative to PAF and PDF, the "change in the percentage of species in an ecosystem that experience an *increase* in stress" due to the emission of a chemical may be one alternative option for the best-available basis (Pennington and Payet 2001b). The change in the percentage of species that experience an *increase* in stress is estimated using the same approach as the *number* or Potentially Affected *Fraction* (PAF) of species. However, to estimate this change in the fraction of species that experience an *increase* in stress, no assumptions are made as to which species are being stressed or whether there is an overlap with stresses from other chemicals (or chemical clusters). Hence, model uncertainty is lower.

[17] The merits, uncertainties, environmental relevance and approach selection are presented in detail elsewhere (Pennington and Payet 2001b, Hauschild and Pennington 2001).

6 Conclusions

Toxicological characterization factors in Life Cycle Assessment (LCA) must account for all stages in the cause-effect chain; namely fate, exposure, and endpoint effect. Midpoint indicators, such as measures of a chemical's persistence in the environment, help to double check the results of such integrated fate-exposure-effect approaches and provide an important basis for parallel precautionary indicators. The question remains, however, "at which endpoints do we make the comparisons?"

The following issues were outlined in this paper and will require further consideration in consensus building initiatives, such as the SETAC/UNEP initiative:

1) Fate and exposure models with a spatial component are required to take variations of the human population density into account. Both the quantitative significance and the political implications of this issue ('individual versus population risk') require further consideration.
2) Improved approaches are needed to provide best estimates of (human and eco-) toxicological potency with measures of the associated uncertainty. The influence and interactions of background mixtures need to be addressed, particularly when considering whether thresholds exist.
3) Ongoing research and discussion is warranted to identify how best to consider differences in toxicological severity. Again the influence of background mixtures needs to be considered.
4) Alternatives exist for the ecotoxicological effect endpoint measures: based on important species versus for entire ecosystems; choice between (1) the *number* or Potentially Affected *Fraction* (PAF) of species, (2) the percentage of species that experience an *increase* in stress as the result of an emission, and/or (3) the Potentially *Disappeared* Fraction (PDF) of species. The choice of endpoint may influence whether dietary exposure is important for aquatic species, which must be considered. These options need to be compared and the 'best-available' endpoint(s) identified.
5) Parameter, model and scenario uncertainties associated with fate, exposure and toxicological characterisation are likely to remain high, despite consensus building exercises. Decision makers, practitioners and researchers, at every stage of LCA (inventory, impact assessment, normalization, valuation) need to transparently deal with such uncertainties, as well as variance and co-variance.

Acknowledgements and Cautions. This paper provides a summary of some, but not all, of the issues currently being discussed in the context of the characterization of toxicological impacts in LCA. As is evident from the references, many of these issues are evolving and research is ongoing. The reader is advised to consult the latest drafts of many of the references for updates and to participate in consensus-building initiatives like those of SETAC/UNEP.
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