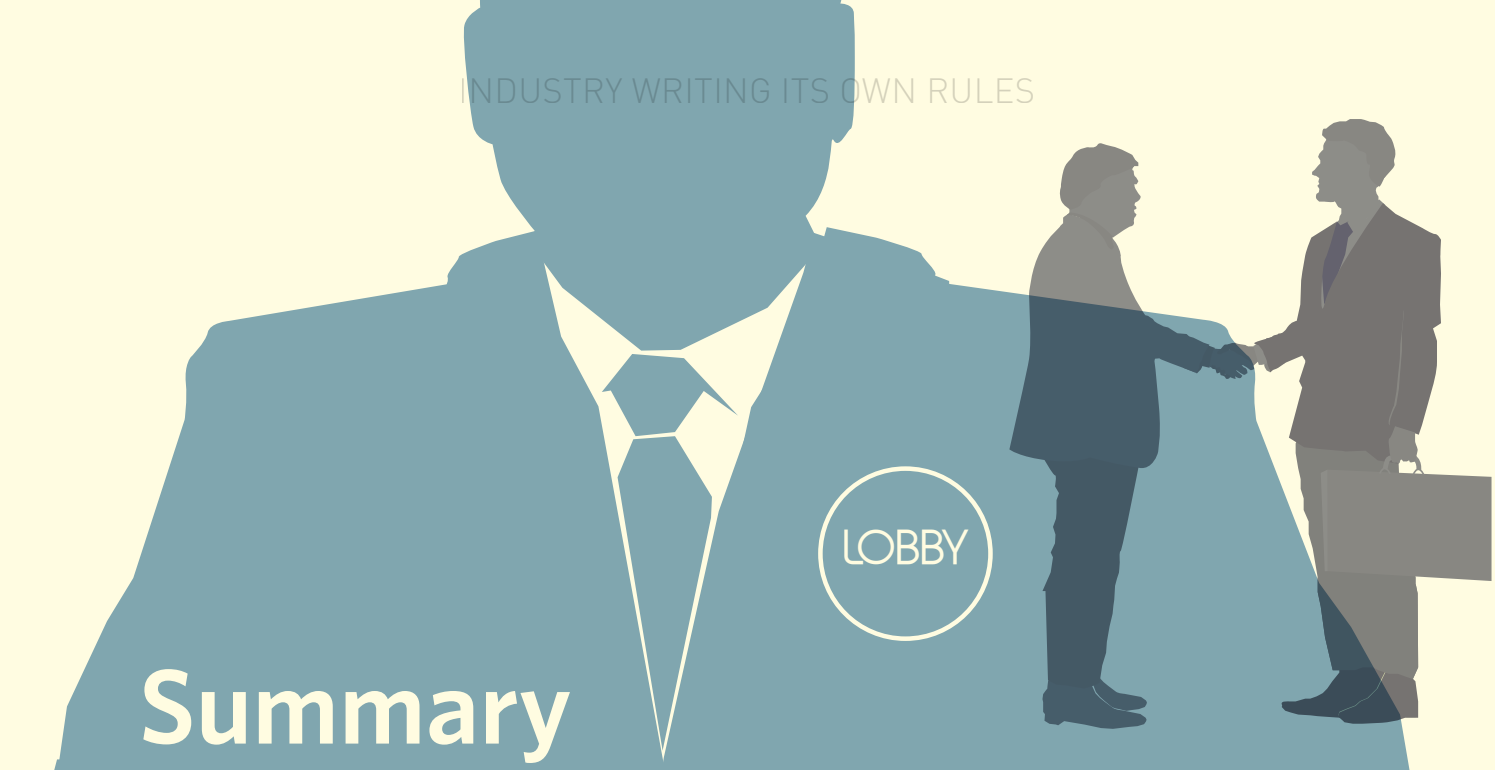
INDUSTRY WRITING ITS OWN RULES

générations FUTURES

Pesticide Action Network Europe

Contents

A research report written by the **Pesticide Action Network Europe**
Author: **Hans Muilerman**
Brussels, January 2018.
Pesticide Action Network Europe, Brussels
Génération Futures, Paris



Summary

Research done by the Pesticide Action Network reveals that in 92% (11 out of 12) of the EU-methods for pesticide risk assessment examined, it was the industry that designed and/or promoted their regulatory use. Industry is writing its own rules. This is a major conflict of interest. The cases concern criteria and methods (risk assessment methodologies) on HOW the rules of the pesticide Regulation 1107/2009 should be used in decision-taking on individual pesticides. In most cases European Food Safety Authority, EFSA, drafted the guidelines on the use of these criteria and methods. Such methods are used to dismiss tumours observed in animal toxicity testing of pesticides, to approve carcinogenic pesticides in our food, to classify polluting pesticide metabolites in our groundwater as irrelevant, to allow the dying of 50% of the insects in every spraying turn, to construct 'safe' levels for harmful pesticides without any experimental evidence, among others.

Industry, spearheaded by industry lobby group ILSI (International Life Sciences Institute), developed their desired methods during the past 15 years in a series of invited-only meetings with industry employees and a few university professors that generally shared their views. Next it tried to get its allies in regulatory expert panels that draft opinions on the methods like the panels of EFSA, IPCS/WHO (World Health Organisation/ International Program on Chemical Safety), JMPR (WHO Joint Meeting on Pesticide Residues) and other agencies.

In 75% (9 out of the 12) of the risk assessment methods studied by the Pesticide Action Network, industry-linked experts managed to get a seat in EU and global panels where these methods were produced. Generally there were only a handful of experts present in the panels that decided on far-reaching opinions about the methods. Only rarely were experts present in these meetings that are actively conducting experimental scientific work. In any case, not much science is used for drafting opinions on risk assessment methods in panels. “Expert judgement” is the prevailing practice, which is in fact just the opinions and ‘feelings’ of those that are present in the room. The global scientific societies that bundle the hundreds of thousands of scientists that do scientific research in the world are not involved nor asked to do a peer-review of these methods of risk assessment, which is the standard procedure for scientific work. In none, 0% (0 out of 12) of the methods studied by the Pesticide Action Network, the method was peer-reviewed by independent academic scientists.

Since a solid conflict-of-interest policy was lacking in the beginning of this century in most agencies, many expert panels have been dominated by experts that support the views of industry. In the case of TTC (Threshold of Toxicological Concern; a method to design safe levels for pesticides) up to 77% (10 out of the 13) of the experts in the EFSA-working group were linked to industry and were promoting this method in the past.

Food Authority EFSA is known for having close ties to industry. In 50% (6 out of the 12) of the methods studied by the Pesticide Action Network, EFSA and other agencies had exclusive meetings with industry on the design of the methods, sidelining other stakeholders.

Industry obtained most of its inspiration from the US where citizens are not protected by the precautionary principle and the burden of proof on harmfull effects of pesticides is put largely on the public. An entirely different system therefore from the EU system. Yet, in 67% (8 out of the 12) of the methods studied by the Pesticide Action Network, an US-origin could be seen. Without a doubt the US-type of risk assessment is invading the EU-system through the backdoor.

The 12 methods studied here all are designed to lower the level of protection of the public and to enable the approval of pesticide that can cause harm. On top of this, the methods adopted are even misused in practice. In 92% (11 out of 12) of the methods studied by the Pesticide Action Network misuse was observed in actual decision-making of EU pesticide approval.

A full revision of the EU risk assessment methods is needed, according to the Pesticide Action Network. Fully independent scientists that are actively conducting experimental work as a daily practice should be tasked to do this to protect the public with the newest scientific insights and knowledge.

Introduction

European risk assessment of chemicals and decision-making has to be based on current scientific and technical knowledge[1]. This rule has to be respected particularly during the implementation of the European Union (EU) Regulations by the European Commission in the final decision taking, such as is the case of the approval of pesticides. The best available science should be used to protect EU citizens and the environment against the harm that chemicals may cause. This is what the European law mandates and what people expect from regulators, and therefore this is what the EU Commission should deliver. Nevertheless, for several risk assessment methodologies (pesticide and GMO risk assessment[2], Threshold of Toxicological Concern[3]), the criteria and (test) methods that are the basis for decision-taking, it has been demonstrated that science can be twisted and turned. Industry lobby organisations, such as ILSI (International Life Sciences Institute) and ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), as well as industry-linked experts have managed to impose their ideas of risk assessment on European risk assessment on food.

Since these ideas are generally drafted to serve the interests of industry, the European opinions and guidelines that embrace them, will inevitably be "biased" and will not provide the high level of protection for humans, animals and the environment that the European Law foresees. Still, the extent to which regulatory documents are embracing industry ideas is unknown. An independent scientific system correcting such unacceptable influence by the industry is missing at European level and there is an urgent need to make the this influence transparent.

1. Regulation 1107/2009, Art.4, An active substance shall be approved in accordance with Annex II if it may be expected, in the light of current scientific and technical knowledge .... meet the requirements provided for in paragraphs 2 and 3.
2. http://earthopensource.org/earth-open-source-reports/gmo-myths-and-truths-2nd-edition/
3. PAN E report on TTC

The Pesticide Action Network, with this analysis, aims to present the extent of this type of (hidden) industry advocacy in this crucial area of implementing EU laws by taking a sample of risk assessment methodologies that lower the protection for EU citizens, animals, the environment and its ecosystems.

European Commission's health service DG SANTE has claimed repeatedly that European policy on pesticides is based on science[4]. This "mantra" however is generally not based on facts and the purpose seems to be mainly to frame DG SANTE's policy in a positive way. Food Authority EFSA, which was established in 2003, is the agency that has an important role to play in defining the scientific basis of decisions. EFSA's role is to have the final word on the science used for the pesticide approval process. The regulation that lays down the principles for the establishment of EFSA (177/2002; Art. 6.2[5]) requires that EFSA does risk assessment as follows: "*Risk assessment shall be based on the available scientific evidence and undertaken in an* ***independent, objective and transparent*** *manner*". Despite the words independent, objective and transparent being used, there is a lot of doubt on the actual independence and objectivity of EFSA[6]. EFSA even has been condemned several times on these points by the EU Ombudsman for maladministration[7,8]. First of all, EFSA bases its scientific conclusions almost entirely on studies sponsored and in many cases carried out by industry itself on its own products. Data are produced in a clear "conflict of interest" process. At the same time independent academic science that could function as a 'control' and counterbalance is rarely taken into account by EFSA[9]. The experimental basis of the risk assessment therefore is questionable.

It is not only academic science that is dismissed. Academic scientists also are a minority if it comes to the expertise used in EFSA's panels and working groups[10]. This comes together with the fact that several experts included in EFSA-panels have financial conflicts of interests. EFSA, in its first 8 years of existence, was very reluctant to adopt a policy on conflicts of interest and only agreed to do so after being forced by the European Parliament

4. https://ec.europa.eu/commission/2014-2019/andriukaitis/announcements/presentation-commission-proposals-endocrine-disruptors-envi-committee-brussels-16-june-2016_en
5. REGULATION (EC) No 178/2002 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 28 January 2002
6. www.pan-europe.info/press-releases/2012/11/10-years-efsa-10-years-blind-love-industry
7. www.pan-europe.info/press-releases/2014/03/european-ombudsman-condemns-food-authority-efsa-twice-maladministration
8. www.pan-europe.info/press-releases/2016/02/commission-found-guilty-maladministration-eu-ombudsman
9. PAN E report Missed and Dismissed
10. www.pan-europe.info/press-releases/2013/03/efsa%E2%80%99s-opinion-endocrine-disrupting-chemicals-adds-confusion-and-undermines

that blocked EFSA's budget[11] for some time. After removing the most obvious experts with a conflict of interest from the panels and working groups in 2012, many questionable experts remained in place and are still present today[12]. A survey done by the French journalist Stephane Horel[13] calculates that more than 50% of the experts in the EFSA-panels have financial ties with industry, even after the new policy was implemented. And when experts were replaced, they were generally not replaced by academic scientists with expertise on the field but by Member States' civil servants. National experts may (have to) serve the policy of their country and might act more like lobbyists than providing scientific expertise. EFSA's expert panels therefore are still far from independent.

The experts in panels and working groups are the ones that draft the Guidelines for the methodologies of risk assessment. EFSA is also wearing a double cap, the one of writing (or at least approving) the guidelines for risk assessment methodologies, and at the same time applying their own designed methods. No peer-review by truly independent scientists is done on the work of EFSA.

For a long time it seemed like the regulatory world of EFSA and the academic world were totally separated and even not interested in each other's existence. Academic scientists didn't consider the risk assessment methodologies to be purely scientific at all given the many assumptions and (non-scientific) policy-elements. Regulatory experts in turn had a general dislike of academic scientists and branded their work sometimes as "hypothesis-driven" and "like a hobby"[14]. However, when EFSA started dealing with pesticides that are endocrine disruptors this changed and academic scientists, notably the global Endocrine Society, started expressing their concern[15]. This concern from professionals in the field even led to hostile communication between academic scientists and the experts in panels such as of EFSA[16]. From a distance it therefore looks like currently we have two types of science: the science produced through research in the academic world and the 'regulatory

11. www.corporateeurope.org/blog/european-parliament-cracks-down-efsa
12. www.pan-europe.info/press-releases/2012/06/conflicts-interest-still-evident-new-esfa-expert-panels-0
13. https://corporateeurope.org/pressreleases/2013/10/more-half-experts-eu-food-safety-authority-have-conflicts-interest
14. PAN report A Poisonous injection
15. Zoeller et al., A path forward in the debate over health impacts of endocrine disrupting chemicals, Environmental Health 2014, 13:118
16. www.nature.com/nature/journal/v535/n7612/full/535355c.html?WT.ec_id=NATURE-20160721&spMailingID=51873914&spUserID=MTc5NzY5Nzc4MTM1S0&spJobID=962855827&spReportId=OTYyODU1ODI3S0

science' produced by external experts with seats at EFSA-panels and at other European institutions. It appears as if there is a (growing) gap between these two sides, while they are both 'throwing mud at each other'.

The question therefore remains which kind of science is at the basis of the methods used by EU Commission to approve pesticides. In the past, PAN Europe revealed a few cases showing that industry and industry lobby groups developed risk assessment methodologies and tried to persuade regulatory committees to adopt them[17], [18]. We would like to find out if there is a pattern, a large scale 'infection' of industry ideas in EU risk assessment for pesticides.

Influencing the methodology guidelines is of course a very effective way of lobbying. The benefit in this case is limited to the profits of a handful of chemical companies and disregards the health risks posed to millions of EU citizens and the environment. With this report PAN Europe tries to find out to what extent industry has been writing "its' own rules" and to shed some light on the underlying drive and the "science" used to draft guidelines for risk assessment methods. In this report we will only look at the methods used by EFSA and to a limited extent also by the Standing Committee during decision-making, which is of a more political nature[19].

17. PAN E report on TTC
18. PAN report A Poisonous injection
19. www.pan-europe.info/press-releases/2014/05/new-attack-eu-policy-regarding-endocrine-disruption-health-dg-sanco-prepares

Methodology

Risk assessment methodologies (criteria for evaluation of risk) were selected from the opinions produced by Food Authority EFSA (peer reviews[20]) that are in actual use. We selected those risk assessment methods (criteria) that tend to question adverse effects found in pesticide experimental safety testing (alleged 'false positives') and tend to lower the level of protection of humans and the environment (alleged 'unrealistic' high level of protection). In current (traditional) risk assessment one might read that for a certain pesticide (e.g. Bupirimate) thyroid follicular adenomas were observed in rat studies, but not considered relevant for humans[21]. This criterion of "human relevance" is actually bypassing risk assessment rules and deserves a closer examination on how it is applied. Another, peer review by EFSA analyses the potential of the pesticide Phosmet to cause liver cancer and finally dismisses all the data showing liver tumours because of "historical control data"[22]. Once again, another one of these criteria is being used to dismiss positive experimental findings. One more example is the one of the pesticide Buprofezin whose metabolite is a genotoxic carcinogen; the EU law is clear that such a chemical should be banned. Nevertheless another criterion called "margin of exposure" is discussed[23] to permit the pesticide on the market. These types of criteria are collected for our sample. These assessment criteria of course have a big potential of serving commercial interests and/or could lead to cost reduction for industry. The methods selected are methods that are in frequent use and have a major impact on final decisions.

20. www.efsa.europa.eu/en/search/site/peer%20review
21. www.efsa.europa.eu/en/efsajournal/pub/1786
22. www.efsa.europa.eu/en/efsajournal/pub/2162
23. www.efsa.europa.eu/en/efsajournal/pub/4207

The list of assessment criteria or methods collected was analysed in the following way:

1. We evaluated the opinions of the guideline for the risk assessment methodology in question drafted by Food Authority EFSA on its scientific merit and looked at any reference to a potential industry origin. We looked at the members of the EFSA working groups that drafted the opinion, their potential conflicts of interests and their scientific record, we looked at similar EU institutes like SCHER to find out about the background of methods used.
2. We carried out an internet search and looked at the websites of the industry lobby groups that are active on risk assessment tools, we scrutinised the EU funds like FP7 that generously supports institutes, including those from industry, and evaluated documents we received by access-to-documents requests.
3. We thoroughly read the scientific literature[24] to compare the EFSA opinions with the scientific literature, and to assess the scientific record of those drafting opinions on methodologies.

In the analysis of the methodologies we have tried to answer the following questions:

A. How can the risk assessment method be described?

B. Who developed the risk assessment method? Was there any US origin?

C. In what way was the risk assessment method introduced and adopted in regulation, in Europe and globally?

D. How is the risk assessment method currently in use and what is the effect on the level of protection of humans and the environment?

E. Did academic or other independent scientists express an opinion on the risk assessment method?

F. Is the risk assessment method misused in the implementation phase of decision making?

24. PUBMED and ScienceDirect

Analysis

SELECTION OF RISK ASSESSMENT METHODOLOGIES

Based on careful reading of many EFSA opinions available[25] the following hazard evaluation criteria for risk assessment were selected:

- human relevance (possibility to claim that adverse effects in animals are not relevant for humans)
- margin of exposure (possibility to claim that exposure is negligible) & safe thresholds for genotoxic carcinogens (possibility for chemicals without threshold, such as carcinogens, to apply a threshold)
- historical control data (possibility to qualify observed high cancer incidence as non relevant)
- EPPO bee risk assessment (possibility to ignore chronic exposure to bees)
- micro/mesocosms for aquatic risk assessment (possibility to relax environmental standards)

25. www.efsa.europa.eu/en/search/site/peer%20review

recovery of non-target organisms (possibility to allow mass destruction of organisms by pesticides)

non relevant metabolites (possibility to allow groundwater pollution by metabolites); guideline used currently was [26], politically adopted in 2003, confirmed later by EFSA]

extended one generation reprotoxicity test (possibility to reduce costs of testing)

AOP (possibility to bypass expensive animal testing)

And additionally, the methods evaluated before by PAN Europe or other NGOs:

threshold of toxicological concern (possibility to bypass expensive animal testing)

probabilistic risk assessment of mixtures (possibility to claim mixture effects are irrelevant)

substantial equivalence of GM crops (possibility to approve GM crops without chronic testing)

26. https://ec.europa.eu/food/plant/pesticides/approval_active_substances/guidance_documents/ hidden under "guidance" and "fate and behaviour": Assessment of the relevance of metabolites in groundwater

HUMAN RELEVANCE

A. HOW CAN 'HUMAN RELEVANCE' BE DESCRIBED?

Human relevance' is a risk assessment criterion that questions what is the relevance of an adverse effect observed in animal studies for humans. Since it is prohibited to test the safety of pesticides in humans due to ethical reasons, animal studies are used as a default. Given the evolutionary resemblance of humans with other mammals, adverse effects observed in smaller mammals such as rodents (rats mice) and rabbits but also dogs and other species are considered relevant for humans. However, animals are not identical and thus it cannot be excluded that differences between the test animal and humans may exist and this is the element of discussion in the 'human relevance' tool.

B. WHO DEVELOPED IT? WAS THERE ANY US ORIGIN?

Industry, for decades, has been fighting evidence showing that their chemicals are carcinogenic. Numerous attempts have been undertaken to disqualify the results, often by claiming that there is a safe level of exposure (threshold) or that the effects in animals are not relevant for humans or that the studies are not performed according to GLP, or that

27. http://blog.stbsenterprises.com/quit-smoking/tobacco-companies-hide-dangers-of-smoking-for-years/
28. www.independent.co.uk/voices/at-last-the-tobacco-industry-admits-the-link-it-has-always-denied-1149930.html
29. www.asbestosnation.org/facts/asbestos-companies-hid-the-danger-for-decades/
30. The Secret History of the War on Cancer, Davis, Devra, Published by Basic Books, New York, 2007

the data are within "historical control data", etc. Starting from the cigarette industry[27],[28], the asbestos industry[29], the pharmaceutical industry and the chemical industry[30] we see that a whole range of tactics have been developed to prevent a ban on their commerce of a chemical.

One idea developed in the US was to include 'mode of action' (MoA) into the risk assessment discussions. The efforts focused in the international body IPCS (International Programme on Chemical Safety) of the World Health Organisation to develop a 'framework' based on MoA to compare first qualitatively and then quantitatively if there are differences in MoA between the experimental animals and humans. In 1998 an IPCS-workshop was convened to discuss this idea.

Industry lobby group ILSI (Meek/ Syngenta, 2003[31]) was the motor behind the 'human relevance' approach. In 2006 they were successful in getting it adopted by IPCS/WHO[32]. This happened because the same people involved in developing this industry tool, managed to infiltrate into the WHO working group -covered as academics or civil servant (Bette Meek, Alan Boobis[33], Joseph Schlatter)- and to get the idea adopted. As proudly acknowledged[34] they state it is the "same framework" (the IPCS/WHO framework and the ILSI-framework) and quote a range of industry studies (Boobis, Meek, Patton) that gradually developed the tool.

C. IN WHAT WAY WAS 'HUMAN RELEVANCE' INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

The criterion of 'human relevance' was introduced at IPCS/WHO in the period 1998 to 2006 and dominated by industry employees and experts defending industry views.

At European level it was adopted by EFSA's pesticide panel[35]

31. Meek, M. E., Bucher, J. R., Cohen, S. M., Dellarco, V., Hill, R. N., Lehman-McKeeman, L. D., Longfellow, D. G., Pastoor, T., Seed, J., and Patton, D. E. 2003. A framework for human relevance analysis of information on carcinogenic modes of action. Crit. Rev. Toxicol 33:591–653.
32. Boobis, A. R., Cohen, S. M., Dellarco, V., McGregor, D., Meek, M. E., Vickers, C., Willcocks, D., and Farland, W. 2006. IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit. Rev. Toxicol. 36:781–792.
33. See background Boobis and Schlatter, PAN report on TTC
34. Journal of Toxicology and Environmental Health, Part B: Critical Reviews, Re: Guyton, Kathryn Z., Barone, Stanley, Jr., Brown, Rebecca C., Euling, Susan Y., Jinot, Jennifer, Makris, Susan (2008). Mode of Action Frameworks: A Critical Analysis. Journal of Toxicology and Environmental Health, Part B, 11(1): 16–31
35. EFSA. 2006. Opinion of the Scientific Panel on Plant Health, Plant protection products and their Residues on the scientific principles in the assessment and guidance provided in the field of human toxicology between 2003 and 2006. EFSA J. 346:1–13.

D. HOW IS 'HUMAN RELEVANCE' CURRENTLY USED AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

The 'human relevance' criterion is used almost in a standard way by applicants who generally claim the lack of human relevance when serious adverse effects have been demonstrated in animal testing. Also in the peer-reviews of Food Authority EFSA "human relevance" is very often used in the risk assessment of pesticides. For instance the thyroid effects of Amitrole are claimed not to be relevant for humans given the differences of the human and rat organs[36]. The same for bladder tumours caused by Bifentrin[37]. On the pesticide 1,3-Dichloropropene EFSA states[38]: *"...Although, results indicate that 1,3- dichloropopene can be mutagenic, the relevance of these results to mammalian tumour formation is uncertain owing to the high concentrations or doses used...."*.

On the pesticide Dichlorvos EFSA states[39]: " *Following the outlines of the conclusion given in the PPR panel opinion (EFSA-Q-2005-246) it is plausible to assume that for forestomach tumours in the mouse a threshold can be set and the relevance for humans are low depending on the unique structure of forestomach in relation to human stomach".*
On the pesticide Ethoprophos EFSA states[40]: " *Increased incidences of thyroid 'C' cell tumours in male rats at high dose levels, uterine polyps and tumours in female rats. Clear threshold and association with general toxicity. Limited relevance to man".*

All these EFSA-opinions have in common that any experimental evidence for their claim of non-relevance is lacking.

36. Revised Assessment Report (RAR) for Amitrole, 2012.
37. Draft Assessment Report Bifenthrin, 2008.
38. EFSA Scientific Report (2006) 72, 1-99, Conclusion on the peer review of 1,3-dichloropropene
39. EFSA Scientific Report (2006) 77, 1-43, Conclusion on the peer review of dichlorvos
40. EFSA Scientific Report (2006) 66, 1-72, Conclusion on the peer review of ethoprophos

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON 'HUMAN RELEVANCE'?

A peer-review conducted on this WHO/IPCS framework[41] however shows that the framework has many shortcomings and is simply not operational. Our scientific knowledge is limited to use 'human relevance' in practice and for now it is mainly based on the quicksand of assumptions and speculations.

Shortcomings among others are:

- The assessment is based on expert judgement ('plausibility could reasonably be excluded'), and will, depending on the knowledge and judgement of the people involved, reach a different conclusion; the framework is not standardised and the decisions are subjective
- The level of evidence needed to establish reasonable exclusion (not relevant for humans) is not specified (for instance the extent of quantitative differences)
- The lack of knowledge of the underlying causes of human diseases makes it generally impossible to use 'human relevance' and base it on experimental data
- Human relevance does not take into account the potential for chemical effects to act additively with background exposures creates extra uncertainty. This is totally omitted by IPCS/WHO
- It disregards multiple MoA as well as MoA that function in an interactive manner; the assumption of the IPCS/WHO framework that M0As are mutually exclusive has no scientific justification; instead risk assessors should choose a system biology approach to the chemical's toxicology, the entire physiology of cell, organ, and organism
- A more complete picture of the contributing modes of action would give a better picture of adverse outcomes including across duration and life stage of the exposure, developmental events, disease status, and (quantitative) ranges of susceptibility; the IPCS/WHO human relevant framework's mono-focus is therefore inadequate. How MoA-based cross-talk with different outcomes should be used in regulation remains unclear.

41. Journal of Toxicology and Environmental Health, Part B: Critical Reviews Mode of Action Frameworks: A Critical Analysis Kathryn Z. Guyton , Stanley Barone Jr. , Rebecca C. Brown, Susan Y. Euling, Jennifer Jinot & Susan Makris.

Another scientist claims that the 'human relevance' criterion is part of the industry toolbox to cast doubt on observed effects; Melnick[42] writes: "*Common strategies used to deny reliability or relevancy of tumour data for assessing health risks to humans include: a) claiming that doses/exposures used in animal studies were too high to cause an effect at human exposures (even when no nonlinear processes have been identified), b) claiming that the chemical induced essential precursor ["toxic"] changes in the animal at "high doses" that would not occur at lower doses (even when a consistent causal relationship between the "essential precursor change" and tumour induction has not been demonstrated), c) promoting untested mechanistic hypotheses of tumour induction in animals that are claimed to not occur in humans, d) proclaiming that tumours induced in rodents are not predictive of tumour induction in humans, e) declaring certain tumour sites [e.g., fore stomach] are irrelevant because they are not present in humans, or f) discrediting the design, conduct, and interpretations of studies at the laboratory that identified carcinogenic effects*".

Timotis[43] adds to this regarding WHO/IARC: "*From its outset, the International Agency for Research on Cancer's (IARC's) program for the evaluation of carcinogenic risks for humans had to resist strong direct and indirect pressures from various sources to protect its independence. External experts for Monographs working groups were selected on the basis of competence and the absence of conflicts of interest. The IARC did not use unpublished or confidential data, so readers could access the original information and thus follow the groups' reasoning. The strength of the original program lay in its scientific integrity and its transparency. Since 1994, however, the IARC appears to have attributed less importance to public health-oriented research and primary prevention, and the Monographs program seems to have lost some of its independence. Criteria for evaluating carcinogenicity related to mechanism(s) of action are not necessarily used as originally intended, to ensure better protection of public health. Evidence for carcinogenicity provided by the results of experimental bioassays has been disregarded on the basis of only suggested mechanistic hypotheses. If tests show those hypotheses to be incorrect, or if they do not account adequately for the wide range of susceptibility in humans, serious consequences for public health may follow*".

42. Ronald L. Melnick, Jerrold M. Ward, James Huff, War on Carcinogens: Industry Disputes Human Relevance of Chemicals Causing Cancer in Laboratory Animals Based on Unproven Hypotheses, Using Kidney Tumors as an Example, International Journal of Occupational and Environmental Health 2013 VOL. 19 NO. 4 255
43. Tomatis L, The IARC monographs program: changing attitudes towards public health, Int J Occup Environ Health. 2002 Apr-Jun;8(2):144-52.
44. Huff J, IARC monographs, industry influence, and upgrading, downgrading, and under-grading chemicals: a personal point of view. International Agency for Research on Cancer, Int J Occup Environ Health. 2002 Jul-Sep;8(3):249-70.

Huff (2002)[44] has similar observations: "*The first IARC Monographs Volume was distributed in 1972, and over the 23 years through 1993, under the leadership of Dr Lorenzo Tomatis, 59 IARC Monographs were completed. Since then (starting with Volume 62: 1995), a new attitude seems to have pervaded the IARC Monographs program, resulting in an increasing influence of or partiality for industry and a diminishing dedication to public and occupational health and safety concerns, and for primary prevention. Some of this attitude comes from an apparent misguided scientific zest prematurely to endorse purported or hypothetical mechanisms of chemical carcinogenesis or modes of action of chemicals causing cancer in experimental animals. These speculations are in turn used cavalierly to discount the value of experimental evidence for predicting probable carcinogenicity to humans. Most often this is accomplished by opining that the mechanism(s) of carcinogenicity in animals would not be operative in humans. End of explanation".*

And goes on to say "*During the last decade industry has had increasing and often decisive influence on IARC's Monograph Series: Evaluation of Carcinogenic Risks to Humans IARC consistently "downgraded" [lowered the risk evaluation of] more chemicals than it "upgraded" in the 1990s: acrylonitrile, amitrole, atrazine, di(2-ethylhexyl) phthalate (DEHP), ethylenethiourea (ETU), glasswool, insulation [fiberglass], d-limonene, melamine, rock (stone) wool, saccharin and its salts, slagwool, and sulfamethazine as examples. These downgrades were based most often on "modes of action" (a naïve and unproven furtive metaphor for "mechanism") that IARC (and industry, and all too frequently U.S. regulatory agencies) stated were operative only in animals and were not relevant to humans, and thus a hope-we-are-right leap to "safe for humans." DEHP [and 1,3-butadiene] is a most egregious example of science manipulation and misrepresentation, and thus perpetuation of harm to humans based on speculative mechanistic behavior*".

Some authors[45] feel that WHO is sometimes used as a "front" by business interests operating through certain committees. According to Huff (2002) the international health organizations should recognise their vulnerability and take steps to protect their credibility and reputation from being hijacked by business commercial interests.

45. The manipulation of international scientific organisations, B.I.Castleman et al., editorial, INT J OCCUP ENVIRON HEALTH, 1998

F. IS 'HUMAN RELEVANCE' MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

Given the comments made by independent scientists, it is very clear that 'human relevance' is misused on a large scale. Decisions on human relevance are done by 'expert judgement' and the framework is not standardised, it's subjective. The level of evidence is not specified. The lack of scientific knowledge on the development of human diseases in fact totally disqualifies the use of 'human relevance' in such a broad sense. Cumulative effects and multiple mechanisms of action are simply ignored.

The examples presented above show that the reasons for dismissing effects are not based on scientific facts but on assumptions and speculations and the personal belief spectrum of the experts at EFSA.

MARGIN OF EXPOSURE/ THRESHOLDS

A. HOW CAN THE CRITERION BE DESCRIBED?

The 'margin of exposure' (MOE) criterion states that if the margin between actual exposure in humans and a certain effect level/ no-effect-level in animal testing is high enough, the concern is low and the use of the substance is acceptable. The acceptable health level can be a NOAEL (no observed adverse effect level) of animal studies, or BMD (benchmark dose, for instance the dose at which level 10% of the animals show the harmful effect), or another derived (such as probabilistic) 'safe' level. MOE brings the concept of safe exposure levels for humans into play even for chemicals for which little data are currently available. This creates additional uncertainties and questionable calculations. MOE supposes that a 'safe' threshold of chemicals in organisms is always present, even if these chemicals are genotoxic carcinogens. MOE is used many times to oppose a 'hazard' approach and to propose a convenient risk assessment approach for industry.

The 'margin of exposure' (MOE) is proposed by industry primarily for genotoxic (and carcinogenic) substances when they feel there is an urgent need to prevent their banning. This is because EU law states that people should not be exposed at all to genotoxic substances, since no safe level can be guaranteed. One of the criteria industry uses to counter this EU policy is the 'margin of exposure' (MOE), a default margin of observed harm, of 1000 or 10.000 with testing outcome. This criterion in fact is not proposed to implement EU rules on a high level of protection of humans but to undermine the implementation of the EU policy. Adopting 'safe' thresholds through the backdoor will ensure continued use of hazardous substances.

B. WHO DEVELOPED MOE? WAS THERE ANY US ORIGIN?

A MOE approach is discussed for a long time already. For instance, by US EPA, where MOE in 1993 is mentioned as an acceptable alternative for risk managers[46]. MOE is also heavily promoted by industry lobby group ILSI since the beginning of this century for genotoxic carcinogens[47].

In 2002 a special ILSI expert group was set up[48] with the following objectives:

1. to propose a structured approach for the evaluation of genotoxic carcinogens in food following a critical review of the approaches currently available; and
2. to evaluate the margin of exposure approach for food-borne substances that are genotoxic and carcinogenic.

C. IN WHAT WAY WAS MOE INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

Coincidentally (or not), in 2003 the newly installed EU Food Authority EFSA started a working group of its scientific panel[49] on this topic with several experts with a link to the work of ILSI (e.g. Renwick, Schlatter, Bridges, Greim, Larsen), while other ILSI-linked experts became members of the EFSA scientific committee (Barlow). Not surprisingly, in 2005 EFSA published an opinion[50] with a predictable outcome: " *the Scientific Committee therefore recommends using a different approach, known as the margin of exposure (MOE)*". EFSA however, excluded the use of MOE for substances that are deliberately added to food, it can only be used for substances that are unavoidable. In a later opinion EFSA[51] however, stated the approval of applying the MOE in the evaluation of production impurities of active substances found in food, including

46. www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments
47. J. O'Brien, A.G. Renwick, A. Constable, E. Dybing, D.J.G. Mu¨ller, J. Schlatter, W. Slob, W. Tueting, J. van Benthem, G.M. Williams, A. Wolfreys, Approaches to the risk assessment of genotoxic carcinogens in food: A critical appraisal, Food and Chemical Toxicology 44 (2006) 1613–1635
48. J. O'Brien, A.G. Renwick, A. Constable, E. Dybing, D.J.G. Müller, J. Schlatter, W. Slob, W. Tueting, J. van Benthem, G.M. Williams, A. Wolfreys
49. Ada Knaap, Christer Anderson, Paul Brantom, Jim Bridges, Riccardo Crebelli, Helmut Greim, John Christian Larsen, Douglas McGregor, Andrew Renwick and Josef Schlatter
50. Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic (Request No EFSA-Q-2004-020) (ADOPTED ON 18 OCTOBER 2005)

pesticides, that are both carcinogenic and genotoxic.

The opinion of the EFSA panel was preceded by a EFSA/WHO-meeting "with support of ILSI". [52] The meeting was flooded by the experts that had worked on an opinion in ILSI working groups (e.g. Andrew Renwick, Joseph Schlatter, James Bridges, Helmut Greim, Wouter Slob, Jan Van Benthum, Erik Dybing, Susan Barlow, Bernhard Bottex, etc.) employees of the industry (Coca Cola, Danone, P&G, Pepsi, Unilever, Nestle, etc.) and experts from EU national agencies, while almost all other stakeholders were excluded (not-invited). The "consensus" was reported in a subsequent publication[53] with a heavy ILSI dominance. A 'consensus', which was reached in a meeting between industry and selected regulators, lacking objectivity.

D. HOW IS MOE CURRENTLY USED AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

Much of the work done by ILSI on MOE is taxpayer-funded. The EU even funded ILSI's project "FOSIE" under the 5th Framework program (with a subsidy of €754.000 Euro) coordinated by ILSI experts (Kleiner - now EFSA management) and with several of the usual experts connected to the program[54] (Susan Barlow, Alan Boobis, James Bridges,Erik Dybing, Luc Edler, Diane Benford, Corrado Galli, Ada Knaap, John Christian Larsen, Bette Meek, Iona Pratt, Andrew Renwick, Joseph Schlatter, Angela Tritscher (Nestle, now WHO), etc.). FOSIE was a program that ran from 2000 until 2003 and was focused on qualitative and quantitative methodologies for risk assessment of chemicals in food and diet.
MOE is used in EFSA peer reviews as a standard risk assessment methodology. This happened for instance for the pesticide Buprofezin with the carcinogenic and mutagenic metabolite Anilin. It reduces the level of protection of humans and the environment since pesticides that should be banned are approved and people and the environment exposed.

51. EFSA Scientific Committee; Scientific Opinion on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578.
52. EFSA/WHO International Conference with support of ILSI Europe on Risk Assessment of Compounds that are both Genotoxic and carcinogenic – New approaches, 16-18 November 2005, Brussels, Belgium.
53. S. Barlow, A.G. Renwick, J. Kleiner, J.W. Bridges, L. Busk, E. Dybing, L. Edler, G. Eisenbrand, J. Fink-Gremmels, A. Knaap, R. Kroes, D. Liem, D.J.G. Mu¨ller, S. Page, V. Rolland, J. Schlatter, A. Tritscher, W. Tueting, G. Wu¨rtzen, Risk assessment of substances that are both genotoxic and carcinogenic; Report of an International Conference organized by EFSA and WHO with support of ILSI Europe, Food and Chemical Toxicology 44 (2006) 1636–1650
54. A.G. Renwick, S.M. Barlow, I. Hertz-Picciotto, A.R. Boobis, E. Dybing, L. Edler, G. Eisenbrandg, J.B. Greig, J. Kleiner, J. Lambe, D.J.G. Mu¨ller, M.R. Smith, A. Tritscher, S. Tuijtelaars, P.A. van den Brandt, R. Walker, R. Kroes, , Risk characterisation of chemicals in food and diet, Food and Chemical Toxicology 41 (2003) 1211–1271

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON MOE?

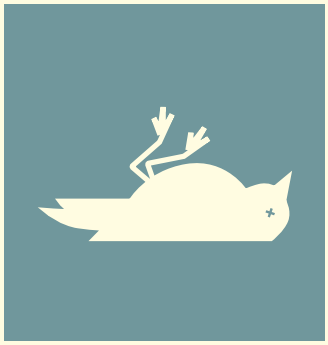
Abraham and Ballinger[55] discuss the attempt of industry (ILSI) for carcinogenic pharmaceuticals to change the testing requirements (getting rid of the obligation to test two life-time rodent species) and conclude: "*our findings raise the spectre that changes to pharmaceutical carcinogenicity-testing standards and subsequent 'validation' may have been a massive exercise of boundary-work in which the politico-economic project of decreasing the chance that companies' products are defined as carcinogenic has masqueraded as a purely 'techno-scientific' process*". They refer to Bernstein's (1955) life-cycle theory of regulatory agencies that regulatory agencies start by following their mission to protect the public, generally after a big disaster, but gradually are captured by industry and stop following their mission (administrative drift) until a new disaster reinvigorates a regulatory resurgence, commencing a new cycle.

F. IS MOE MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

The use of MOE for substances for which no safe threshold has been demonstrated cannot be supported scientifically. It could only be a political decision to use these unscientific margins. The fact that EFSA engages in the MOE criterion means it is acting outside its mandate, which has to be purely scientific. Politicians have already decided on carcinogenic and genotoxic substances and the decision is no exposure at all. Using MOE in risk assessment, as EFSA does, is a misuse of its power and undermines decisions made by politicians. For many food contaminants (like acrylamide, furan, HCDB, ethyl carbamate) EFSA has used MOE. Kropp et al.[56] demonstrates an obvious misuse of MOE for PFOA.

55. John Abraham and Rachel Ballinger, Science, politics, and health in the brave new world of pharmaceutical carcinogenic risk assessment: Technical progress or cycle of regulatory capture?, Social Science & Medicine 75 (2012) 1433e1440

56. Timothy Kropp, Jane Houliha, Human health risks from exposures to perfluorooctanoic acid: A critique of Butenhoff et al. 2004, Regulatory Toxicology and Pharmacology, Volume 42, Issue 1, June 2005, Page 145



RECOVERY OF NON-TARGET ORGANISMS

A. HOW CAN THE METHOD BE DESCRIBED?

Recovery is used for environmental risk assessment, notably in aquatic risk and terrestrial (arthropods) risk assessment. It is the 'assumption' that, organisms are harmed or killed by pesticides, they (or their fellow organisms) return to be vital again within a certain period of time, hence the population "recovers". As a result observed adverse effects in 'non-target' organisms are considered acceptable. Killing 50% of the organisms (non-target arthropods, bees) is the acceptable benchmark and a higher tier is allowed even to go above this benchmark, i.e. if more than 50% are killed, higher tier methods could still result in the same verdict: acceptable. The EU guideline on terrestrial risk assessment[57] from 2002 is not very clear why it uses 'recovery' in the higher tiers[58] and just refers to ESCORT2 (European Standard Characteristics of Non-Target Arthropod Regulatory Testing). The ESCORT-proceedings were a result of EPPO/SETAC-organised meetings, meetings not coordinated by EU.

For terrestrial organisms the ESCORT-meetings are also organised as EPPO/SETAC meetings. In ESCORT, as reported

57. SANCO/10329/2002 rev 2 final, 17 October 2002, DRAFT Working Document Guidance Document on Terrestrial Ecotoxicology Under Council Directive 91/414/EEC

58. It is accepted for the in-crop area, that the application of these products may result in effects above the threshold value of 50% if "recovery" or at least the "potential for recovery" is demonstrated. For the in-crop "it has to be demonstrated that there is a potential for re-colonisation / recovery at least within one year but preferably in a shorter period, depending on the biology (seasonal pattern) of the species" (EC 2002). For the off-crop situation, the acceptable time period is less clearly defined ("within an ecological acceptable time period").

by Candolfi et al., (2000[59]), it is suggested that in-crop recovery for arthropods should take place within one year. For the off-crop situation, it is only stated that the duration of the effect and the range of taxa affected should be taken into consideration. According to Candolfi et al., (2000), the detection of effects of a pesticide active substance in the latter case, however, should not necessarily result in the denial of its registration, but instead, result in risk management options. These risk management options are specified in Candolfi et al., (2001[60]). And who is Candolfi one might wonder. He works for Novartis Crop protection.

The picture becomes even more worrying when one takes a closer look into who else helped drafting a 'guideline' as a result of these meetings: Neumann (Novartis), Heimbach (Bayer), Campbell (Zeneca), Romijn (Rhone-Poulenc) are a few.

For aquatic toxicity a same reference to HARAP (Higher tier aquatic risk assessment for pesticides) and CLASSIC (Community level aquatic system studies - interpretation criteria) -meetings can be observed. These are the notorious HARAP and Classic-meetings mentioned in Chapter 3.8 of this report for aquatic risk assessment.

B. WHO DEVELOPED THIS CRITERION? WAS THERE ANY US ORIGIN?

It is clear that chemical industry was at the steering wheel in SETAC-meetings with (industry-friendly?) national experts and consultants as their counterpart. Other stakeholders as well as independent scientists were lacking. And no US-origin.

59. Candolfi M, Bigler F, Campbell P, Heimbach U, Schmuck R, Angeli G, Bakker F, Brown K, Carli G., Dinter A., Forti D, Forster R, Gathmann A, Hassan S, Mead-Briggs M, Melandri M, Neumann P, Pasqualini E, Powell W, Reboulet J-N, Romijn K, Sechser B, Thieme Th, Ufer A, Vergnet Ch, Vogt H. 2000a. Principles for regulatory testing and interpretation of semi-field and field studies with non-target arthropods. Journal of Pest Science 73, 141-147

60. Candolfi MP, Barrett KL, Campbell P, Forster R, Grandy N, Huet M-C, Lewis G, Oomen P A, Schmuck R, Vogt H. 2001. Guidance document on regulatory testing and risk assessment procedures for plant protection products with nontarget arthropods. Report of the SETAC/ESCORT 2 Workshop, Wageningen, The Netherlands, SETAC-Europe, Brussels, Belgium.

C. IN WHAT WAY WAS THIS CRITERION INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

SETAC-meetings (HARAP, CLASSIC, ESCORT) with industry employees and national experts drafted 'guidelines' for risk assessment including this element of 'recovery'. Next DG SANCO in 2002 published a draft guidance on terrestrial ecotoxicology and aquatic ecotoxicology, referring to these SETAC-meetings. The SANCO guidance for aquatic toxicity was renewed in 2015 based on an EFSA opinion[61], while EFSA just started reviewing the guidance on terrestrial ecotoxicology[62] with a panel of experts who have links to the industry (e.g. Brock, Capri, Pickford).

The 2013 aquatic guidance -remarkably- now allows for two options, ETO, ecological threshold option, accepting negligible population effects only, and ERO, ecological recovery option, "accepting some population-level effects if ecological recovery takes place within an acceptable time period". This looks more like a political compromise than science. For ERO, organisms can recover (it may take three generations), or organisms can migrate, including certain conditions, see below a quote from the guideline[63]. For the aquatic guideline, consultant Brock, working for industry as well as government, is a constant actor in meetings and publications and has many 'hats'. He is prominent in SETAC-meetings[64], delivers data on micro/mesocosms with his consultancy/university, is part of the EFSA PPR-panel (evaluating his own data, drafting guidance), publishes with industry.

In 2016, EFSA started reviewing the issue of 'recovery' in ecological risk assessment[65]. First an external scientific report was commissioned by EFSA, summarising academic literature. From this report[66] it appears

61. SANTE-2015-00080, 15 January 2015. GUIDANCE DOCUMENT ON TIERED RISK ASSESSMENT FOR PLANT PROTECTION PRODUCTS FOR AQUATIC ORGANISMS IN EDGE-OF-FIELD SURFACE WATERS IN THE CONTEXT OF REGULATION (EC) No 1107/2009
62. www.efsa.europa.eu/en/efsajournal/pub/3800
63. The substance is not persistent in the aquatic environment, the exposure regime is short-term or pulsed, and the time between pulses is sufficient for recovery. The physicochemical environment and ecologically important food-web interactions are not altered by the stressor, or are quickly restored. The generation time of the populations affected is short. Delayed effects on reproduction due to short-term exposures can be excluded. There is a ready supply of propagules of eliminated populations through active immigration by mobile organisms or through passive immigration by, for example, wind and water transport
64. Brock TCM, Alix A, Brown CD, Capri E, Gottesbüren BFF, Heimbach F, Lythgo CM, Schulz R and Streloke M (Eds), 2010a. Linking aquatic exposure and effects: risk assessment of pesticides. SETAC Press & CRC Press, Taylor & Francis Group, Boca Raton, FL, USA, 398 pp.
65. Scientific Committee, 2016. Scientific opinion on recovery in environmental risk assessments at EFSA. EFSA Journal 2016; 14(2):4313.
66. M. Kattwinkel, J. Römbke, M. Liess; Ecological recovery of populations of vulnerable species driving the risk assessment of pesticides. Supporting Publications 2012:EN-338. [98 pp.]. Available online: www.efsa.europa.eu/publications

that "recovery" can only be expected in specific cases, see quote below[67]. If the environment is already under stress, like in agricultural areas, external recovery (outside the fields) cannot be expected to occur. Additionally, ecological stress may increase due to synergistic effects of different pesticides used, which should be taken into account.

D. HOW IS THIS CRITERION CURRENTLY APPLIED AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

Denmark recognises that the issue of "recovery" is very complex and refuses to take it into account for now. Nevertheless, DG SANCO (former DG SANTE) adopted the criterion and "recovery" has been used throughout the years at national level mainly (the Standing Committee of members states forced SANCO to abandon banning pesticides solely based on environmental risks[68]).

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE USE OF THIS CRITERION?

No, academic scientists are generally not interested in regulatory issues since science is generally subject to political demands. No literature found.

67. 1. Based on the results for aquatic invertebrates, most species usually recover within five generation times. The absolute time of internal recovery depends strongly on the reproduction capacity of the species.

    2. Migration from uncontaminated areas is a main driver identified for external recovery. In many studies, where such re-colonization sources were present, recovery occurred within one generation. Especially taxa with a non-synchronised life cycle could make efficient use of such external recovery.

    3. If recovery from external sources is assumed for mobile species, it has to be ensured that the magnitude of re-colonization from such sources is a realistic estimation, in particular in landscapes heavily influenced by agriculture. Additionally, the spatial scale depends on the taxa under considerations.

    4. Environmental stress generally acts in addition or synergistically to pesticide stress and hence recovery has to be evaluated with the ecological context. This is especially true for endangered species that are under particular stress.

    5. Indirect effects based on competition and predation can play an important role on the magnitude of effect and the duration of recovery. This is especially true for taxa on higher levels of the food web (e.g. the lack of food for birds caused by the decrease of arthropod populations after the use of insecticides).

    6. In agricultural landscapes pesticide exposure reoccurs every year and consists of a mixture of different substances applied at different times of the year. Hence, even if a species can recover in experimental studies within a certain time, this has to be related to realistic exposure scenarios within a year and also long-term exposure profiles over multiple years.

68. PAN report Resubmission

F. IS THE METHOD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

- Not much information is available on the use/misuse of recovery; the reason is that risk assessment for the environment is mainly done at national level
- In the EFSA peer review on the pesticide active substance Captan[69], ESCORT2 was used to decide on the acceptability of effects on non-target organisms. Acute toxicity of half of the organisms (50% killing) in a laboratory experiment is considered acceptable (note that all other effects like on behaviour, long-term effects are not studied) and since this threshold was not exceeded, no higher tier was necessary to grand approval

In the Captan authorisation in the Netherlands[70] it turns out that non-target arthropods are killed for >90% in-field and >75% out-field during safety assessment tests. Industry doesn't have to choose to use 'recovery' to escape from a ban because it can carry out an "extended lab test", which concludes that Captan is suddenly far less toxic and the authorisation is granted.

69. EFSA Scientific Report (2009) 296, 1-90, Conclusion on the peer review of captan
70. Herregistratie Captosan, 2014, https://english.ctgb.nl/

HISTORICAL CONTROL DATA

A. HOW CAN THE METHOD BE DESCRIBED?

'Historical control data' (HCD), are data collected from the unexposed "control" groups of past experiments and can be used, particularly in long-term animal testing (e.g. for carcinogenicity), to evaluate if animals from the control group of the new experiment (concurrent control) are healthy and evaluate therefore, whether there is an overall problem with the experiment conducted. If the data of the historical controls are very different from the concurrent control data this indicates that there is a problem with all the experiment and it should be repeated. 'Historical control data' are not designed to be used instead of the concurrent control group.

According to OECD guidelines, the use of 'historical control data' should be done only when these data derive from the same laboratory and from animals of the species, strain and age, generated during the past five years[71].

Several papers from the scientific literature confirm that the concurrent control groups are the most valid or in fact the only valid control group and warn against the biasing effect of including historical control data (see Haseman, 1984[72], Hardisty, 1985,[73] and Cuffe, 2011). Haseman (1984) says there are a few rare instances where historical control data can

71. OECD guideline 451
72. Haseman JK. Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environmental Health Perspectives. 1984; 58: 385–392.
73. Hardisty JF. Factors influencing laboratory animal spontaneous tumor profiles. Toxicol Pathol. 1985; 13(95–104).

be useful, such as in cases with borderline effects where only a marginal increase over concurrent controls can be seen, or in the case of rare tumours. Even then, he stipulates that extreme care must be taken to ensure that any sources of variability in the historical control data can be identified[74]. The indiscriminate use of such HCD rests on the premise that the test animals are susceptible to spontaneous tumor formation (not treatment related) and this does not change over time. However, this is not always the case[75]. While an increasing tumor susceptibility over time may compromise the validity of the highest recorded incidence in control animals and enhance the risk of a false positive result, indiscriminate use of historical tumor incidences in cases of decreasing tumor susceptibility over time may introduce the risk of false negative results. HCD should be used with care and only in limited restricted cases.

B. WHO DEVELOPED THE USE OF THIS CRITERION IN RISK ASSESSMENT? WAS THERE ANY US ORIGIN?

The use of HCD in the hazard evaluation of risk assessment was designed in the US under the National Toxicology program when more than 400 long-term chemical carcinogenesis studies in rodents were evaluated[76]. It is noteworthy that (pesticide) industry and industry's ILSI lobby group didn't push very much for HCD to be included in risk assessment in their EU-subsidised 'wish-list' of FOSIE[77]. The issue of HCD was left to the individual chemical companies to deal with, to defend it and to include in their application dossiers[78],[79].

74. Haseman JK. Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environmental Health Perspectives. 1984; 58: 385–392.
75. Tennekes et al., The stability of historical control data for common neoplasms in laboratory rats and the implications for carcinogenic risk assessment, Regulatory Toxicology and Pharmacology 40 (2004) 293–304
76 Haseman JK, Data analysis. Statistical analysis and use of historical control data, Regulatory Toxicology and Pharmacology, 21, 52-59, 1995.
77. A.G. Renwick, S.M. Barlow, I. Hertz-Picciotto, A.R. Boobis, E. Dybing, L. Edler,G. Eisenbrand, J.B. Greig, J. Kleiner, J. Lambe, D.J.G. Mu¨ller, M.R. Smith, A. Tritscher, S. Tuijtelaars, P.A. van den Brandt, R. Walker, R. Kroes, Risk characterisation of chemicals in food and diet, Food and Chemical Toxicology 41 (2003) 1211–1271.
78. ULRICH DESCHL, BIRGIT KITTEL, SUSANNE RITTINGHAUSEN, GERD MORAWIETZ, MANFRED KOHLER, ULRICH MOHR, AND CHARLOTTE KEENAN , The Value of Historical Control Data—Scientific Advantages for Pathologists, Industry and Agencies, TOXICOLOGIC PATHOLOGY, vol 30, no 1, pp 80–87, 2002
79. Marine Carlus, Laëtitia Elies, Marie-Claude Fouque, Pierre Maliver, Frédéric Schorsch, Historical control data of neoplastic lesions in the Wistar Hannover Rat among eight 2-year carcinogenicity studies, Experimental and Toxicologic Pathology 63 (2011) 645– 656

C. IN WHAT WAY WAS THIS EVALUATION CRITERION INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

HCD was considered a standard approach in the evaluation of findings in risk assessment at the time EFSA was created (2004). In EPCO-meetings (coordination of European risk assessment before 2004 by German- and UK-institutes) HCD was an accepted element in risk assessment. Industry did put forward HCD in its pesticide applications as it was advantageous in cases where carcinogenic effects were observed in their own animal studies. EFSA even obliged the use of HCD in some cases as a full alternative to the concurrent controls.

D. HOW IS THE EVALUATION CRITERION CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

HCD is used in EU risk assessment on a large scale for dismissing effects observed in experimental animal studies. In many cases the HCD collected may reveal a number of 'spontaneous' adverse effects (e.g. control mice have developed tumors). If during an animal experiment an adverse effect (e.g. tumor) is observed in the treated animal group (higher than the concurrent controls) the concurrent control can be replaced by HCD that report more adverse effects (tumors) and therefore the adverse effect are considered not significant and therefore 'spontaneous' rather than treatment related. Even if the concurrent control (untreated) group had developed significantly less adverse effects. Therefore, positive adverse effects may be evaluated as non-treatment related. The level of protection of humans is lowered by HCD; without HCD some pesticides would be banned and others restricted.

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE USE OF THIS CRITERION?

Yes, several academic scientists stressed the need to use concurrent controls as the first and most appropriate group used for decision-making[80]. Use of HCD should be restricted to rare tumors and borderline cases. Tennekes[81] notes that HCD change over time and cannot be used indiscriminately. A large study done by Mesnage et al.[82] suggests that the diets (animal feed) given to test rodents are contaminated and in many cases results in far too many "spontaneous" responses in controls and producing false data. And this could also be the case for historical control data. All diets examined were contaminated with pesticides (1-6 out of 262 measured), heavy metals (2-3 out of 4, mostly lead and cadmium), PCDD/Fs (1-13 out of 17) and PCBs (5-15 out of 18). Several of these contaminants were analysed at levels that are reported to be hazardous in literature.

F. IS THE HCD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

Yes, on a large scale, these are a few examples:

- In the DAR for the pesticide Acetochlor[83] HCD was used to get rid of a treatment-related effect (post-implantation losses). HCD was used throughout the DAR indiscriminately and replaced the concurrent control. For Acetochlor[84] EFSA remarkably notes the absence of HCD as a 'data gap', for "stomachal and femoral tumors" in order to conclude on their relevance. They next obliged industry to provide HCD, apparently to have an 'alibi' for negating these effects.

80. JK. Haseman, J. Huff and GA. Boorman, Use of historical control data in carcinogenicity studies in rodents, Toxicologic Pathology, 12 (2), 1984, 126-135.
81. Tennekes et al., The stability of historical control data for common neoplasms in laboratory rats and the implications for carcinogenic risk assessment, Regulatory Toxicology and Pharmacology 40 (2004) 293–304
83. Robin Mesnage, Nicolas Defarge, Louis-Marie Rocque, Joël Spiroux de Vendômois, Gilles-Eric Séralini, Laboratory Rodent Diets Contain Toxic Levels of Environmental Contaminants: Implications for Regulatory Tests, PLOS ONE | DOI:10.1371/journal.pone.0128429 July 2, 2015
84. DAR Acetochlor, B - 6: TOXICOLOGY AND METABOLISM.

Also, EFSA writes that lung adenomas (benign tumors) and carcinomas (malignant tumors) are observed with increased incidences in females, "often above the historical control values". EFSA therefore uses HCD instead of the concurrent controls to conclude that these tumors were not treatment-related.

- For the pesticide Metam-sodium[85] changes in heamatology and clinical chemistry and effects on liver enzymes were dismissed based on HCD. This is a clear misuse of HCD. Numerous other (very severe) effects of Metam (such as developmental toxicity) were 'whitewashed' by HCD. EFSA doesn't use HCD to evaluate the concurrent controls and the study quality but uses HCD throughout the report in place of the concurrent controls to evaluate positive scientific findings as 'false' positives.
- For the pesticide Phosmet[86], the same typical EFSA-approach is followed: "Increased incidence of liver tumours is observed in mice at the highest dose level (14 mg/kg bw/day, 2-year mouse study), higher than controls but within the same range as historical control data". Once again, dismissing adverse effects because of HCD. Also, reduction of brain cholinesterase was observed in the same study, clearly above the controls and with a dose-related trend. Now a second study with only controls was initiated by the applicant in an apparent attempt to get favourable historical reference intervals[87].
- For the pesticide Prosulfocarb[88] the EFSA standard approach is followed: "The increased incidence of lung tumours in females was considered by the experts as not substance-related after comparison with additional historical control data". Concurrent controls are disregarded as a standard procedure.
- Same story for Picloram[89]: "This was a slightly increased incidence of benign liver tumours, within the historical control range.

85. EFSA Scientific Report (2008) 203, 1-97, Conclusion on the peer review of metam
86. European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance phosmet. EFSA Journal 2011;9(5):2162.
87. DAR Phosmet, B - 6: TOXICOLOGY AND METABOLISM, 2004.
88. EFSA, Conclusion regarding the peer review of the pesticide risk assessment of the active substance prosulfocarb, 27 July 2007
89. Conclusion on the peer review of the pesticide risk assessment of the active substance picloram,, European Food Safety Authority, 2009

THE EXTENDED ONE-GENERATION REPRODUCTIVE TOXICITY TEST

A. HOW CAN THE METHOD BE DESCRIBED?

The extended one generation reproductive toxicity test guideline (EOGRTS), can assess reproductive and developmental toxicity within a single study using up to 75% fewer animals than the current two generation test and related tests. The test misses effects that could be observed in the second generation (OECD TG 416) but could have advantages if endpoints for developmental neurotoxicity (DNT) and developmental immunotoxicity (DIT) are included. However, this is just an option (cohort 2 and 3) and can be ignored by industry. This might be the result in practice if there is no clear obligation to include these endpoints since DNT and DIT require more animals for first generation offspring and be more costly.

B. WHO DEVELOPED THIS CRITERION? WAS THERE ANY US ORIGIN?

In 2000, the ILSI Health and Environmental Sciences Institute (HESI) formed the Agricultural Chemical Safety Assessment (ACSA) Technical Committee to design a toxicity testing scheme that would incorporate current understanding of pesticide toxicology and exposure and recognize the specificity of agricultural products. In April 2001, a workshop was held in Washington DC on "Developing Strategies for Agricul-

tural Chemical Safety Evaluation" (HESI, 2001) to begin development of an improved testing approach[90]. In 2006 (ACSA) proposed a whole new testing paradigm, which constituted a tiered approach of toxicity testing. Part of this paradigm was a proposal for an alternative protocol for OECD TG 416 which required only one generation of animals while being more informative in data obtained[91]. The ILSI taskforce included several (industry) consultants (Weinberg, LLC, Exponent, Susan Barlow), industry experts (Dupont, Dow, Bayer, Syngenta, ILSI), US-EPA experts and -remarkably- Herman Koeter, a director of EFSA.

C. IN WHAT WAY WAS THIS EVALUATION CRITERION INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

The ILSI proposal was introduced at the OECD. In this multi-stakeholder process (with a big group representing industry) the EOGRTS was adopted in 2011. The relevant OECD document says[92]: "This Test Guideline (TG) is based on the International Life Science Institute (ILSI)-Health and Environmental Sciences Institute (HESI), Agricultural Chemical Safety Assessment (ACSA) Technical Committee proposal for a life stage F1 extended one generation reproductive study as published in Cooper et al., 2006[93]. Denmark and others put pressure to include the neurotoxicity and immunotoxicity endpoints. Industry published studies claiming that with fewer animals more information can be obtained[94] on the questionable condition that an F2 generation is not needed.

90. Neil G. Carmichael, Hugh A. Barton, Alan R. Boobis, Ralph L. Cooper, Vicki L. Dellarco, Nancy G. Doerrer, Penelope A. Fenner-Crisp, John E. Doe, James C. Lamb IV & Timothy P. Pastoor (2006) Agricultural Chemical Safety Assessment: A Multisector Approach to the Modernization of Human Safety Requirements, Critical Reviews in Toxicology, 36:1, 1-7.
91. Ralph L. Cooper, James C. Lamb IV, Sue M. Barlow, Karin Bentley, Angela M. Brady, Nancy G. Doerrer, David L. Eisenbrandt, Penelope A. Fenner-Crisp, Ronald N. Hines, Lorraine F. H. Irvine, Carole A. Kimmel, Herman Koeter, Abby A. Li, Susan L. Makris, Larry P. Sheets, Gerrit J. A. Speijers & Karen E. Whitby (2006) A Tiered Approach to Life Stages Testing for Agricultural Chemical Safety Assessment, Critical Reviews in Toxicology, 36:1.
92. OECD (2011), Guidance Document supporting TG 443: Extended One Generation Reproductive Toxicity Study, Series on Testing and Assessment, No. 151, OECD, Paris
93. Cooper, R.L., J.C. Lamb, S.M. Barlow, K. Bentley, A.M. Brady, N. Doerr, D.L. Eisenbrandt, P.A. Fenner-Crisp, R.N. Hines, L.F.H. Irvine, C.A. Kimmel, H. Koeter, A.A. Li, S.L. Makris, L.P. Sheets, G.J.A. Speijers and K.E. Whitby (2006), "A Tiered Approach to Life Stages Testing for Agricultural Chemical Safety Assessment", Critical Reviews in Toxicology, 36, 69-98.
94. I. Fegert, R. Billington, P. Botham, E. Carney, R.E. FitzGerald, T. Hanley, R. Lewis, M.S. Marty, S. Schneider, L.P. Sheets, B. Stahl, B. van Ravenzwaay, Feasibility of the extended one-generation reproductive toxicity study (OECD 443), Reproductive Toxicology 34 (2012) 331– 339

D. HOW IS THE EVALUATION CRITERION CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

The extended one generation test is part of the pesticide data requirements[95] and reads: "The OECD extended one-generation reproductive toxicity study may be considered as an alternative approach to the multi-generation study". Nothing on additional endpoints. Only in the section of developmental toxicity tests one can read that the results of EOGRTS can be used, apparently with the specific endpoints. For many pesticides the, not very sensitive, 2-generation study (OECD TG 416) is already performed in the last decades and the experience with the 1-generation is still limited. However, some information will be lost if the F2 is not considered. Not including the endpoints in F1 on DNT/DIT groups reduces the value of OGRTS substantially.

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE USE OF?

Some national institutes also promoted the substitution by EOGRTS, claiming a limited need (3 out of 176 studies showed reprotoxicity in F2 that was not visible in F1) to do F2 generation studies[96]. Their assessment might be biased a bit by available data of old and insensitive OECD protocols that used by interested parties only (industry). No good independent evaluation of the merits of 2-gen versus 1-gen regarding their protection of human health is available. Most studies are industry-linked and promote the less animal/less costs elements of EOGRTS.

95. COMMISSION REGULATION (EU) No 283/2013 of 1 March 2013

96. Emiel Rorije, André Muller, Manon E.W. Beekhuijzen, Ulla Hass, Barbara Heinrich-Hirsch, Martin Paparella, Erna Schenk, Beate Ulbrich, Betty C. Hakkert, Aldert H. Piersma, On the impact of second generation mating and offspring in multi-generation reproductive toxicity studies on classification and labelling of substances in Europe, Regulatory Toxicology and Pharmacology 61 (2011) 251–260

F. IS THE METHOD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

On the pesticide 2,4-D the EOGRTS was used for the European dossier[97] and although DNT/DIT was performed based on US-requirements, the applicant refused to submit these elements to the European dossier.

The lack of inclusion of DNT/DIT studies in EOGRTS by industry can be considered misuse. At the time of designing EOGRTS the additional endpoints were a big element is the promotion for the substitution of 2-gen. If in practice DNT/DIT is dropped, together with the additional indicators (endpoints) of endocrine disruption that were not included in the 2 generation, many will feel misled. The emphasis of industry on animal welfare is likely an element of misleading national experts and politicians.

97. Renewal Assessment Report (RAR) for the substance 2,4-D, February 2013.

RELEVANT METABOLITES

A. HOW CAN THIS EVALUATION CRITERION BE DESCRIBED?

The active substances of pesticides have to be tested by industry. However, this is much less the case for metabolites, impurities and pesticide formulants. For many years these metabolites and impurities didn't get much priority in risk assessment and this is only slowly changing after 20 years of EU decision-taking. For groundwater a special low standard was chosen, (0.1 µg/L) for pesticides and metabolites to prevent groundwater from being polluted and non-potable in the future. Directive 91/414 however mentioned "relevant metabolites", suggesting that some metabolites can be "irrelevant". Only in 2003, a published EU-SANTE draft guideline[98] dealt with this matter. The guideline describes a scheme to determine whether a metabolite is relevant (and thus subject to the 0.1 µg/L limit) or not relevant using criteria of biological activity, genotoxicity and toxicological hazard for regulatory decision-making. The term "relevant metabolites" is also used in the Drinking Water Directive, which states that concentrations of pesticides and their relevant metabolites in drinking water must not exceed 0.1 µg/L.

The evaluation of relevant metabolites is done in a step-wise approach. Metabolites are screened for biological activity. It is sufficient to demonstrate that the biological activity of a metabolite is clearly less than 50% of the activity of the parent molecule. Next metabolites are screened for their genotoxic potential by at least the following package of in vitro genotoxicity studies: Ames test, gene mutation

98. GUIDANCE DOCUMENT ON THE ASSESSMENT OF THE RELEVANCE OF METABOLITES IN GROUNDWATER OF SUBSTANCES REGULATED UNDER COUNCIL DIRECTIVE 91/414/EEC, Sanco/221/2000 –rev.10- final, 25 February 2003

test with mammalian cells, and chromosome aberration test. Equivocal (unclear or contradicting) results in in vitro studies should be substantiated by in vivo experiments. Mutagenic metabolites (any category) are considered relevant. The third step is testing for classified pesticides (acute toxicity, mutagenic, reprotoxic, etc.) if the metabolite has a similar toxicity; often however information will be lacking. Last step, if the first three have been passed, if the consumer intake is acceptable (substance exposure levels are not considered toxic). Again, generally information on the metabolite will be absent and TTC, the Threshold of Toxicological Concern, can be used. This, as explained in the next section, can raise the level of acceptance for pollution 7.5-fold from 0,1 to 0,75 µg/L in groundwater.

However, the story doesn't end here. If an TTC-threshold is set for an apparent 'non-relevant metabolite", industry can ask for 'refined risk assessment' and pollution can be allowed to increase 100-fold (from 0.1 µg/L to 10 µg/L) if the daily acceptable intake for consumers is acceptable (not exceeding the health standard ADI). Even above 10 µg/L, exposure to a non-relevant metabolite can be acceptable after 'careful evaluation' and therefore the pesticide can be approved, according to the SANTE guideline.

B. WHO DEVELOPED THE USE OF THIS CRITERION IN RISK ASSESSMENT? WAS THERE ANY US ORIGIN?

The SCP, Scientific Committee of Plants[99], made a first draft on relevant metabolites and introduced the US-FDA threshold of concern, as promoted by industry and ILSI[100], [101]. Members of the working group of SCP were Prof. Hardy (Chairman), Committee Members: Dr. Delcour-Firquet, Mr. Koepp, Prof. Maroni, Dr. Moretto, Dr. Nolting, Prof. Savolainen, Prof. Silva Fernandes, Dr. Sherratt and invited experts, Dr. Boesten, Dr. Carter, Prof. Dybing, Dr. Forbes, Dr. Lambré, Dr. Luttik, Prof. Rueff, Prof. Slakinoja-Salonen, Dr. Tarazona, Prof. Vighi.

99. Opinion of the Scientific Committee on Plants regarding the Draft guidance document on relevant metabolites (Document SANCO/221/2000-Rev.2 of October 1999) (opinion adopted by the Scientific Committee on Plants on 30 November 2000)

100. Munro IC, Ford RA, Kennepohl E, Sprenger JG (1996). Correlation of structural class with No-Observed-Effect-Levels: a proposal for establishing a threshold of concern. Food Chem. Toxicol. 34, 829-867

101. Lewis SC, Lynch JR, Nikiforov AI (1990). A new approach to deriving community exposure guidelines from "no-observed-adverse-effect-levels". Regul. Toxicol. Pharmacol. 11, 314-330

C. IN WHAT WAY WAS THE METHOD INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

Through regulatory procedure and drafting guidelines, first the SCP, next DG SANTE and finally EFSA. EFSA asked with its 'own-initiative' a mandate in 2008, to work on 'relevant metabolites' (signed by Mr. Tony Hardy). The main rational for this mandate request however, is the residue definition, whether metabolites should be included in the residue definition for dietary exposure. The EFSA-opinion[102] by a working group with quite a number of experts with ILSI-background (Alan Boobis, Susan Barlow, Angelo Moretto) did not conclude that industry should properly test the metabolites of the pesticide active ingredients but promoted the use of alternative methods that are much cheaper like QSAR and TTC, despite their questionable reliability.

D. HOW IS "RELEVANT METABOLITES' USED AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

The guidance on 'relevant metabolites' is used on a large scale in pesticide risk assessment and decision-taking. Metabolites are classified non-relevant as a standard procedure and dozens of metabolites have been classified non-relevant already. As an example, for the following 17 pesticides, captan, carfentrazone-ethyl, chloorpyrifos, chloorthalonil, cyazofamid, dichlobenil, dimethenamide, dimethenamide-P, fluazifop-P-butyl, isoxaflutool, metalaxyl-M, mesotrione, nicosulfuron, S-metolachloor and trifloxystrobine, The Netherlands classified 37 metabolites non-relevant since 2002[103]. A further 18 pesticides are expected to have non-relevant metabolites too. A good overview for Europe is lacking. An industry article gives some background for a range of EU member states[104].

102. EFSA Panel on Plant Protection Products and their Residues (PPR); Scientific Opinion on Evaluation of the Toxicological Relevance of Pesticide Metabolites for Dietary Risk Assessment. EFSA Journal 2012;10(07): 2799
103. Drinkwater en 'niet relevante' metabolieten van bestrijdingsmiddelen, CLM Onderzoek en Advies BV Utrecht, november 2002
104. V. Laabs, C. Leake, P. Botham, S. Melching-Kollmuß, Regulation of non-relevant metabolites of plant protection products in drinking and groundwater in the EU: Current status and way forward, Regulatory Toxicology and Pharmacology 73 (2015) 276e286

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON 'RELEVANT METABOLITES"?

Academics are generally not involved in regulatory issues and this is also the case for non-relevant metabolites. They, however, publish their work on the adverse effects of the metabolites[105],[106],[107]. These interesting studies are disregarded by the regulatory community (branded as non-protocol studies and useless for regulation).

Denmark (DK) protested fiercely in 1999 against the approach on "relevant metabolites'. DK believes that the high level of protection of the groundwater is violated. Only CO2, inorganic salts and naturally occurring substances should be classified as non-relevant metabolites, not all kinds of chemical substances based on a very little information (mainly a few in vitro genotoxicity studies).

Dutch water companies commissioned a consultant to look at non-relevant metabolites[108] and they criticized the use of several points, such as the use of an outdated guideline (1999), no public information on the health effects of the non-relevant metabolites, metabolites that are formed <10% are not assessed, no information to water companies and the public.

Industry is very happy with this evaluation approach on pesticides and promotes the use for general EU/national water legislation[109] too.

105. Josef Velisek, Alzbeta Stara, Eliska Zuskova, Antonin Kouba, Effects of three triazine metabolites and their mixture at environmentally relevant concentrations on early life stages of marbled crayfish (Procambarus fallax f. virginalis), Chemosphere 175 (2017) 440e445

106. Quan Zhang, Chenyang Ji, Lu Yan, Meiya Lu, Chensheng Lu, Meirong Zhao, The identification of the metabolites of chlorothalonil in zebrafish (Danio rerio) and their embryo toxicity and endocrine effects at environmentally relevant levels, Environmental Pollution 218 (2016) 8e15

107. Zhenzhen Liu, Zhengwei Fu, Yuanxiang Jin, Immunotoxic effects of atrazine and its main metabolites at environmental relevant concentrations on larval zebrafish (Danio rerio), Chemosphere 166 (2017) 212e220

108. Drinkwater en 'niet relevante' metabolieten van bestrijdingsmiddelen, CLM Onderzoek en Advies BV Utrecht, november 2002

109. V. Laabs, C. Leake, P. Botham, S. Melching-Kollmuß, Regulation of non-relevant metabolites of plant protection products in drinking and groundwater in the EU: Current status and way forward, Regulatory Toxicology and Pharmacology 73 (2015) 276e286

F. IS 'RELEVANT METABOLITES' MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

Here, we focus on the EU part of decision-making, the EFSA risk assessment and approval by DG SANTE. The situation in EU member states differs from country to country, with Denmark being most strict by not-accepting any non-relevance of metabolites.

- For the pesticide Tritosulfuron, the metabolite TBSA was acutely toxic, showed reproductive effects, in the ovaries and uterus, resulting in a proposed classification R2 (EU classification system, probably reprotoxic). TBSA also had clastogenic potential (disruption or breaking of chromosomes) in a standard *in vitro* test. A repetition of the test however didn't show this negative effect clearly and this was the reason for the EFSA[110] to conclude that there is no clastogenic potential. The metabolite TBSA classified "harmful if swallowed" (R22), and " Harmful: Danger of serious damage to health by prolonged exposure if swallowed"(R48/22) is therefore considered 'not relevant' and is allowed to pollute the groundwater and drinking water.
- For the pesticide active ingredient Nicosulfuron (reported to cause liver tumors that were, however, not considered relevant), none of the 6 metabolites was considered relevant[111], based on in vitro genotoxicity testing and acute toxicity. Three of the metabolites exceeded the TTC-threshold of 0,75 µg/L and a consumer risk assessment was done and the exposure considered acceptable. It is noted that in the 2003 SANCO guidance only acute toxicity and genotoxicity are asked to be evaluated, and not other potential toxicity (comparable to the parent substance).
- For the pesticide Fluazifop-P[112] metabolite 'X' was not relevant (by checking the high ecotoxicity of Fluazifop, data on genotoxicity, data on acute toxicity), while metabolite IV lacked data. While EFSA proposed classification R2 (Classification probably reprotoxic) for Fluazifop, this should automatically classify any metabolite as relevant. But EFSA failed to do so. Relevant or not, data gap or not, this will not prevent an approval by DG SANTE.

110. Opinion on the Toxicological Relevance of the Soil and Groundwater Metabolite TBSA1 of Tritosulfuron in the Context of the Human Risk, Assessment, Scientific Opinion of the Panel on Plant Protection Products and their Residues (PPR Panel), (Question No EFSA-Q-2007-128), Adopted on 11 December 2007
111. EFSA Scientific Report (2007) 120, 1-91, Conclusion on the peer review of nicosulfuron
112. European Food Safety Authority; Conclusion on the peer review of the pesticide risk assessment of the active substance fluazifop-P. EFSA Journal 2012;10(11):2945.

- For the pesticide active substance Captan, two of the 7 metabolites, THPI and THPAM, exceeded the groundwater standard and even the 0,75 TTC-trigger value. The Rapporteur Italy tried to classify them all non-relevant based on some toxicological data and mainly on reasoning (assumptions and speculations). In this case EFSA protested, also saying that because of the C2-classification (probably carcinogenic) of the parent pesticide, convincing evidence needs to be provided to shown that the metabolite has no carcinogenic potential. In the end it was concluded to a data gap for the two metabolites, to approve the pesticide and ask the applicant to deliver additional information later on.
- For the pesticide Terbuthylazine three metabolites were considered relevant[113] (and exceeded the groundwater standard in some cases) while another 5 were considered non-relevant but since toxicological data are lacking EFSA could not conclude on the consumer risk (data gap). For the environment, the risk for aquatic life was considered low. Academic research at the same time demonstrates adverse effects of the metabolites on early life stages[114].

113. Conclusion on the peer review of the pesticide risk assessment for the active substance terbuthylazine in light of confirmatory data submitted. EFSA Journal 2017;15(6):4868

114. Josef Velisek, Alzbeta Stara, Eliska Zuskova, Antonin Kouba, Effects of three triazine metabolites and their mixture at environmentally relevant concentrations on early life stages of marbled crayfish (Procambarus fallax f. virginalis), Chemosphere 175 (2017) 440e445

BEE TOXICITY TESTING

A. HOW CAN THE EPPO BEE TOXICITY TESTING METHOD BE DESCRIBED?

For many years bee toxicity testing was done mainly based on acute toxicity on adult bees and weak field tests (Directive 91/414). Chronic toxicity testing was not considered necessary, neither were the effects on behaviour, on larvae or on other pollinators. The tests had to be done according to EPPO (European and Mediterranean Plant Protection Organisation)-guidelines. This only changed in 2013 when new data requirements were adopted at EU-level: chronic tests, larval tests, tests on bumble bees and solitary bees. Still sub lethal effects (demonstrated many times in academic literature, such as feeding and mating behaviour) were not compulsory: "*Tests investigating sub-lethal effects, such as behavioural and reproductive effects, on bees and, where applicable, on colonies may be required*". Many effects on bees are being missed and even the chronic studies will have to be conducted after a renewal of the approval of pesticides, in some point in the future.

B. WHO DEVELOPED THE EPPO METHOD? WAS THERE ANY US ORIGIN?

The method was developed by EPPO, the European and Mediterranean Plant Protection Organisation, an intergovernmental organisation that brings together representatives from West-African, European, and West Asian countries and draft guidelines for testing of pesticides on different species. The task of designing guidelines for bees was delegated to an international, informal group of experts called ICPBR, the

International Committee of Plant-Bee Relationship (now renamed ICPPR: International Commission on Plant Pollinator Relationship). ICPBR has working groups with scientists, government officials and industry experts. Pesticide industry of course has great interest in this working group. The meetings were sponsored by the pesticide industry[115]. For the 3 working groups on bees, out of the total of 17 experts, 6 were from industry: Roland Becker (BASF), Mike Coulson (Syngenta), Nathalie Ruddle (Syngenta), Ed Pilling (Syngenta), Christian Maus (Bayer Crop Science) and Mark Miles (Dow Chemicals), exactly the companies that produce chemicals that are thought to be responsible for bee dying. Not surprisingly, the working group of ICPBR proposed that loss of 30% of bee brood is acceptable as well as loss of 50% of eggs and individuals at larvae stages[116]. The European Beekeeping Coordination states that no beekeeper can survive if 30-50% of its future colonies die systematically[117].

C. IN WHAT WAY WAS EPPO BEE TOXICITY TESTING METHOD INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

The European Commission had no bee experts and delegated the work on testing and guidelines to EPPO. EPPO however has no bee experts either in its staff and delegated the work to ICPBR and its working groups. For many years ICPBR dictated the testing and guidelines on bees. Most of the real bee experts within ICPBR were either industry staff or industry-friendly scientists. Given the lack of expertise, the detrimental work of ICPBR remained off the radar of regulators, politicians and the civil society. The founding of Food Authority EFSA in 2003 did not change this manipulation of science. Only after citizens and beekeepers massively expressed their concerns through public actions and petitions, EFSA, in a very late phase, started investigating the cause of bee mortality (2008). It only got involved after politicians felt the need to react to the concerns of the public in almost all European countries. From that time on, EFSA did good scientific work.

115. pub.jki.bund.de/index.php/JKA/article/download/116/102
116. http://bee-life.eu/en/doc/151/
117. http://bee-life.eu/en/doc/151/

Given the lack of proper tests conducted by industry, EFSA based their opinions on the work of thousands of academic scientists that published their works on bees and bee mortality. This was an innovation since EFSA likes to base its opinions solely on industry safety tests[118] despite Regulation 1107/2009 that obliges them to take academic research into account. As a result of EFSA's work, in 2013 the EU Commission decided to impose restrictions on the use of three neurotoxic insecticides, Imidacloprid, Thiamethoxam and Clothianidin, as a first step.

Some civil servants also played an apparent double-role in ICPBR. UK regulator Helen Thompson and France regulator Anne Alix as well as German Jen Pistorius were prominent in ICPBR and vigorously defended the proposals. As soon as EFSA started working on bees, they tried to get a seat in EFSA working groups as well; they managed to get a seat in a 2012 PPR-working group (Thompson, Alix, Pistorius) but once it became publicly known that they had a close connection to industry they were no longer invited. And soon both ladies turned into employees of the same pesticide companies, Thompson to Syngenta and Alix to Dow Chemicals.

D. HOW IS THE EPPO BEE TOXICITY TEST METHOD CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

The one-sided guidelines developed at ICPBR have caused massive and widespread harm to bees and other pollinators. Even now, good tests are not available, or not adopted and at least not performed for the currently 500 pesticides in use. The level of protection of the ICPBR proposals was likely close to zero. A close network of experts with a certain mission was capable of pushing the rules in one direction. It will still take years before proper tests and proper rules are put in place. The EU Commission is to blame, as well as EFSA in its first 8 years. Crucial independent scientists were kept at a distance. Despite an important body of scientific research showing harm, the fact could be denied for years. Only NGOs and the public helped to change this situation. Involving independent academic scientists (with a tracked-record of good studies and no link to industry whatsoever) to do a peer-review could prevent similar disasters in the future. This will help regulators who have little expertise and do not follow actual scientific developments.

118. PAN E report Missed and Dismissed

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE EPPO BEE TOXICITY TEST METHOD?

Dozens of academics published their results showing that pesticides cause changes of behaviour of bees and other pollinators. Scientists started all kinds of public action, took part in documentaries and addressed their concern to the public[119]. They were however 'knocking on closed doors' for a long time.

F. IS THE EPPO METHOD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

Of course, all decisions were based on EPPO-guidelines and no further information (widely available in scientific literature) was used until a few years ago. Furthermore, in several identified cases, despite evidence or suspicion of harm to bees from tests based on EPPO-guidelines, the industry, supported by the the Rapporteur Member State (the selected EU member state that analyses the dossier submitted by industry), considered the results as non-relevant and dismissed them. Now a new EFSA guideline is published which is based on available experimental evidence (mainly independent sources) but EU member states in majority refuse to use the guideline

119. www.disasterinthemaking.com/

MICRO/MESOCOSM FOR AQUATIC RISK ASSESSMENT

A. HOW CAN THE TEST METHOD BE DESCRIBED?

Microcosms studies of chemicals/pesticides in aquaria are defined as being smaller than 5 cubic meters or shorter than 15 meter length, while mesocosm studies are done in experimental ditches of bigger than 15 cubic meters or longer than 15 meter. Surface water (close to intensive agriculture) is 'mimicked' in these systems with (clean) water, waterorganisms, (clean) sediment and aquatic plants. Pesticides are added to the desired level and the (lethal) effects on aquatic life is monitored. These systems function as a "higher tier" study overruling the lower tier studies of pesticide activity on known sensitive organisms. There is a lot of discussion if these systems can represent the situation of ditches and canals in the intensive sprayed agricultural areas. Microcosm and mesocosm systems are widely used in pesticide approvals; their attractiveness can easily be explained because the standards for aquatic toxicity can be made less strict in numerous ways compared to the lower tier studies. This is partly due to the system itself (clean water, no pollution, variety of organisms) and statistical methods applied but also because uncertainty factors are lowered or not used anymore in higher tier (the reasoning is that higher tier studies are more realistic; we will come to that).

B. WHO DEVELOPED THE TEST METHOD? WAS THERE ANY US ORIGIN?

Pesticide Directive 91/414 already provided for higher tier aquatic assessment in case pesticides failed to pass the lower tier assessments. The Directive didn't prescribe a validated method but referred to the outcome of a 1991 SETAC meeting[120] as a reference of how to conduct mesocosms. After a range of this kind of (SETAC) meetings, additional ones were held in 1998 (HARAP)[121] and 1999 (CLASSIC)[122]. Both meetings were sponsored heavily by pesticide industry, AgrEvo, Cyanamid, BASF, Bayer, Monsanto, FMC, Novartis, Rhone-Poulenc, Zeneca, Springborn and the outcome of the meetings is still the basis for current EU aquatic risk assessment. German and Dutch experts (Dutch Wageningen University/Alterra and German institutes) were the main experts representing national institutes but the meetings were dominated very much by pesticide industry employees while no other stakeholders were invited. Not much distance was observed between the different interests, important experts freely moved through the revolving door from government institute to industry. F. Heimbach (Bayer) was a prominent expert as well as S. Maund (Syngenta), P.J. Campbell (Zeneca) and D.J.S. Arnold (AgrEvo UK). And from the government institutes T. Brock (Wageningen), W. Heger (UBA) and M. Streloke (BBA) had a high profile.

J. Giddings was one of the few (industry/Springborn) US-representatives; he was involved in US-EPA micro- and mesocosm studies in the 80-ties.

120. SETAC — Guidance document on testing procedures for pesticides in freshwater mesocosms/Workshop Huntingdon, 3 and 4 July 1991
121. Campbell et al. (eds), Guidance document on Higher tier aquatic risk assessment for pesticides (HARAP), SETAC, 1998
122. Giddings et al. (eds), Community level aquatic system studies - interpretation criteria (CLASSIC), SETAC, 1999.

C. IN WHAT WAY WAS THE TEST METHOD INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

HARAP was a SETAC/OECD/EC workshop, creating the impression that guidance was delegated to a meeting/working group that had to generate a consensus. A public-private partnership of regulators and industry. CLASSIC was -besides industry- also sponsored by OECD and European Commission. It is noteworthy that rules that should protect a public good against dangerous chemicals produced by industry are developed by industry itself in industry-sponsored meetings. Apparently this was not considered a conflict of interest in the test methods agreed. Initially a guideline was developed in 2002[123] by DG SANCO which refers to the 'international guidelines' of HARAP and CLASSIC. The uncertainty factors (10 - 100) used in lower tiers can be reduced in these systems or even get deleted, based on 'expert judgement'.

Despite the mentioned uncertainties of these systems (no fish present in the cosms, long-term effects difficult to assess, no real imitation of agricultural surface water, etc.) SANCO concludes that uncertainty is reduced without proper argumentation. Scientific studies underpinning this assumption are lacking.
In 2013 an EFSA guideline (revision) was published[124]. It states that: "*Micro- and mesocosm studies performed for PPP authorisation aim to simulate realistic natural conditions and environmentally realistic PPP exposure regimes*", and again HARAP and CLASSIC are mentioned as an important guideline source. Main expert in the EFSA PPR-panel and in the working group on the revision: Theo Brock. Quoting mainly his own work at Alterra institute (part of Wageningen University).

123. Working Document - Guidance Document on Aquatic Ecotoxicology in the context of the Directive 91/414/EEC, Sanco/3268/2001 rev.4 (final), 17 October 2002

124. http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2013.3290/abstract

D. HOW IS THE TEST METHOD CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

Microcosm and mesocosm systems are widely used in national pesticide authorisations if the substances fail to pass the lower tier at European level of approval. At EU level aquatic risks are no reason for non-approving a pesticide, no matter how dangerous this chemical is for the environment. This is of course illegal, but decided at political level in the so-called 'comitology', the meetings of the Standing Committee of national representatives[125]. This means that most decisions on aquatic systems are taken at national level and not easily accessible. At the same time EU Commission doesn't monitor what happens at national level and ignores if their Regulation is violated or not. Since these artificial aquatic systems will have little resemblance to agricultural surface water (containing many pesticides at the same time, many times little or limited aquatic life, many times polluted with fertilizers or low on oxygen, polluted sediment, etc.) they will underestimate risks in real life. All additional stress factors in the generally highly polluted agricultural surface waters are ignored.

The Table below (see power point Theo Brock[126]) illustrates this; it is a promotion power point to sell the idea of mesocosms, and thus not the worst example. The principle of the EU Directive/Regulation was to take the most sensitive organism as a point of departure for deriving 'safe' standards. The biggest manipulation is done with sensitivity distribution (statistical approach that allows for a 'safe' cut-off level) that simply dismisses data on harm to organisms that are below a certain cut-off level. This has nothing to do with science but is a pure political decision. For the example on neonicotinoids, a geomean 'safe' chronic standard is derived of 0,516 µg/L for crustaceans while at the level of 0,024 µg/L already all *Caenis robusta* (arthropod) die in 28 days, 20 times lower. Mesocosms are also not protective given the example on Pyrethroids. A 'safe' value of 6,3 ng/L harms crustaceans (1,9 ng/L, EC10) as well as fish (<5 ng/L). The options to manipulate mesocosms are limitless, the number of applications of pesticides and exposure period, the types and number of organisms included, mortality vs. EC10, use of geomean, cherry-picking on tiers, and of course the 'recovery' option.

125. http://ec.europa.eu/food/plant/standing_committees/sc_phytopharmaceuticals_en

126. www.efsa.europa.eu/en/events/event/131106

Pesticide	Tier 1, few standard organisms, chronic exposure	Tier 2A, more organisms, chronic	Tier 3, mesocosm
Neonicotinoid insecticide- effect	Chironomus riparius, 1,14 µg/L (28 d, EC10)	* Caenis robusta (crust.), 0,024 ug/L (28 d., mortality) * Asellus aquatius (ins.), 1,0 µg/L (28 d. mortality)	Treshold option (no recovery) 0,05 ug/L (21 days exposure, one application of the pesticide).
Neonicotinoid insecticide - standard (UF 10)	0,114 µg/L	0,0024 ug/L, resp. 0,1 µg/L	
Neonicotinoid insecticide - geomean approach		0,516 µg/L, resp. 2,469 µg/L	
Pyrethroid insecticide	2,0 ng/L (21 d., NOEC)	* 1,9 ng/L , Crust.,(Gammarus pulex) - only 3 org.! * 45 ng/L Ins. (Chironomus riparius) - only 1 org.!!!	* Threshold option: 2,5 ng/L (4-6 weeks exposure) * Recovery option, 6,3 ng/L (number of applications less than in the field); fish not included in cosm
Pyrethroid insecticide - standard	0,2 ng/L	0,19 ng/L, resp 4,5 ng/L	
Pyrethroid insecticide - geomean approach		0,313 ng/L	5,32 ng/L for fish, demonstrating fish is harmed below 5 ng/L.

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE TEST METHOD?

Pesticides are polluting surface water for decades. Stehle at al.[127] analysed available monitoring data and concluded that for insecticides in 44,7% of the cases (n=1566) the regulatory acceptable levels were exceeded. It is clear that the implementation (and enforcement) of the rules is failing. Not only at European level the protection of the aquatic environment has been dropped, also at national level other interests apparently prevail.

Research also demonstrates that aquatic ecosystems are in decline. A continuous decline of water ecosystems[128] by pesticides is observed and hundreds of pesticides can be found in rivers, streams, canals and ditches all over Europe.

Academic scientists for some time now demonstrate that the current pesticide risk assessment for water is far from conservative. Schafer at al. (2007)[129] showed that structure and function of aquatic systems are changing. Liess (2013)[130] came to the same conclusion, pointing at the 'culmination' effect of pesticides.

Therefore, the repeated belief expressed in EFSA guidelines about the 'conservativeness' or even 'over conservativeness' of EFSA risk assessment tools should be questioned.

Charley Krebs and Judy Myers[131] point out that ecologists are bad at prediction, and wonder if our shortcomings in this department may be due in part to over-reliance on simplified models, laboratory microcosms, and field mesocosm studies. They brand this the "Volkswagen syndrome" that alludes to VW's recent attempts to, er, "simplify" the results of their cars' emissions tests: "*The push in ecology has always been to simplify the system first by creating models full of assumptions, and then by laboratory experiments that are greatly oversimplified compared with the real world. There are very good reasons to try to do this, since the real world is rather complicated, but I wonder if we should call a partial moratorium on such research by conducting a review of how far we have been led astray by both simple models and simple laboratory population, community and ecosystem studies in microcosms and mesocosms*".

127. Sebastian Stehle, Ralf Schulz, Pesticide authorization in the EU—environment unprotected?, Environ Sci Pollut Res (2015) 22:19632–19647
128. Mikhail A. Beketov, Ben J. Kefford, Ralf B. Schäfer, and Matthias Liess, Pesticides reduce regional biodiversity of stream invertebrates, PNAS | July 2, 2013 | vol. 110 | no. 27 | 11039–11043
129. Schafer RB, Caquet T, Siimes K, Mueller R, Lagadic L, Liess M. 2007. Effects of pesticides on community structure and ecosystem functions in agricultural streams of three biogeographical regions in Europe. Sci Total Environ 382:272–285.
130. Matthias Liess, Kaarina Foit, Anne Becker, Enken Hassold, Ida Dolciotti , Mira Kattwinkel, Sabine Duquesne, Culmination of low-dose 1 pesticide effects, Environ Sci Technol. 2013 Aug 6;47(15):8862-8. doi: 10.1021/es401346d.
131. www.zoology.ubc.ca/~krebs/ecological_rants/the-volkswagen-syndrome-and-ecological-science/

F. IS THE TEST METHOD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

There is always a big discussion on design and use of cosms. On the pesticide Cyprodinil[132], an outdated design was used, fish was included but the impact not recorded, zooplankton population was reduced in all tests. Nevertheless the mesocosm was acceptable, according to EFSA.

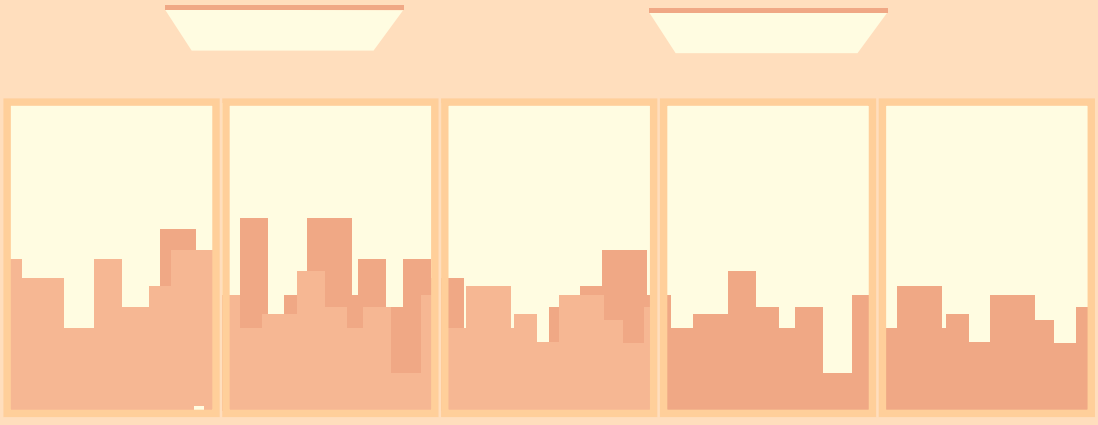
No justification is given if these systems are a proper simulation of the practice in agricultural waters (mixtures, aquatic organisms, sediment, oxygen, etc.). Their use remains largely a black box. On the pesticide Imidacloprid (Admire[133]), the substance disappears in 6-15 days for 50% from the mesocosm. In reality in surface water (esp. near glasshouses) there is a constant, year-round exposure of aquatic life.

132. www.efsa.europa.eu/en/efsajournal/pub/329
133. https://toelatingen.ctgb.nl/toelating/?id=2091&category=PPP

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

A. HOW CAN TTC BE DESCRIBED?

TTC is a fixed level of exposure to chemicals that is deemed to be of no concern for humans. The level is defined by applying a default factor of 100 on the lowest 5th percentile of a statistical curve of NOAELs (No observed adverse effect level) of chemicals in the database used. This means that in 95% of the cases (if the database would be reliable, and if the NOAELs would be reliable) where TTC is applied for a chemical with unknown toxicity, the TTC would be protective and in 5% not. TTC is approved by EFSA for screening and priority setting but in reality it is used in full risk assessment as a final decision tool. This is the case when pesticide metabolites in groundwater exceed the (default) standard for groundwater protection[134], allowing a 7,5 times exceedance of the legal standard.



134. www.efsa.europa.eu/en/efsajournal/pub/2799

B. WHO DEVELOPED TTC? WAS THERE ANY US ORIGIN?

TTC was adopted and promoted by industry lobby group ILSI in the late 90s. Munro and colleagues, industry consultants from Cantox and RIFM[135], started -based on older US-FDA ideas on thresholds- to collect data for underpinning TTC-thresholds[136] and subsequently experts and scientists connected to ILSI went on to promote the tool[137]. An ILSI expert group was established and an ILSI workshop organised in Paris in 1999[138].

C. IN WHAT WAY WAS TTC INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

The PAN Europe report on TTC[139] describes the introduction and ultimate adoption of TTC in EFSA. Several experts of the network of ILSI managed to get seats in EFSA panels and could promote the adoption by EFSA. Remarkably, EFSA had a closed meeting with ILSI in 2011, excluding other stakeholders, before the adoption of TTC. In a case of the EU Ombudsman, EFSA tried to hide its responsibility in organising this joint meeting[140].

In 2014, also remarkably, EFSA organised a 'review' of its own TTC-opinion with many experts that again were not very independent nor objective[141]. At that time WHO was also suddenly involved.

The table below gives an impression of the network of experts linked to ILSI that managed to be part of regulatory panels and meetings:

135. I. C. MUNRO, R. A. FORD, E. KENNEPOHL and J. G. SPRENGER, Proposal for Establishing a Threshold of Concern, Food and Chemical Toxicology 34 (1996) 829-867
136. Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G., 1996. Correlation of structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. Food Chem. Toxicol. 34, 829–867.
137. R. KROES, C. GALLI, I. MUNRO, B. SCHILTER, L.-A. TRAN, R. WALKER and G. WUÈ RTZEN, Threshold of Toxicological Concern for Chemical Substances Present in the Diet: A Practical Tool for Assessing the Need for Toxicity Testing, Food and Chemical Toxicology 38 (2000) 255±312
138. Report on Threshold of Toxicological Concern for Chemical Substances Present in the Diet, ILSI Europe Threshold of Toxicological Concern Task Force, 83 Avenue E. Mounier, Box 6, B-1200 Brussels, Belgium.
139. PAN E report on TTC
140. www.pan-europe.info/press-releases/2014/03/european-ombudsman-condemns-food-authority-efsa-twice-maladministration
141. www.efsa.europa.eu/en/events/event/141202

Connection ILSI/ promoting TTC	Part of EFSA/ILSI closed meeting in 2011	Member of the wg. that drafted the EFSA opinion, 2008 - 2012	Member of EFSA's expert group to review TTC, 2014
Barlow	Barlow	Barlow (chair) (*)	
Boobis		Boobis	Boobis (**)
Bridges	Bridges	Bridges	
Galli		Galli	
Gundert Remy	Gundert Remy	Gundert Remy	Gundert Remy
Piersma	Piersma	Piersma	
Schlatter		Schlatter	Schlatter
Renwick	Renwick		Renwick
Felter	Felter		Felter (***)
Dewhurst	Dewhurst		Dewhurst
Cheeseman	Cheeseman		Cheeseman

(*) Please note the chair of the EFSA wg. Ms. Barlow was involved in scientific misconduct[142], (**) Mr. Boobis was removed from EFSA panels in 2012 because of serious conflicts of interests (ILSI chair board of trustees), and (***) Ms. Felter is an industry employee of P&G.

D. HOW IS TTC CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

TTC is currently in use for pesticides where testing requirements are lacking such as on metabolites and isomers and for metabolites exceeding the groundwater standard[143]. TTC is also used for food additives, cosmetics and other areas with data-poor chemicals.

142. Changing Conclusions on Secondhand Smoke in a Sudden Infant Death Syndrome Review Funded by the Tobacco Industry, Elisa K. Tong, Lucinda England, and Stanton A. Glantz, PEDIATRICS Vol. 115 No. 3 March 2005

143. http://ec.europa.eu/food/plant/pesticides/approval_active_substances/guidance_documents/ hidden under "guidance" and "fate and behaviour": Assessment of the relevance of metabolites in groundwater

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE USE OF TTC?

Academic scientists are not interested in a regulatory tool like TTC. The only academic scientist that looked at it, Prof Millstone, called the text unscientific, cherry picking science that ignores basic scientific findings and is based on numerous assumptions and wishful thinking[144].

F. IS TTC MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

TTC is also misused. The EFSA opinion talks about screening and priority-setting, while in reality TTC is used as a full and final risk assessment tool (safe - not safe).

144. Letter Prof. Millstone to EFSA, 15 March 2015.

PROBABILISTIC RISK ASSESSMENT OF PESTICIDE RESIDUES IN FOOD

A. HOW CAN THE PROBABILISTIC METHOD BE DESCRIBED?

Normally, in risk assessment of pesticide residues in food, a deterministic method is used. The allowable levels (MRLs, maximum residue levels) are matched with available diets in Europe and the outcome is compared to the health standards, the chronic ADI (acceptable daily intake) or the acute ARfD (acute reference dose). In a "refined" calculation (if the ADI or ARfD is exceeded) the average level of human exposure (based on monitoring data) can be used. For cumulative risk assessment such a deterministic procedure is very well possible if the levels of exposure of pesticide residues that work in a cumulative way (CAGs, cumulative assessment groups[145]) are added up, matched with diet data and compared to a CAG health standards. However this could mean that pesticides in the cumulative group exceed the health standards. It is therefore proposed not to use a deterministic approach but a probabilistic one[146], a simulation between exposure data and diet data, resulting in a curve of probability. This curve will then be cut-off at some level and this level will be used for checking safety of food.

145. www.efsa.europa.eu/en/efsajournal/pub/3293
146. www.efsa.europa.eu/en/press/news/160127

B. WHO DEVELOPED THIS CRITERION? WAS THERE ANY US ORIGIN?

Probabilistic modelling was discussed in Europe but not used as such; USEPA on the other hand used probabilistic methods for the distribution of consumption data in dietary risk assessment of pesticides. ILSI in 1998 concluded that probabilistic modelling is the method for aggregate exposure[147]. The method was further developed by a Dutch institute RIKILT (research institute Wageningen university) for cumulative exposure[148]. Industry lobby group ILSI went on to promote the use of probabilistic modelling[149] and included RIKILT in their EU subsidised program FOSIE (of 754.000 Euros) that proposes the use of probabilistic modelling as a tool for risk assessment in food[150] with ILSI-linked experts like Renwick, Boobis, Kleiner and Barlow. This went on in subsequent taxpayer-subsidised EU programs Acropolis (3.000.000 Euro) on probabilistic modelling, coordinated by food trader Freshfel and with, once again, many ILSI-linked experts involved like Boobis, Meek and Moretto [151], and currently Euromix (8.000.000 Euro) a program of national institutes, coordinated by the Netherlands.

C. IN WHAT WAY WAS THIS EVALUATION CRITERION INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

The introduction was done first in WHO. Industry-linked people and industry employees like Boobis, Meek, Kleiner, Olin and Rodriquez in fact outnumbered other participants in the small WHO-planning group[152] and a discussion in a 2007-Berlin WHO/IPCS meeting was

147. ILSI, 1998. Aggregate Exposure Assessment, An ILSI Risk Science Institute Workshop Report. ILSI Press, Washington, DC.
148. P. E. Boon, H. van der Voet and J. D. van Klaveren, Validation of a probabilistic model of dietary exposure to selected pesticides in Dutch infants, Food Additives and Contaminants, Vol. 20, Supplement 1 (October 2003), pp. S36-S49
149. R. Kroes, D.Mu¨ller, J. Lambe, M.R.H. Lo¨wik, J. van Klaveren, J. Kleiner, R. Massey, S. Mayer, I. Urieta, P. Verger, A. Visconti, Assessment of intake from the diet, Food and Chemical Toxicology40 (2002) 327–385
150. A.G. Renwick, S.M. Barlow, I. Hertz-Picciotto, A.R. Boobis, E. Dybing, L. Edler, G. Eisenbrand, J.B. Greig, J. Kleiner, J. Lambe, D.J.G. Mu¨ller, M.R. Smith, A. Tritscher, S. Tuijtelaars, P.A. van den Brandt, R. Walker, R. Kroes, Risk characterisation of chemicals in food and diet, Food and Chemical Toxicology 41 (2003) 1211–1271
151. PAN report A Poisonous injection
152. PAN report A Poisonous injection

upgraded to the WHO/IPCS framework in a published article[153]. The framework put a very high burden of proof on regulators to show cumulative behaviour, and promoted probabilistic risk assessment as a higher tier in case of cumulative assessments. The close cooperation between WHO and industry groups like ILSI continues. Also in 2011 a WHO/OECD/ILSI meeting was organised in Paris to discuss cumulative exposure, once again with familiar names like Boobis, Meek, Moretto and industry employees. Several of the same people volunteered for positions in the panels of EFSA. Boobis and Moretto both managed to be part of the EFSA PPR panel on cumulative assessment and work in the same direction as the WHO-framework. Only when EU Commission in 2011 intervened and put an end to the unreasonable high level of proof that was adopted by the PPR panel and promoted the use of CAGs, the first level of defence of the panel against the introduction of cumulative assessment was demolished. However, now they focus fully on probabilistic assessment to restrict the effects of cumulative assessment on the use of pesticides. This happened mainly in the EU-funded programs Acropolis, again with several of the same people. Probabilistic risk assessment is now also supported by EFSA[154] and EU Commission.

D. HOW IS THE EVALUATION CRITERION CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

Current use is in try-outs and the real decisions on input and cut-off levels are referred to risk managers, i.e. EU Commission and the member states in the Standing Committee[155].

153. M.E. (Bette) Meek, Alan R. Boobis, Kevin M. Crofton, Gerhard Heinemeyer, Marcel Van Raaij, Carolyn Vickers, Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework, Regulatory Toxicology and Pharmacology 60 (2011) S1–S14.
154. www.efsa.europa.eu/en/press/news/160127
155. http://ec.europa.eu/food/plant/standing_committees/sc_phytopharmaceuticals/index_en.htm

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE USE OF PROBABILISTIC MODELLING FOR RISK ASSESSMENT?

Academic scientists are familiar with probabilistic modelling but not with probabilistic risk assessment. The latter has several political elements like an arbitrary cut-off levels, political decisions on the input (is below detection limit equal to zero?). No academic scientists scrutinised the approach taken by EFSA and the EU-funded consortiums. Critique by PAN Europe that probabilistic modelling with national monitoring data is unrealistic (consumers do not buy their food in every shop in their country but generally only in one or two) and probabilistic modelling allows to choose a cut-off level that has an unknown relation to the level of protection of humans, is ignored.

F. IS THE METHOD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

Probabilistic modelling for cumulative risk assessment is waiting (since 12 years already) for the final introduction of cumulative risk assessment by EFSA.

SUBSTANTIAL EQUIVALENCE (SAFETY OF GMO'S)

A. HOW CAN THE METHOD BE DESCRIBED?

According to OECD[156], "*substantial equivalence is a concept, first described in an OECD publication in 1993, which stresses than an assessment of a novel food, particularly one that is genetically modified, should demonstrate that the food is as safe as its traditional counterpart*".

Hence, in cases where a new food or food component is found to be 'substantially equivalent' to a food or food component that already exists, then safety and nutritional assessment are also considered comparable and can be treated in the same way.

B. WHO DEVELOPED THE METHOD? WAS THERE ANY US ORIGIN?

Industry lobby organisation ILSI already in 1996 had a position on the safety assessment of GMOs[157] based on substantial equivalence, developed with a non-disclosed working group. In 1997 they started a "task force on novel foods". Subsequently an ILSI workshop was convened in 1998 on testing methods for novel foods derived from

156. https://stats.oecd.org/glossary/index.htm

157. D. A. JONAS. E. ANTIGNAC, J.-M. ANTOINE, H.-G. CLASSEN, A. HUGGETH, I. KNUDSEN, J. MAHLER, T. OCKHUIZEN, M. SMITH, M. TEUBER, R. WALKER and P. DE VOGEL, The Safety Assessment of Novel Foods, Food and Chemical Toxicology 34 (1996) 93 l-940

genetically modified organisms with dozens of industry employees and authored by Kleiner and Neumann. Dutch expert Harry Kuiper (Rikilt, part of University of Wageningen) functioned as the rapporteur of the meeting. From 2001 on, Kuiper and colleagues Kleter and Kok worked for this ILSI taskforce together with industry employees and industry consultants such as Munro[158]. In parallel, Kuiper worked for the EU-funded program ENTRANSFOOD that was supported by Commission and industry and had the same topic, risk assessment of GMOs[159]. While working for ILSI, Kuiper cs. published several reports proposing "comparative assessment" (rebranding an older term called "substantial equivalence") for risk assessment of GMOs. Conventionally bred plants and GMOs are considered equivalent if no significant differences are identified in the comparison of the most important plant components. This simplifies risk assessment and prevents a more comprehensive assessment. Next, the concept was discussed in a WHO/FAO working group in 2000, chaired by Kuiper. Between 2001 and 2003 the "substantial equivalence" tool took its final shape by Kuiper and colleagues.

C. IN WHAT WAY WAS THE METHOD INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

In 2003 Food Authority EFSA started the new EFSA GMO panel, with no surprise, Kuiper as a chair. EFSA staff was headed by Suzy Renckens who in 2008 went through the revolving door to Syngenta. More industry-linked experts worked on an EFSA guideline for GMOs. Kuiper and Kleter were still members of the EFSA-panel on GMOs in 2010 (while at the same time working for ILSI) and had a big influence. ILSI stated that the guidelines developed at EFSA and WHO are a big success of the work of ILSI[160]. The 'substantial equivalence' assessments at EFSA make use of an ILSI-database, again clear conflicts of interests. Substantial equivalence (SE) is currently used worldwide for assessing GMO's and is a matter of great debate. GM-soy that is considered SE to normal soy, but testing reveals that GM soy had 12–14% lower amounts of isoflavones, compounds that play a role in sex hormone metabolism, than non-GM soy.

158. www.testbiotech.org/en/node/426
159. www.testbiotech.org/en/node/426
160. www.testbiotech.org/en/node/426

D. HOW IS THE METHOD CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

A comparison is made of the composition of the GMO compared with the non-GM isogenic variety, with regard to the levels of certain basic components such as carbohydrate, protein, and fat. If they fall roughly within the same range, the GMO is deemed substantially equivalent to the non-GM isogenic variety. Despite the loose approach taken in these comparative assessments, they often reveal significant differences in composition between the GMO and the diverse comparator dataset used by the company applying for approval of the GMO. This reveals that the properties of the GMO are outside the range of the non-GMO comparator data, including even the historical data. But even in these extreme cases, according to scientists who have served in regulatory bodies, the differences are dismissed as not being "biologically relevant"[161].

Toxicity testing of GMO's that could put an end to the discussions (which industry also dislikes because of the costs) meet great anger. Prof Seralini was exposed to fierce orchestrated attacks of industry[162] when he demonstrated tumours in rats in GMO-studies.

The question if GMO's are more toxic than non-GMO's remains unanswered. Several scientists published research showing adverse effects but given the reality that most GMO's simply are approved based on substantial equivalence, a good answer is not available. Based on the precautionary principle, given the lacking toxicity testing, GMO's are a concern.

161. http://earthopensource.org/earth-open-source-reports/gmo-myths-and-truths-2nd-edition/

162. www.motherearthnews.com/natural-health/nutrition/gmo-safety-zmgz13amzsto

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE METHOD?

Yes, several did. Prof. Millstone states: "*Substantial equivalence is a pseudo-scientific concept because it is a commercial and political judgment masquerading as if it were scientific. It is, moreover, inherently anti-scientific because it was created primarily to provide an excuse for not requiring biochemical or toxicological test*".

F. IS THE METHOD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

The method was designed to bypass actual toxicity testing.

ADVERSE OUTCOME PATHWAY

A. HOW CAN THE METHOD BE DESCRIBED?

The Adverse Outcome Pathway (AOP) is an alternative to animal testing and got momentum when the ban on animal testing for cosmetics in Europe was adopted. AOP tries to elucidate the mechanism of action and other key elements originating from exposure of an organisms to a chemical and leading to adverse effect(s). In-vitro tests and other mechanistic studies could help identifying the mechanism of action to help finding key elements and signposts of the route towards adverse effects. OECD puts this in their guideline as follows, they *"believe AOPs provide a useful structure within which existing knowledge can be organized, from which key uncertainties and research priorities can be identified, and through which we can improve predictive approaches needed to advance regulatory ecotoxicology"*[163]. The AOP for a given toxic effect is described but never validated. The level of confidence you can have to predict toxicity of an unknown chemical is unknown and no effort is done to validate the AOP. It is up to the final user of AOP, the regulator at country-level, to decide for him/herself how much trust they have in the tool. Nevertheless AOP are developed at OECD-level and published as official OECD-AOP's.

163. PAN Europe report on AOP page 18

B. WHO DEVELOPED THE METHOD? WAS THERE ANY US ORIGIN?

Chemical industry and animal welfare groups are at the basis of AOP, supported by several governmental institutes (US-EPA, EU-JRC). In Europe chemical cosmetics umbrella group Colipa started in 2005, working on AOP in a public-private partnership with EU Commission, hence using public money of EU-research. Other industry groups joined (ILSI, Ecetoc) as well as animal welfare groups and US-EPA experts. Other stakeholders were kept at a distance in their invited-only meetings with a majority of industry-employees (Dow, Novartis, BASF, etc.) and experts from industry lobby group ILSI (Meek, Boobis)[164].

It very much looks like a network of industry and regulators with EU-JRC, EFSA, ECHA, OECD, industry[165] decided on important issues without influence of politicians and the public.

AOP is based on previous US-ideas on risk assessment promoted by US National Academy of Sciences in its publication on "Toxicity testing in the 21st century: a vision and a strategy. The OECD-meetings are open for everyone, also stakeholders, but are dominated by those with most resources and very much the same people from industry, US-EPA and EU-JRC.

C. IN WHAT WAY WAS THE METHOD INTRODUCED AND ADOPTED IN REGULATION, IN EUROPE AND GLOBALLY?

The gradual production and adoption of several AOP's by OECD has given the green light for their use in risk assessment. On all kind of regulatory opinions and guidelines AOP's or elements of it show up. This is the case for EFSA (AOP's for developmental neurotoxicity[166], OECD/EFSA Workshop on Developmental Neurotoxicity (DNT): the use of non-animal test methods for regulatory purposes, Brussels, 18 October 2016) and their guideline for endocrine disrupting pesticides[167]. There is no formal adoption of AOP or inclusion of AOP in any regulation but regulators or experts in panels who support AOP try to include it as a risk assessment tool.

164. Maurice Whelan, Melvin Andersen, Toxicity Pathways – from concepts to application in chemical safety assessment, JRC Report EUR 26389 EN, 2013

165. Elisabet Berggren, Patric Amcoff, Romualdo Benigni, Karen Blackburn, Edward Carney, Mark Cronin, Hubert Deluyker, Francoise Gautier, Richard S. Judson, Georges E.N. Kass, Detlef Keller, Derek Knight, Werner Lilienblum, Catherine Mahony, Ivan Rusyn, Terry Schultz, Michael Schwarz, Gerrit Schüürmann, Andrew White, Julien Burton, Alfonso M. Lostia, Sharon Munn, and Andrew Worth, Chemical Safety Assessment Using Read-Across: Assessing the Use of Novel Testing Methods to Strengthen the Evidence Base for Decision Making, volume 123 | number 12 | December 2015 • Environmental Health Perspectives

166. www.efsa.europa.eu/en/events/event/161018b

167. www.efsa.europa.eu/en/supporting/pub/1210e

D. HOW IS THE METHOD CURRENTLY IN USE AND WHAT IS THE EFFECT ON THE LEVEL OF PROTECTION OF HUMANS AND THE ENVIRONMENT?

AOP's are used as an absolute tool for risk assessment to base final decisions on, rather than an indication by a predictive tool. Even more worrying is the misuse of AOP to overrule the outcome of animal testing[168]. It is not so much the case that the 'official' AOP's published by OECD are used, but that all kind of partial or self-designed AOP's (only structural resemblance, QSAR, or only part of the mechanism of action) are included without any broader discussion. The level of protection that AOP's can provide is unknown since the reliability of AOP's is not known as they are not validated. When AOP's are misused one can certainly expect that the level of protection is decreased.

E. DID ACADEMIC OR OTHER INDEPENDENT SCIENTISTS EXPRESS AN OPINION ON THE METHOD?

At OECD-level a range of experts are involved but they are generally supporters (believers) of AOP's and not very critical. Academic scientists are interested in AOP but not interested on how AOP's are applied in risk assessment. Academic scientists that comment to AOP are mostly critical, saying that mixture effects are not taken into account, AOP focuses on operators and not the general public, and more than 100 cancer experts warn that our current understanding of mode-of-actions is so limited that AOP's will underestimate risks[169].

168. PAN Europe report on AOP
169. PAN Europe report on AOP

F. IS THE METHOD MISUSED IN THE IMPLEMENTATION PHASE OF DECISION MAKING?

Yes, AOP is misused to overrule the outcome of animal testing, notably in a range of EFSA-opinions of individual pesticides[170] And again by EFSA to disqualify observed effects in epidemiology studies between pesticides and Parkinson's disease[171].
At the moment EFSA is taking AOP on board as a general risk assessment tool. This happened for epidemiology studies on Parkinson's disease, but now more general for epidemiology studies[172]. While being the most realistic 'safety test' available, EFSA managed to disregard epidemiology studies during its existence since 2004. Because of the IARC-opinion on Glyphosate that is largely based on epidemiology-studies, the pressure rises to take them into account[173].
The first idea EFSA embraced was to draft a long list of conditions[174] that epidemiology studies should meet before taken into account (known exposure level, etc.) which would lead to dismissing epidemiology studies. Now EFSA turns to AOP for help.

170. PAN Europe report on AOP
171. www.efsa.europa.eu/en/supporting/pub/955e
172. www.efsa.europa.eu/en/press/news/170612
173. www.iarc.fr/en/media-centre/iarcnews/2016/glyphosate_IARC2016.php
174. www.efsa.europa.eu/en/supporting/pub/798e

SUMMARY OF THE ANALYSIS, PART 1.

Method/ Chapter	HR – 3.1	MOE – 3.2	Recovery – 3.3	HCD – 3.4	EOGRTS – 3.5	Metabolites – 3.6
Who developed and/or promoted? (timing)	ILSI	ILSI, starting 2002	Industry and a range of national experts (Heimbach, P. Oomen) in ESCORT-meetings	US-NTP Industrials companies like Bayer, BASF, Novartis, Sanofi, etc.	ILSI and their branch ACSA/ HESI	The SCP in 1999. With a prominent role for TTC as promoted by ILSI. A 'mini' evaluation of metabolites and wide options to escape regulation.
Main experts defending industry views	Meek, Boobis****, Schlatter, Vickers (*) (WHO)	Renwick, Schlatter, Benford, Barlow*****, Bridges, Larsen, Greim	Candolfi, Neumann, Romijn, etc.	Rittinghausen (Fraunhofer Inst.), Niemann (BfR), Greim, Edler,	Cooper, Barlow*****, Lewis, Van Ravenswaaij, Koeter (EFSA)	ILSI connections in SCP, Moretto, Dybing.
US background?	Yes, US EPA	Yes, US EPA		Yes, US-NTP	Yes, ACSA/HESI	Yes, TTC
Infiltration in EU panels (EFSA)? (adoption)	No (no specific opinion developed on HR)	Yes, EFSA opinion, Renwick, Schlatter, Bridges, Greim, Larsen, Barlow*****	Yes, in EPPO	No	No	Likely in SCP and later on in EFSA (Boobis****, Barlow*****, Moretto******)
Infiltration global panels?	Yes, IPCS, WHO	Yes, WHO linked to EFSA/ILSI meeting 2005	Yes, a range of SETAC/EPPO meetings (ESCORT, HARAP, CLASSIC)	No	Yes, OECD	No
Exclusive meetings with regulator/ EFSA/industry?		Yes, 2005 invited only industry-regulators;	Yes, ESCORT 1,2,3 and HARAP/CLASSIC; industry and invited national experts	In preparation of decisions industry communicates at every step with RMS/ SANTE/EFSA.	No	No
Support for the tool by taxpayers money?	No	Yes, 754.000 Euro (EU framework progr.)	No	No	No	No
Scrutiny by independent academic scientists?	No	No	No	No	No	No
Any signs of misuse?	Yes, many in pesticide decisions	Yes, use for genotoxic substances and impurities in food	Yes, ...	Yes, on a large scale in current risk assessment, dismissing the 'real' controls in case of adverse effects	Limited. The promise to make EOGRTS more versatile (including DNT and DIT) has not materialised.	Yes, even deviating from the guideline, especially in the beginning by MS and EFSA's PPR-panel, and later less by EFSA-staff opinions

SUMMARY OF THE ANALYSIS, PART 2.

Method/Chapter	Bees – 3.7	GMO's – 3.11	COSMS – 3.8	TTC – 3.9	PRA – 3.10	AOP – 3.12
Who developed and/or promoted? (timing)	EPPO, IPCBR working groups (industry dominance, Bayer, Syngenta)	Industry/ILSI	Cosms used for decades, like in the US; promoted by pesticide industry	Ind. consultants 1996; promoted by ILSI, 1998	Dutch institute around 2000; promoted by ILSI, 1998	US-NAS ILSI Colipa Ecetoc EU-JRC
Main experts defending industry views	Helen Thompson, Anne Alix, P.Oomen, Jens Pistorius, and 6 industry employees, Syngenta, Bayer, Dow	Kuiper, Keter, Kok, Phipps, Jany, many industry employees, Kleiner***, Munro	Brock, Heger, Streloke and many industry employees (Heimbach, Maund, Arnold, Giddings)	Boobis****, Renwick, Barlow*****, Bridges, Gundert-Remy, Schlatter	Boobis****, Meek, Kleiner***, Moretto******	Boobis****, Meek, Vickers(*), Greim, Deluyker (**), Cronin, Whelan, many industry employees
US background?	No	No, industry in OECD	Partly	Yes, US FDA	Yes, US-EPA	Yes, NAS
Infiltration in EU panels (EFSA) or other EU institutes?	Yes, Thompson, Alix, Pistorius in PPR working group	Yes, Kuiper in EFSA panel,	Yes, in EPPO and Brock in PPR-panel and wg. on aquatic risk assessment	Yes, EFSA PPR panel, adoption 2012	Yes, EFSA 2006 - present; adoption 2016	Yes, EU-JRC, public-private partnership, 2005
Infiltration global panels?	Yes, EPPO includes African and Asian countries	Yes, Kuiper in WHO	Yes, SETAC, while HARAP and CLASSIC sponsored by OECD	Yes, EFSA/WHO, 2014	Yes, WHO, 2007-2011	Access stakeholders to OECD meetings, Meek, Whelan
Exclusive meetings with regulator/EFSA/industry?	?	?	Yes, a range of SETAC-meetings, culminating in HARAP (1998) and CLASSIC (1999).	Yes, 2011, EFSA/ILSI	Yes, 2011, WHO/OECD/ILSI meeting Paris	Yes, EU-JRC-industry meetings on AOP
Support for the tool by taxpayers money?	No, IPCBR meetings sponsored by industry		Partly, OECD and EU Commission sponsored HARAP and CLASSIC	No	Yes, 3 EU funded programs, >11 M Euro	Yes, > 50 million EU-money for research
Scrutiny by independent academic scientists?	No	No	No	No	No	No
Any signs of misuse?	Massive and wide scale misuse of unscientific tool	Massive and wide scale misuse of unscientific tool	The principles of cosms (such as simulating real situation) are violated	Yes, full RA instead of screening		Yes, overruling outcome animal testing.

(*) at WHO secretariat, but publishes a lot with industry(-linked) experts, just as her colleague Angelika Tritscher (formerly Nestle), also many connections to ILSI[175];
(**) Deluyker is now part of EFSA management and previously worked for industry (Pharmacia and Upjohn).
(***) Now in management team EFSA; via revolving door from industry lobby group ILSI
(****) Chair of the Board of Trustees of ILSI for many years
(*****) Known for changing scientific conclusions for tobacco industry[176]
(******) For a long period in regulatory panels (SCP, EFSA) but finally removed by EFSA for financial conflicts of interest

175. S. Barlow, A.G. Renwick, J. Kleiner, J.W. Bridges, L. Busk, E. Dybing, L. Edler,G. Eisenbrand, J. Fink-Gremmels, A. Knaap, R. Kroes, D. Liem, D.J.G. Müller, S. Page, V. Rolland, J. Schlatter, A. Tritscher, W. Tueting, G. Wu¨rtzen, Risk assessment of substances that are both genotoxic and carcinogenic Report of an International Conference organized by EFSA and WHO with support of ILSI Europe, Food and Chemical Toxicology 44 (2006) 1636–1650.

176. Elisa K. Tong, Lucinda England, and Stanton A. Glantz, Changing Conclusions on Secondhand Smoke in a Sudden Infant Death Syndrome Review Funded by the Tobacco Industry, PEDIATRICS Vol. 115 No. 3 March 2005

Conclusions

IN SUMMARY:

- In 11 out of the 12 cases (92%) analysed industry or industry lobby groups (like ILSI) developed and/or promoted the method for regulatory use;
- In 8 out of the 12 cases (57%) a clear US-background for the methods could be found;
- In 9 out of the 12 cases (75%), industry or industry-linked experts managed to get a seat in EU panels that decided on the methods;
- In 9 out of the 12 cases (75%) industry or industry-linked experts managed to get a seat in global panels that decided on the methods;
- In 6 of the 12 cases studied (50%), regulators or EFSA had exclusive meetings with industry on the design of the methods;
- In 3 of the 12 cases (25%) the tool was developed with taxpayers money in public/private partnerships (like FP7);
- In 11 of the 12 cases (92%) the method was misused with the result of lowering the protection of the public even further;
- In 0 of the 12 cases (0%) the method was peer-reviewed by independent academic scientists.

Recommendations

Recommendations:

- All risk assessment methods need to be reviewed urgently by a fully independent panel of academic scientists (nominated by official scientific bodies such as the Endocrine Society) on the use of science; the scientists need to be scientists that actively publish experimental results (no comments, opinions and meeting reports);
- Any bias in methodologies or misuse of current scientific insights shall be a reason for repealing and redefining the methods;
- Drafting guidelines for their own use (EFSA) is a conflict of interest in itself;
- A new or redesigned method shall be drafted by a fully independent panel of academic scientist as a standard procedure, based on current scientific insights
- Food Authority EFSA shall, without delay, impose a strict conflict of interest policy, excluding all experts with financial conflicts of interest in any field of expertise;
- Food Authority EFSA shall always treat stakeholders in an equal way and ensure a numeric balance between commercial and non-commercial forces;