

## Considerations on potency in the development of endocrine disruption regulatory criteria

### Potency is a fact of life

The concept of potency can be evaluated through its intentional or unintentional consequences: potency explains why some drugs (pharmaceuticals) work better and/or at lower rate than others to address the same issue. It is the reason why sweeteners (of natural or synthetic origin) work at concentrations 100X (or more) lower than common sugar (saccharose). Potency explains why heroin is intrinsically more dangerous (and more severely regulated) than marijuana.

Low potency is also the reason why we can safely consume daily a large number of food/drink items containing natural endocrine disruptors (natural phytoestrogens can be found in flaxseed, sesame seeds, pistachio nuts, sunflower seeds, chestnuts, almonds, walnuts, cashews, hazelnuts, soybeans, lentils, navy beans, kidney beans, pinto beans, fava beans, chickpeas, winter squash, green beans, collard greens, broccoli, cabbage, alfalfa sprouts, asparagus, carrots, green peppers, potatoes, zucchini, dried prunes, peaches, raspberries, strawberries, and grains [wheat, rye, oats and barley]).

### My proposed definition

Potency is what distinguishes two substances that produce a similar (intentional or unintentional) effect in an intact organism (e.g. a human being); the substance that requires the lower dose to produce the effect is the more potent.

### Why is potency critical ?

It is scientifically inappropriate to place in the same regulatory category the following substances:

- A substance that produces an adverse effect at a dose equivalent to 1 mg/kg bodyweight/day
- A substance that produces a similar effect at 100 mg/kg bodyweight/day

Placing them in the same regulatory category (e.g. a prohibition category) ignores the fact that the latter is less potent, intrinsically less hazardous and far less likely to cause problems than the former; it is also less likely to require significant mitigation measures to ensure safe uses.

If potency is not taken into account, a large number of substances with tox/ecotox profiles of low concern will be amalgamated with ED substances of more serious regulatory concern. Whether the resulting consequences will be increased cost (more data required), lost uses (through REACH authorisations and restrictions) or complete prohibition, there will be losses of useful tools/solutions, with no contribution to a safer life or a safer environment. Removing from the market (uses of) substances of low concern will create problems where none exist. When decisions are not based on risk assessments but on hazard considerations, taking potency into account is virtually the only way to limit such losses: although it is a poor substitute for exposure evaluation in risk-based decisions (industry's only supported approach), it minimizes the probability of making inaccurate regulatory decisions by distinguishing those substances that are of high concern from those that do not present risks under their normal conditions of use.

### GHS/CLP

GHS and CLP are referred to as a justification for creating ED categories. Yet, the fact that potency is a fundamental principle of classification is ignored when considering whether potency should be a consideration for ED assignment. Potency clearly distinguishes categories for acute toxicity, aquatic toxicity, STOT effects, some physico-chemical properties, etc. The fact that ED often leads to CMR effects and these are not categorized by quantitative potency classes is often used as a reason to

avoid potency considerations for ED assignment. In fact this is inaccurate, potency is taken into account when categorizing CMR effects, in a qualitative rather than quantitative manner:

**Excerpts from UNECE GHS:**

**Chapter 3.6:** Carcinogenicity

**Point 3.6.2:** Classification criteria for substances

**Paragraph 3.6.2.7:** *'The relative hazard potential of a chemical is a function of its potency. There is great variability in potency among chemicals, and it may be important to account for these potency differences. The work that remains to be done is to examine methods for potency estimation. Carcinogenicity potency as used here [for classification purposes] does not preclude risk assessment.'*

Note: the idea that potency may be an intrinsic part of the carcinogenicity potential is clearly acknowledged in GHS.

**Excerpts from CLP (carcinogenicity):**

**3.6.2.2.6.** *'Some important factors which may be taken into consideration [in carcinogenicity classification], when assessing the overall level of concern are:*

*[...]*

*(b) multi-site responses;*

*(c) progression of lesions to malignancy;*

*(d) reduced tumour latency;*

*(e) whether responses are in single or both sexes;*

*(f) whether responses are in a single species or several species;*

*[...]*

*(j) the possibility of a confounding effect of excessive toxicity at test doses;'*

Note: all factors listed above are direct references to qualitative potency.

The same CLP section also recognizes mutagenicity as a particularly important indicator for carcinogenicity potency:

*'Mutagenicity: it is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity in vivo may indicate that a substance has a potential for carcinogenic effects.'*

**Excerpts from CLP, Reprotox:**

**3.7.2.4.1:** *'[...]In the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity.*

*[...]*

Note: this is another qualitative reference to potency : substances that can harm the fetus in the absence of maternal toxicity are intrinsically more potent developmental toxins than others (with the former, protecting the mother won't necessarily protect the fetus). The following excerpt confirms the above statement, by considering two different reprotox categories depending on the presence or absence of maternal toxicity:

**3.7.2.4.3.** *'Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1.[...]*