Who controls the safety of marketed chemicals?

Details

e: ttweed@telenet.be
t: +32 485 926 601

Collaborators

The NGO, Générations Futures (Paris)

Bio

Anthony Tweedale works as a consultant with the aim of advising stakeholders (largely NGOs) in chemicals policy. His main focus is risk assessments and raising awareness of the flood of low-dose and other toxicity findings being published.

Further reading

Tweedale, AC, (2017) The inadequacies of pre-market chemical risk assessment's toxicity studies – the implications, *Journal of Applied Toxicology*, 37(1), 92–104.

Tweedale, AC, (2022) Correspondence on 'Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States', *Environ Sci Technol*, 56, 22, 16533–16534.

R.I.S.K. Consultancy — Rebutting Industry's Science with Knowledge

The reservoir of academia's ignored toxicity findings is dammed by regulators' fidelity to industry's toxicity test methods; the dry racecourse represents the ignored laws that require the former to be evaluated.

Who controls the safety of marketed chemicals?

- Chemical policy should ensure that any chemical entering the market is thoroughly assessed for toxicity hazards and that assessment is periodically updated.
- Anthony Tweedale's independent research finds that, in risk-assessments done for market access, regulators rely almost entirely on insensitive toxicity tests conducted by manufacturers.
- He finds that publicly funded studies return more accurate assessments of low-dose toxicity, but are hardly ever evaluated despite mandates to do so.
- Tweedale also challenges an apparent lack of concern about this critical upstream problem among all stakeholders: regulators, NGOs, and academics.

It should be reassuring to know that, before any chemical is available for sale, it undergoes a risk assessment (RA) to determine its effects on people and the environment. Perhaps you imagine that RAs take account of all information available?

Independent secondary researcher (ie, the analysis of existing research), Anthony Tweedale, from RISK Consultancy, Belgium contends that this isn't the case. He maintains that 'pre-market' RAs – those required periodically for a chemical to remain on the market – are controlled by the manufacturer, 'a party with every interest in their agent being declared safe enough to sell', using toxicity test methods that their pharmaceutical branch created 120 years ago. Since 1981, whenever a regulator needs a new test, these methods are mandated globally, via the Organisation for Economic Co-operation and Development.

Tweedale considers these tests to be 'grossly insensitive'. At the same time, he estimates that at least 10,000 (and accelerating) published toxicity findings in vertebrate animals falsify the claimed 'safe doses' in pre-market RA, by finding hazards at low dose. Even though published toxicity findings are allowed to be considered in pre-market RA, he says they almost never are. He highlights that he has never seen a pre-market RA where the most reliable study was not an industry study. Meanwhile, stakeholders are ignoring the problem. Tweedale advocates for scrutiny of this issue.

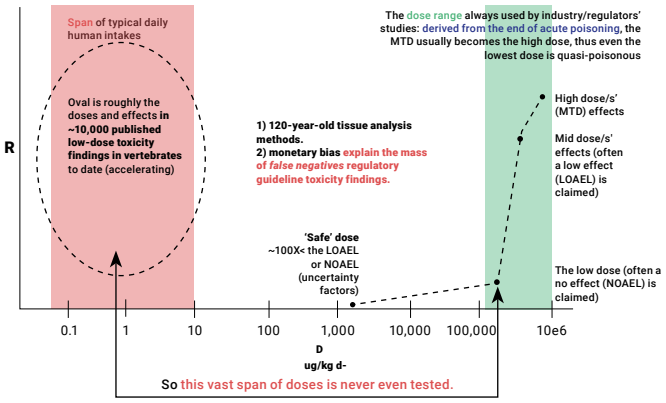
Quality checking pre-market RA

To investigate his concerns, Tweedale randomly selected two marketed chemicals that had successfully undergone pre-market RA under two EU laws, and conducted a review of their published literature and of their RA dossiers: the herbicide bentazon, and the flame retardant hexabromocyclododecane (HBCDD, since phased out in the EU). His results were peer-reviewed and published in the *Journal of Applied Toxicology.*

10,000 published toxicity findings in vertebrate animals alone falsify the claimed 'safe dose' of pre-market research assessments.

His systematic review found that bentazon had 31 published toxicity studies. The pre-market RA listed just seven, and only briefly evaluated four. One overlooked study highlighted how small doses of bentazon can affect sperm formation in rodents. Also, despite reports of teratogenicity (loss of bones) in rodents exposed to bentazon during development, the RA claimed, without citation, that bentazon is not teratogenic. The sperm study's scientific methods were much more objective than industry's key study.

Tweedale found 88 reports of toxicity for HBCDD in the scientific literature, of which the RA mentioned only 13. Among the findings that were overlooked or dismissed in the RA were reports of neurologic/thyroid, metabolic, and immune toxicity, often at low doses. A handful were evaluated with regularly used and, according to Tweedale,



Conceptual model of the overwhelming failure of chemical risk assessments. MTD = maximum tolerated dose; LOAEL = Lowest observed adverse effect level; NOAEL = No observed adverse effect level.

	BPA	Glyphosate
Published toxicity papers found by regulators	3,231	1,628
Categorised 'irrelevant' based on title/abstract only	0	~800
Categorised 'irrelevant' after being read in full	0	~600
Considered 'relevant' so proceeded to evaluation of reliability	3,231	211
Lowest reliable adverse effect found in a study	0.93 ng/kg d-(BMD-1)	10 mg/kg d- (a NOAEL)
Proposed safe dose	0.00000004 mg/kg d-	0.1 mg/kg d-

The difference that evaluating academia's findings (green) can make, vs relying on industry's data (red). Comparison of two contrasting, ongoing European Food Safety Authority risk assessments: bisphenol-A (BPA), assessed by their Panel on Food Contact Materials, Enzymes and Processing Aid; and the herbicide Glyphosate's re-authorisation report, billed as 'the most thorough pesticide evaluation ever'.

'speculative and scientifically illogical' rationales, which he argues are used to downgrade the reliability of academia's findings (see below).

Implications of inadequate RA

While two main EU chemicals laws – REACh (Registration, Evaluation, Authorisation and Restriction of Chemicals (EC) 1907/2006) and the Pesticide Regulation (EC 1107/2009) explicitly require that all the available relevant data is evaluated, Tweedale's review shows these pre-market dossiers only included 13% of bentazon's and 15% of HBCDD's published toxicity findings. This failure to evaluate hazards is illegal under EU laws, yet as he highlights, 'the random selection of these two chemicals shows that this crucial mandate is widely ignored'. This is confirmed by Tweedale's checks of some 60 EU RA dossiers – some contained no published toxicity finding (and averaged <20%). Thus, academia's output – including more and more findings of low-dose toxicity – is almost completely ignored and apparently never relied on.

Across all dossiers, Tweedale finds that most published toxicity papers are dismissed as irrelevant (despite, as he notes, a toxicity finding being always relevant to evaluating a hazard). Remaining papers are evaluated but often with a brief, 'scientifically illogical', claim: eg, the chemical may not be pure, it didn't use oral exposures, it only tested two dose levels, etc. Industry's toxicity tests are simply assumed to be more accurate. In fact, says Tweedale, their chronic-exposure doses are close to poisonous; and since they only look at tissues with natural-light microscopes, a toxic effect may or may not be found (in either case, typically a 100-fold safety factor is applied to the lowest tested dose to derive the 'safe dose' which drives the stringency of regulation). Industry's test methods also sacrifice the test animals at the end of middle age, missing most chronic disease.

Personal response

How do you think academics can motivate regulators to place greater value on independent toxicity studies?

There's an ocean of ignored scientific publications floating around. Regulators prefer to use the insensitive results of industry's toxicity tests. Scientists should use their prestige to publicly complain to regulators: 'You are ignoring our work, sometimes illegally!', and break the dam holding back their findings (with NGOs amplifying the message). Only then could scientists participate in the necessary substantive discussions on 'whose findings are accurate?'.

How would you go about raising public awareness of the risks this issue poses? Do you consider the public to be effective agents for change?

The public is consistently suitably sceptical of industry's motives. But they would be far more outraged (and effect political change) if they realised that the research they fund is disregarded – most is never considered and any evaluations are minimal and subjective. NGOs again are suitably placed to effect this, but they remain ignorant of it. If they felt the urgency of the appearance of two to three published findings of low-dose chemical effects on vertebrates every day, I think this would clarify how inadequate RA dossiers are. Via such pressure, regulators would use systematic reviews as their RA model and enforce laws on evaluating all data, while exposing industry's too-insensitive-to-find-toxicity test methods.

Could you give us some examples of industry-derived 'safe doses' resulting in damage to human or animal health?

Scientists estimate that one 'poster-boy' chemical, bisPhenol-A (bPA), has around 5,000 low-dose toxicity published findings. Yet its REACh registration contains only around 900 published findings – and every one is dismissed without any evaluation (as in all REACh registration dossiers), with every regulator globally continuing to state that bPA's most reliable study is the one paid for by its manufacturers.
The permeation of life with persistent synthetic chemicals is an uncontrolled experiment, with an almost infinite number of variables – it was very hard to prove even that smoking causes cancer. But when in vivo, in vitro, and epidemiologic correlation findings start to converge, it is time to act. Systematic review is the solution.

> **Regulators' and policymakers' stance is that industry's test methods are completely reliable [yet those] have great insensitivities.**

Misdirected solutions?

Tweedale says there is a widespread lack of concern about this, despite his 12 years of efforts to explain the issue with chemicals regulation. Europe's pesticide NGOs are very concerned that academia's output is ignored, yet will focus only on issues downstream of the RA, such as pesticide residues in food. To make matters worse, says Tweedale, the REACh NGOs look only to industry to supply missing or inadequate data. Other NGOs assume that regulators are responsible, yet the regulators' and policymakers' stance is that industry's test methods are completely reliable. Even academics, he says, are not sufficiently aware to complain that their more sensitive rigorous findings are almost entirely ignored.

An alternative approach

'Systematic review is the gold standard,' Tweedale advises. 'It is explicitly impossible to perform systematic reviews without evaluating all data.' He advocates for safety regulators to discuss with academic scientists whose test methods produce accurate results. The involvement of stakeholders would restore public trust that regulators are using high-quality, independent data to help keep them safe.

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