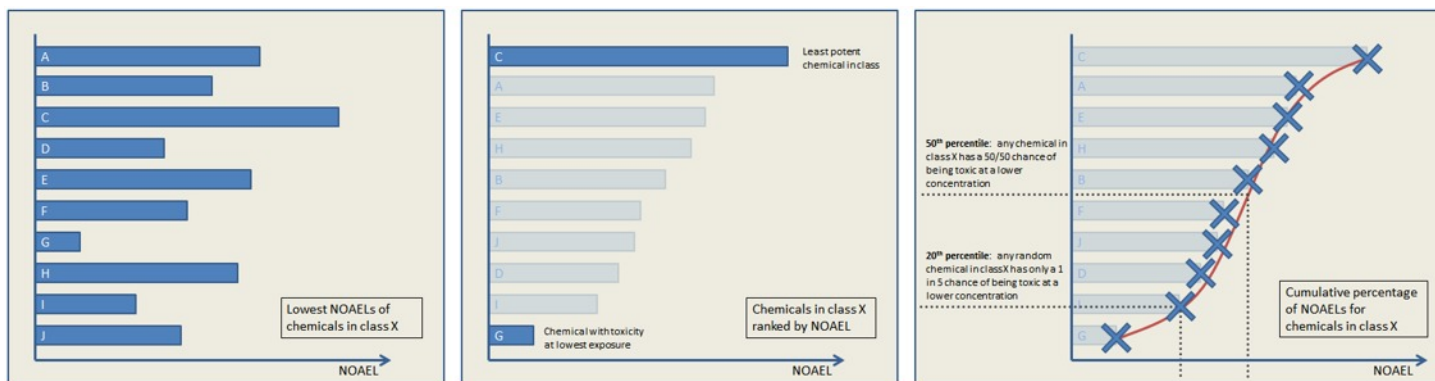


# Thresholds of Toxicological Concern: A Proposal for Reducing Animal Testing in Risk Assessment. (Part 1)



TTCs are a rationale for waiving requirements to generate toxicity data on a substance, in the event that exposure to the substance is deemed highly unlikely to pose a risk to health. Their use will reduce the number animals used in toxicological tests for risk assessment, but other options for reducing animal testing need to be properly considered before TTCs are widely adopted.

**Jan 2012. THERE ARE THOUSANDS UPON THOUSANDS OF CHEMICALS.** There are those which are deliberately manufactured, and those which are the pollutant by-products of the manufacturing process. Then there are those which are the environmental breakdown products and metabolites of these substances, all of which have their own toxicological profiles and number in the thousands more.

We have adequate toxicological data for only a tiny minority of these. Generating enough data is likely impossible so we need to prioritise which ones we test first, deciding when we need toxicological data on a substance, and when we do not.

One rationale which is gathering increasing support is the application of thresholds of toxicological concern (TTCs), a pragmatic, probabilistic approach to risk assessment of substances for which toxicity data are unavailable. It holds that if a substance is unlikely enough to pose a risk to health, then toxicological testing of the substance is not required.

“The TTC is driven by exposure,” says Dr Bennard van Ravenzwaay, Senior Vice President for Experimental Toxicology & Ecology at BASF. “You can calculate what the level is so that if exposure is below the threshold, as a risk assessor you can say you have no concern, and you don’t need to call for the entire dataset to carry out a risk assessment.”

By waiving detailed toxicological testing, in particular tests using animals, TTCs fast-track substances through the risk assessment process, cutting time to market approval from as much as four years down to potentially as little as a few months.

The TTC concept has wide support within the chemicals industry, with the International Life

Sciences Institute (ILSI) and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), among others, advocating for its adoption. TTCs are already used by the UN Joint Expert Committee on Food Additives (JECFA) and the US Food and Drug Administration for deciding when food additives need to be evaluated for toxicity.

Among the EU institutions, the European Food Safety Authority has been evaluating whether to adopt TTCs for the evaluation of food additives in Europe, while the approach is of strong interest in European cosmetics regulation, given the EU’s commitment to end animal experimentation in cosmetics by 2013.

## How TTCs are calculated and used

On being presented with a substance of unknown toxicity, a risk assessor using the TTC approach needs two pieces of information: the molecular structure of the substance; and a person’s likely exposure to the substance.

These two pieces of information allow the substance’s probable toxicity to be calculated, and if the probability of toxicity is low enough, then the risk assessor can waive requirements for further toxicological testing of the substance.

It works like this: Although molecular structure on its own is not an accurate way of predicting toxicity, it is possible to group chemicals according to their structural features and calculate the range of toxicity of chemicals within that group as a whole.

This is done by taking a representative sample of substances from within that class and carrying out toxicological tests on the substances to determine the levels at which they have no adverse effects on living organisms (the No Observable Adverse Effect Level, or NOAEL).

Once you have all the NOAELs for the class, you know the range of toxicity of all the chemicals in the class and can rank the substances according to toxicity from lowest to highest dose (see Figure 1).

This allows you to pick an exposure which serves as a cut-off, so that a certain percentage of chemicals are toxic at lower exposures than the cut-off, and the remainder only toxic at higher levels of exposure.

Because the database of NOAELs is (at least in theory) representative of all chemicals in the class, this means if you choose as a cut-off an exposure at which 50% of the chemicals in the class are toxic, then a random chemical of unknown toxicity from that class would have a 50% chance of being toxic at that exposure, and a 50% chance of not being toxic.

The TTC proposal is to set the exposure threshold so the 5th percentile, resulting in a 1 in 20 chance that a random substance in the class is toxic at this exposure level. As a further safety factor, this exposure level is divided by 100 to give the final maximum allowable exposure under the proposed TTCs. Any higher exposure triggers toxicological testing.

## What are the proposed TTCs?

Current opinion leans toward dividing chemicals into three classes: those with structural flags for genotoxicity; those with structural flags for carcinogenicity via a non-genotoxic mechanism (Cramer class II and III); and those with no flags for toxicity (Cramer class I).

The choice of Cramer classifications themselves was initially fairly arbitrary but has acquired acceptance because it seems to work and it is easy to apply. Cramer classes II and III

have been merged because the distinction between the two was too arbitrary.

Genotoxic substances are treated separately (as are a number of other substances, including steroids, dioxins and organophosphates) because their toxicity cannot be predicted from the NOAEL distributions within the Cramer classes.

When the 95th percentile NOAELs for the three classes are divided by 100 and converted to whole-body equivalent exposures, the TTC for genotoxic substances is set at 1.5µg per person per day [note: since genotoxic substances are believed to not have a threshold below which they have no effect, this value is based on the risk of cancer for a lifetime of this level of exposure not exceeding 1 in 1 million]; for Cramer class II and III at 90µg per person per day; and for Cramer class I at 1800µg per person per day.

### TTCs: a pragmatic approach

TTCs are a purely probabilistic method of assessing risk from chemical exposures, purported to be almost as accurate as exhaustive toxicological testing. Its proponents argue that, since the TTC is so accurate, there are only marginal benefits to be gained from actually doing low-dose toxicity testing.

Since these marginal benefits of thorough toxicological testing come at great cost in time, money and lives of laboratory animals testing, they are not actually worth it. TTCs should therefore replace obligations to test, with the money thereby saved spent on something else.

The acknowledged disadvantage of using TTCs is they do not generate specific toxicity data on any substances. Adoption of the TTC is being opposed by groups such as the World Wildlife Fund (WWF) and Pesticide Action Network (PAN), who favour approaches to risk assessment based on substance-specific assessments of toxicity.

Van Ravenzwaay believes the disagreement stems from different perspectives on what one feels one needs to know about chemicals: "This is when worlds collide. One side says if exposure stays below this value, then the likelihood the substance is safe is extraordinarily high. The other side, especially prevalent here in Europe, wants to classify and label everything it can, which requires toxicological testing.

"If the wish of our society is to know all the intrinsic properties of all the chemicals on this planet, then the TTC is something that will only be useful as a preliminary tool. If we don't need

to know everything because of resources, animal welfare etc. then the TTC may reduce the amount of testing."

Van Ravenzwaay is likely overstating society's wishes: what groups like PAN and WWF really want is for chemicals to have an adequate pedigree of safety before being brought to market, not for every substance to be tested exhaustively for all their intrinsic properties.

Few would disagree that the line on testing has to be drawn somewhere. The question is, should we accept that TTCs show us the right place to draw it?

### A note of caution

We know there is a great deal of industry interest in the use of TTCs, so it is worth considering the benefits to industry of adopting the TTC as a principle in risk assessment. We might, after all, have reason to be suspicious of the recommendations of an industry which has historically been loath to publish toxicity data on chemicals, is threatened by findings that chemicals may harm health, and resists regulation which would result in generation of more data; especially so, now that the chemicals industry is expected to foot the bill for this testing.

Hans Muilerman, Chemicals Officer at PAN Europe, explains how there is a great deal to gain financially from the use of TTCs: "If you look at the commercial effects, you see you don't need to do [as much] animal testing anymore, so it will save [industry] millions and millions of Euros. It will bring them easier access to the market because it will take them less time to do the risk assessments, which take three or four years to do, so it's a huge commercial advantage to use the TTC."

It is fair enough that the chemicals industry should support a regulatory initiative which works to its advantage, but these interests need to be balanced with critiques of the proposal. Are these forthcoming?

In 2011, EFSA's Scientific Committee published a draft opinion favouring its use in the risk assessment of chemicals in food (EFSA 2011, PDF) Although it acknowledges some issues, such as whether the TTCs derived from the original databases are valid for new chemicals and non-carcinogenic end points (an issue we will touch on in next month's article), the Committee's critique extends only as far as issues to which advocates of the TTC have already responded. Engagement with on-going controversies is limited.

According to WWF's response to EFSA's draft opinion (not currently publicly accessible), these controversies include: the need to take into account mixture effects and exposure to substances from multiple sources; evidence that substances can have effects at low doses, particularly during critical windows of development; the possibility of reducing animal testing with alternative strategies to TTCs; and the consequences of waiving testing requirements for on-going efforts to develop hazard profiles for substances.

An indication as to why EFSA's Committee produced the draft opinion it did can be found in the composition of the working group responsible for the preparatory work in developing the opinion. According to research by PAN, 10 of the 13 working group members have published in favour of or advocated for use of TTCs, while 8 of the 13 have formal links with ILSI, an industry science group promoting the use of TTCs. (PAN Europe 2011, PDF)

That so many members of the working group have a publishing history favouring use of the TTC, and a majority are affiliated with ILSI, should at least bring into question the ability of the working group as a whole to provide EFSA with objective advice about the use of TTCs.

Nor is a predominance of opinion favouring the TTC confined to EFSA's working group: in the published literature there is an overall lack of critical evaluation of the TTC. Although there are plenty of papers on how the TTC might be applied to new areas, tweaked for reliability and more precise thresholds might be set, they all operate the same working assumption that the TTC is something which ought to be adopted. Not one thorough critique from first principles has ever been published in a peer-reviewed journal.

To be fair to EFSA's working group, under these conditions anyone would be hard-pressed to conduct a balanced review of the TTCs merits. And to be fair to EFSA, if the pool of experts on the TTC is almost entirely composed of people who favour its use, it is going to be equally challenging to put together a balanced panel to review the TTC itself (not that this is an excuse for failing to do so, of course).

In the absence of published critiques of the TTC, next month we will articulate some of the problems surrounding the use of the TTC, from internal inconsistencies of its logic as a proxy for estimating risk to health from chemicals, to its consistency with the basic principles of post-REACH chemical regulation in Europe.

### References and Further Reading

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