

A WHITE PAPER

ENSURING A HIGHER LEVEL OF PROTECTION FROM PESTICIDES IN EUROPE

**THE PROBLEMS WITH CURRENT PESTICIDE RISK ASSESSMENT
PROCEDURES IN THE EU – AND PROPOSED SOLUTIONS**

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Introduction

The current model of pesticide risk assessment that determines the approval of pesticide substances in European Union (EU) is problematic, as it fails to prevent the use of harmful chemicals in the production of our food. These chemicals not only place farmers' health at risk, but also that of residents, wildlife, ecosystems, and consumers, since pesticides contaminate the environment as well as our food. However, the agribusiness industry has become such a profitable sector that evidence on the effects of pesticides on workers, consumers, the general population, animals, and the environment is often overlooked to protect the interests of the market and its economic operators, such as manufacturers, importers, exporters, traders, industries marketing pesticide products, and downstream industries. On a political level, the pesticide industry benefits from a situation where current short-term economic imperatives pressure EU farmers into keeping these products in use. If EU farmers decide to stop using certain pesticides, they may be 'punished' during their transition by the marketplace, as they will be competing with farmers in non-EU countries who continue using these chemicals. EU farmers should be able to improve their practices without being penalized for doing so.

Pesticides are biologically active substances that are designed to poison living organisms (the target pests). Due to their toxic properties, pesticides are only approved for use after the producer has demonstrated that they are "safe" for humans and the environment, under realistic conditions of use. Assertions of the "safety" of pesticides at the European Union level are based largely on predictions and modelling tools. "Safety" is therefore not demonstrated, but presumed. For example, doses to which most people are exposed on a daily basis are not directly tested for safety. Instead, the safety of these typically low doses is extrapolated from higher doses stated not to cause specific adverse effects in industry-sponsored animal studies (e.g. with rodents). Doses 10 or 100 times lower are then assumed to be safe for humans and other species, without actually being tested. This is of concern, since current scientific knowledge shows that exposure to chemicals, particularly during the early life stages, at low environmental doses may trigger alterations in the hormone, nervous or immune system, leading to dysfunction and

disease later in life – even though these effects are not evident at the higher doses that are tested for regulatory approvals.^{1,2}

The authorisation of pesticide active ingredients and the placement of pesticide products on the market in the EU are governed by Regulation (EC) 1107/2009 (Box 1).

Decisions to authorise the use of pesticides are based mainly on a risk assessment of the active ingredient(s) and not on the whole pesticide product. The risk assessment is conducted with reference to a set of studies that must include studies of mammalian toxicity, ecotoxicity, metabolism, and production of potentially toxic metabolites, as well as models to predict the compound's environmental concentrations and an estimate of a safe level of exposure for workers, consumers, and others. The assessment must, in theory, also include studies from the scientific peer-reviewed open literature on the active ingredient and its metabolites.

The authorisation procedure for a new pesticide active substance starts when the applicant – the company that has commercial interest in placing the substance on the market – submits an “application” (dossier) with the required data (sometimes up to 100,000 pages, as in the case of glyphosate) initially to a Member State of its choice (called the Rapporteur Member State or RMS for short) and to the European Commission. The RMS then provides an assessment. For renewals, the Commission, not the applicant, distributes the dossiers on pesticide active substances to the Member States on the basis of a country quota³. Most of the data in the dossiers are produced by pesticide companies and their contracted laboratories and are unpublished.

¹ Myers JP et al (2016). Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. *Environmental Health* 15:19. <https://doi.org/10.1186/s12940-016-0117-0>

² Vandenberg LN et al (2012). Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. *Endocr Rev* 33(3): 378-455.

³ PEST Committee (2018). EU authorization procedure for pesticides – application for approval of active substances and draft assessment reports: Preparatory questions with answers by Prof Dr Hensel, BfR. PEST Committee Meeting of 15 May 2018.

Box 1: Regulation 1107/2009 and hazard-based cut-off criteria

The purpose of Regulation 1107/2009 is “to ensure a high level of protection of both human and animal health and the environment” and, in parallel, to safeguard “the competitiveness of Community agriculture”. Recognising that some population groups are more susceptible to pesticide exposure than others, it calls for particular attention to be paid “to the protection of vulnerable groups of the population, including pregnant women, infants and children”. It emphasises that the precautionary principle must be applied when there is a potential risk in the authorisation of a pesticide substance, even if there is no scientific consensus on the issue (recital 8).

According to the regulation, an active substance shall be approved if “in the light of current scientific knowledge” it fulfils certain approval criteria and if it is expected that plant protection products containing the active substance and residues found in food and the environment will have no harmful effects on humans, animals, the environment and its ecosystems (Article 4.1).

The criteria for authorisation are based on the hazardous properties of the substance – the potential for the substance to cause certain serious diseases – and are therefore hazard-based. According to Annex II of the regulation, “an active substance, safener or synergist” cannot be approved if it is carcinogenic, mutagenic, toxic to reproduction, or endocrine disruptive for humans. For the environment, it cannot be a POP (persistent organic pollutant), PBT (persistent, bioaccumulative, and toxic), endocrine disruptive to non-target organisms or toxic to bee colonies. These are known as hazard “cut-off” criteria because if the substance has any of these properties, as revealed in scientific tests, it must be automatically banned. However, in certain cases, “derogations” are permitted.

Box 1: continued

The regulation addresses other toxic effects as well, such as the ability of the substance to cause neurotoxicity or immunotoxicity during the early life stages of mammalian development, or other critical effects of “particular significance”. However, these are not treated as “cut-offs” and therefore authorisation can be permitted with certain restrictions (for detailed information refer to Annex II, point 3, Reg. 1107/2009).

The hazard-based pesticide regulation resulted from a triologue agreement between the European Parliament, European Council, and European Commission. The three parties recognised that hazard cut-off criteria are necessary to protect public health and the environment from serious harm. A study requested by the European Parliament’s Committee on the Environment, Public Health and food Safety in 2008ⁱ, before the adoption of the regulation, concludes on the importance of the cut-off criteria:

- *Hazard-based cut-off criteria are justified where a preventive approach is needed.* The absence of evidence from epidemiology studies does not equate to absence of effects. Accumulation of firm evidence can take many years, due to the long latency periods between low-level exposures and some health impacts. In the absence of such evidence and where negligibility of exposure cannot be assured, hazard-based criteria are important tools for prevention.
- *The proposed cut-off criteria reflect the seriousness of associated health effects.* The health impacts associated with low-level chronic pesticide exposure are serious. The cut-off criteria reflect this and address the increasingly strong emerging evidence that certain chemicals can interact with the physiological systems of living organisms.

ⁱThe benefits of strict cut-off criteria on human health in relation to the proposal for a regulation concerning plant protection products. Milieu Ltd, European Parliament, Policy Department Economic and Scientific Policy, IP/A/ENVI/ST/2008-18.

For previously approved active substances for which renewed approval is requested, the application must be submitted at least three years before the expiration of the previous approval. The application is sent to a co-rapporteur Member State as well. A copy is also sent to the European Food Safety Authority (EFSA) and to other Member States.

The role of the RMS is to assess the completeness and admissibility of the dossier, the applicant's requests to keep certain information confidential, and finally whether the dossier fulfils the approval criteria (Reg. 844/2012). This process involves communication exchanges with the applicant and where necessary also with EFSA and the Member States.

Due to the size of the application, RMS do not have the capacity to go through every individual study, let alone to examine the original (raw) data of each one to confirm the applicant's interpretation of the data. Furthermore, evaluation of these dossiers requires diverse types of scientific expertise. Ideally, they should be assessed by a diverse group of qualified experts – which, however, is rarely the case.

Once it has finalised its assessment, RMS submits its draft or renewal assessment report (DAR or RAR) with its recommendations to the EU Commission and EFSA⁴. EFSA starts a peer review of the assessment by sharing it with the applicant, with Member States, and subsequently with the public, requesting comments by a specified deadline. EFSA staff collect all comments (including EFSA's own) and invite the applicant to respond. EFSA then asks the RMS to review the applicant's responses to check that the comments have been addressed and that there are no remaining information gaps. During this process, EFSA may organise teleconferences, expert groups, or expert consultations. Subsequently EFSA adopts a conclusion on whether the active substance is expected to meet the approval criteria set out in Reg. (EC) 1107/2009. EFSA then communicates its conclusion to the applicant, Member States, and the EU Commission, giving the applicant some time to respond. Finally, EFSA publishes its opinion.

In many cases, EFSA's opinion includes a list of data gaps and/or concerns. If these data gaps cannot be resolved in a short period of time, they are requested to be submitted by a later date as "confirmatory information". Under the current legislation, any concerns,

⁴ EFSA is a European agency funded by the European Union that operates independently of the European legislative and executive institutions (Commission, Council, Parliament) and EU Member States.

especially a “critical area of concern”, should lead to a non-approval. However, in many cases, the area of concern is left to individual Member States to decide on, in their national authorisations.

Following EFSA’s opinion, the EU Commission presents a review report and draft regulation, in most cases including the obligation for the applicant to submit confirmatory information in a few years’ time, to the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF), consisting of representatives of Member States. The final decision is taken by this committee.

The company’s delivery of the confirmatory information is often delayed. In many cases, no experimental data are provided, but reasoning and speculation are sent instead, which then typically results in the authorisation of those pesticides without the outstanding data gaps having been filled and/or with the specified areas of concern unresolved. Often these data gaps or areas of concern involve the impacts of pesticide and their metabolites on the environment, such as contamination of groundwater and toxic effects on non-target organisms (e.g. wild pollinators, birds and aquatic organisms).

Once the active substance is approved, the applicant may register its product(s) in the EU countries of interest. Each product (formulation), containing one or more authorised active ingredient(s) together with other substances, is then assessed at the national level for its toxicity, through a much less rigorous process that focuses only on the acute toxicity (severe but time-limited effects that are not long-term). Therefore, the safety of the whole pesticide product, which is what people, animals and the environment are exposed to, is not thoroughly assessed, even though it is known that mixtures of chemicals may interact additively or synergistically and may increase the toxic potential of individual chemicals⁵.

Despite the process being long and detailed, several pesticides that have passed through it and are being used today continue to pose risks to human health and the environment. Several trends indicate that humans and the environment are not being sufficiently protected from these harmful chemicals, including the abnormally high rate of

⁵ Kortenkamp A, Faust M (2018). Regulate to reduce chemical mixture risk. *Science Magazine*. 361: 224-226. <http://science.sciencemag.org/content/361/6399/224>

development of diseases in farming families and residents in agricultural areas⁶, the high levels of pesticide residues detected in food⁷ and the environment^{8,9}, and the decline of biodiversity and wildlife in agricultural areas^{10,11}.

In an effort to improve the risk assessment process for pesticides, we have collated in this document a description of the problems and have proposed appropriate solutions. Our aim is to help to improve the current system to ensure the high level of protection for humans, animals and the environment that is stipulated in the European pesticide Regulation (EC) 1107/2009.

⁶ Bellanger et al (2015). Neurobehavioral Deficits, Diseases, and Associated Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union.

<https://academic.oup.com/jcem/article/100/4/1256/2815066>

⁷ PAN Europe (2017). How many pesticides did you eat today? Plenty, according to European Food Safety Authority. April 13. <https://www.pan-europe.info/press-releases/2017/04/how-many-pesticides-did-you-eat-today-plenty-according-european-food-safety>

⁸ Stehle S, Schulz R (2015). Pesticide authorization in the EU — environment unprotected? *Environmental Science and Pollution Research* 22(24):19632–19647.

<https://link.springer.com/article/10.1007%2Fs11356-015-5148-5>

⁹ Stehle S (2015). EU – European Union or Environment Unprotected? *The EcoTox Blog*. Sept 21.

<http://www.master-ecotoxicology.de/ecotox-blog/eu-european-union-or-environment-unprotected/>

¹⁰ Hallmann CA et al (2017). More than 75 percent decline over 27 years in total flying insect biomass in protected areas. *PLOS ONE* 12(10): e0185809.

¹¹ Woodcock BA et al (2015). Impacts of neonicotinoid use on long-term population changes in wild bees in England. *Nature Communications* 7:12459. DOI:10.1038/ncomms12459.

SHORTFALLS OF THE CURRENT EU PESTICIDE RISK ASSESSMENT AND PROPOSED SOLUTIONS

1. Structural shortfalls

1.1. Safety testing for risk assessment is carried out by the company that stands to profit from a favourable assessment

Safety testing of a pesticide active substance is carried out by the pesticide companies themselves or their sub-contractors. Companies have a clear commercial interest in their pesticide being classified as safe in order to place it on the market. This is a conflict of interest that creates an enormous risk of bias in, for example, the design, conduct, and interpretation of studies. This bias could lead to toxic effects being hidden, misrepresented, or misinterpreted (as not exposure-related, spontaneously occurring, or irrelevant to humans, etc).

Proposed solutions

Safety testing should be performed by laboratories that are independent of the industry. Tests should be commissioned not by industry but by a public independent body such as EFSA. The test material should be supplied to the laboratory by industry via EFSA or another official body. Industry should pay for the full costs of conducting and managing the required tests but must not be able to choose the laboratory or the scientists that carry out the studies, or the design and conduct of the studies.

As long as the pesticide industry is allowed to keep data on toxicity and the environmental fate of pesticides confidential, the public will have no confidence in the safety of its products or the adequacy of the assessment and approval processes. This is a powerful reason why studies should be commissioned by public regulators and why all the data from testing and assessment processes should be in the public domain.

1.2. Lack of transparency in reporting of animal studies

Currently there is no requirement that all safety tests done by industry are registered in advance and all their results reported. This makes it possible for industry to keep studies secret in cases where the outcome is unfavourable. Applicants can “cherry-pick” which studies to include or which adverse effects to report, and which to conceal, in order to influence the conclusion of the assessment.

Proposed solutions

All regulatory studies on test substances (whether or not they are used in the final delivered dossier) should be registered centrally before they commence and the results should be published online (see point 1.3). In case of authorisation renewal, all older studies used as data requirements should also be registered. This is addressed to some degree in the Commission’s proposal on transparency¹² as part of its response to the EU Citizens’ Initiative (ECI) on glyphosate. In this respect we support an initiative towards transparency with the following conditions:

- Data from a test that was not registered prior to the initiation of the experimental work cannot be used in a risk evaluation afterwards.
- No compound or product should be authorised unless all data from all registered studies are submitted.

Such a procedure has been developed in the framework of the Clinical Trial Regulation EU 536/2014 in response to fraud and selective data reporting by the pharmaceutical industry.

¹² EU Commission (2018). Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the transparency and sustainability of the EU risk assessment in the food chain amending Regulation (EC) No 178/2002 [on general food law], Directive 2001/18/EC [on the deliberate release into the environment of GMOs], Regulation (EC) No 1829/2003 [on GM food and feed], Regulation (EC) No 1831/2003 [on feed additives], Regulation (EC) No 2065/2003 [on smoke flavourings], Regulation (EC) No 1935/2004 [on food contact materials], Regulation (EC) No 1331/2008 [on the common authorisation procedure for food additives, food enzymes and food flavourings], Regulation (EC) No 1107/2009 [on plant protection products] and Regulation (EU) No 2015/2283 [on novel foods]. 11 April. <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1523604766591&uri=COM:2018:179:FIN>

1.3. Lack of transparency of industry studies

The full reports of regulatory toxicity studies related to data requirements for pesticide approval are generally unpublished and cannot be evaluated by independent experts or the general public.

In April 2018, as part of its response to the ECI on glyphosate, the Commission proposed¹³ that these studies be published by EFSA upon receipt, as a move towards transparency. Although we welcome this step, we do not agree with the caveat in the proposal¹⁴ specifying that disclosure of data will be weighed against the rights of commercial applicants and that if disclosed, these data may only be used and quoted after requesting and gaining specific authorisation from the private companies that provide the data^{15,16}. Based on the proposal, the companies would be allowed to claim confidentiality based on “intellectual property”, or EFSA could refuse disclosure.

The pesticide industry has systematically fought meaningful disclosure, arguing that these studies could be misused by their competitors in an application outside Europe. Thus, they are likely to continue to withhold permission for independent scientists and consumer organisations who wish to publish findings.

Proposed solutions

The full study reports, including test methods, results, and discussion, from studies used in the regulatory assessment of pesticides should be made publicly available in an easily searchable form to allow unrestricted independent scrutiny. Applicants should not be

¹³ EU Commission (2018). Ibid. <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1523604766591&uri=COM:2018:179:FIN>

¹⁴ See p. 27: Article 32e amending Article 38, General Food: “The disclosure to the public of the information mentioned [...] shall not be considered as an explicit or implicit permission or license for the relevant data and information and their content to be used, reproduced, or otherwise exploited and its use by third parties shall not engage the responsibility of the European Union.”

¹⁵ Corporate Europe Observatory (2018). Better access to industry studies used in EFSA risk assessments insufficient without usage and quotation rights. April 11. <https://corporateeurope.org/pressreleases/2018/04/better-access-industry-studies-used-efsa-risk-assessments-insufficient-without>

¹⁶ European Citizens’ Initiative Press Release: Will business secrecy keep defeating the public’s right to know on food safety? September 2018. <https://www.pan-europe.info/press-releases/2018/09/eci-press-release-will-business-secrecy-keep-defeating-public%E2%80%99s-right-know>

allowed to hide publicly relevant information behind claims that they constitute confidential business information.

Scientists and others must be allowed to examine and cite these data in scientific publications and elsewhere, without being required to obtain the consent of private companies whose primary objective may not be the protection of health and the environment, but to make a profit¹⁷.

1.4. Conflicts of interest in EFSA and national authorities

To ensure the impartiality of its staff and external advisors, EFSA has an independence policy for “professionals contributing to its operations”¹⁸. However, national authorities that take part in risk assessment procedures (either as RMS or by commenting and voting on the authorizations of active substances) are not obliged by EU law to have an independence policy or to declare conflict of interests, so people with ties to the industry may be involved in the Member States’ decisions.

Moreover, even the independence policy of EFSA, which was revised in June 2017, still contains loopholes that will fail to exclude some people with conflicts of interest from the risk assessment process¹⁹.

The current loopholes in risk assessment in relation to potential conflicts of interest include:

- EFSA forbids members of its scientific panels from being employed at, or having direct financial interests in, companies falling under the agency’s remit. However, regarding all other links to industry, it only applies a two-year cooling-off period – and this only applies to matters falling under the specific mandate of the relevant panel or committee and not to EFSA’s remit as a public food safety agency²⁰. Experts working with, or

¹⁷ Cf E Millstone et al (1994), ‘Plagiarism or protecting public health?’, *Nature*, 371(6499):647-8

¹⁸ EFSA (2017). EFSA’s policy on independence.

https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/policy_independence.pdf

¹⁹ Corporate Europe Observatory (2017). ‘New EFSA independence policy likely rejects most Parliament demands’. June 22. <https://corporateeurope.org/efsa/2017/06/new-efsa-independence-policy-likely-rejects-most-parliament-demands>

²⁰ EFSA’s policy on independence, pp. 6-7: “This is why having worked as a self-employed professional or as an employee for a legal entity pursuing private or commercial interests in the sphere of the relevant expert group is deemed incompatible with membership of the Scientific Committee, Scientific Panels and Working Groups for two years after the conflicting activity has ended. This cooling off period applies to all

funded by, the food industry on a given topic can therefore join an EFSA expert group as long as it is on a different topic. For example, an expert whose research on a food additive is funded by a chemical company that also makes pesticides would not be excluded from EFSA's Panel on Plant Protection Products and their Residues (PPR Panel), even if his or her collaboration with industry took place less than two years before or continues into the present. This approach fails to take account of the chemical company's interests as a whole. For example, the independence policy would miss to capture work done by experts on risk assessment methodologies that are not product-specific, even though the chemical company's interests as a whole could benefit from weak or pro-industry-biased methodologies.

- In relation to research funding, even when experts are funded by a company for research on the same topic as the one the panel is looking at, EFSA would accept the expert on the panel as long as the funding they receive did not exceed 25% of the annual research budget that they manage. This is very important, given that research funding is the largest source of financial conflicts of interest at EFSA.
- EFSA does not have the authority to exclude Member States' experts with conflicts of interest from involvement in risk assessment (as RMS or in commenting during the RA procedure). Over 80% of Member State experts involved in the glyphosate assessment refused to disclose their names to the public, so their interests could not be checked²¹.
- EFSA staff are included in limited sections of EFSA's independence policy, hence not all EFSA staff have to publish their declarations of interest online.
- The same RMS may assess a compound more than once (as with glyphosate). In such cases, national experts involved in multiple authorisations are in effect marking their own homework. This is a problem because experts may be reluctant to disagree with their own past decisions. An advantage of avoiding this situation is that diversity of opinions can help reduce bias and challenge entrenched positions.

managerial roles, employment and consultancies, even of an occasional nature, membership in a scientific advisory body and research funding on matters falling under the mandate of the relevant EFSA scientific group" (our emphasis).

²¹ Corporate Europe Observatory (2016). Glyphosate: one pesticide, many problems. June 28. <https://corporateeurope.org/food-and-agriculture/2016/06/glyphosate-one-pesticide-many-problems>

Proposed solutions

EFSA should close the loopholes in its independence policy. Specifically:

- Research funding that an expert receives from a company falling under EFSA's regulatory remit should be considered a conflict of interest, regardless of the amount involved.
- All experts' interests should be considered in relation to EFSA's remit as a whole.
- All EFSA staff – not only management – involved in any step of the risk assessment procedure should publicly declare their interests. EFSA management should ensure that the agency's independence policy de facto applies to EFSA staff every time they request permission to perform "external activities".
- EFSA staff should be barred from accepting any travel funding to industry-sponsored workshops or meetings. Attendance of staff at any industry-sponsored workshop or meeting should be reviewed for value to the agency and paid for only with government or European Commission funding.
- The current two-year cooling-off period on industry interests before an external expert can be appointed to an EFSA panel should be extended to five years²².

The strengthened EFSA independence policy should be applied to all experts involved in all stages of the risk assessment, including national experts from Member States involved as representatives of a RMS or as providing comments in the risk assessment of an active substance. Experts involved in any EU-wide or Member State pesticide risk assessment should not be allowed to maintain anonymity.

The same RMS should not assess a substance twice.

²² The EU Parliament has requested this in the yearly budget discussions.

1.5. Conflicts of interest in risk assessment methodology design

Various scientific guidance documents on methodologies for the risk assessment of pesticides have been developed²³ by different responsible bodies within EFSA, as well as by divisions of the Commission, such as DG SANTE's pesticide unit.

The different types of EFSA guidance documents and their developer bodies include:

- “Cross-cutting guidance”, developed by EFSA Scientific Committee
- “Sector-specific guidance documents”, developed by EFSA expert panels such as the PPR Panel, or EFSA staff units
- “Other assessment methodologies”, developed by EFSA staff and peer reviewed by independent experts.

The guidance documents and opinions prepared by EFSA and Commission expert panels and committees are the basis for EU and national evaluations. EFSA staff have to use these guidance documents in their evaluations. The guidance documents will, however, only be implemented at the national level if the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF) ‘takes note’ of them. Guidance documents aimed at protecting bees and birds, and representing the newest scientific insights, have been halted for years through SCoPAFF's failure to ‘take note’ of them. Thus SCoPAFF effectively dominates the evaluation process.

The pesticide industry has a major influence on the development of the guidance documents and some of the documents have been developed by people with commercial interests. For example, according to Corporate Europe Observatory, in 2017 nearly half (46%) of the experts sitting on EFSA expert panels, which are responsible for “Sector-specific guidance documents”, had ties to the regulated industries²⁴. Ten out of 21 members of the PPR Panel had a financial conflict of interest.

Even if people with conflicts of interest were removed from EFSA roles with immediate effect, the legacy of flawed methodologies that they helped to develop would remain.

²³ EFSA (undated). Guidance and other assessment methodology documents. <https://www.efsa.europa.eu/en/methodology/guidance>

²⁴ Corporate Europe Observatory (2017). Nearly half the experts from the European Food Safety Authority have financial conflicts of interest. 14 June. <https://corporateeurope.org/pressreleases/2017/06/nearly-half-experts-european-food-safety-authority-have-financial-conflicts>

Such methodologies can put public health and the environment at risk (PAN Europe, 2018)²⁵. For example, the EFSA Scientific Committee has ruled that substances that are both genotoxic and carcinogenic can be of “low concern” or “unlikely to be of safety concern”. This view is contrary to the opinion of numerous scientific authorities²⁶, as well as being incompatible with the precautionary principle and Regulation (EC) 1107/2009, which stipulates that a carcinogenic substance can only be used if it has no “contact with humans”. The risk assessment tool that the EFSA Scientific Committee used to reach its decision to allow certain levels of genotoxic carcinogens was the ‘Margin of Exposure’ (MoE) approach.²⁷ This approach was developed by EFSA in a collaboration with the industry-funded lobby group ILSI over many years^{28,29}. The MoE approach is a self-interested corporate innovation masquerading as an objective scientific concept.

In addition, the scientific understanding of chemical toxicology evolves rapidly and it is vital to ensure that risk assessment methodologies are regularly updated to take account of the current state of the science.

Proposed solutions

Risk assessment policy concerns the non-scientific assumptions that invariably frame any risk assessment. Assumptions include substantive, procedural and interpretative factors. Substantive assumptions relate, for example, to what is deemed to be a ‘risk’ or ‘harm’, what is outside the terms of reference, and which data should be deemed relevant. Procedural considerations relate to the ways in which risk assessment should

²⁵ Eg PAN Europe (2018). Industry writing its own rules. <https://www.pan-europe.info/sites/pan-europe.info/files/public/resources/reports/industry-writings-its-own-rules-pdf.pdf>

²⁶ Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (2012). A strategy for the risk assessment of chemical carcinogens, p.4: “In the absence of information to the contrary, it is prudent to assume that chemicals which are genotoxic and carcinogenic have the potential to alter DNA at any level of exposure and that such change could lead to tumour development. Therefore, any level of exposure is considered to carry some degree of carcinogenic risk.” https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/315878/Strategy_for_the_risk_assessment_of_chemical_carcinogens.pdf

²⁷ EFSA (2012). Statement on the applicability of the Margin of Exposure approach for the safety assessment of impurities¹ which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578.

²⁸ EFSA. 2006. EFSA/WHO international conference with support of ILSI Europe on risk assessment of compounds that are both genotoxic and carcinogenic. 16-18 November 2005, Brussels, Belgium. EFSA meeting summary report. ISBN: 92-9199-028-0.

²⁹ Barlow S et al (2006). 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.

be designed and conducted. Interpretative assumptions concern the ways in which data should be interpreted: for example, under what conditions it may be appropriate to treat data from animal and *in vitro* studies as relevant to human risks and when may it be appropriate to discount them. An example of an assumption that is both procedural and interpretative is the policymakers' answer to the question of whether risk assessors should be more concerned to avoid false negatives or false positives, or whether they should be equally concerned to identify and avoid both³⁰.

Such risk assessment policy judgements should be decided by risk managers in advance of the risk assessment and should be in accordance with the relevant provisions of the Codex Alimentarius Commission³¹. The risk assessment policy should be established by risk managers (Commission) in consultation with risk assessors and all other interested parties, to ensure that the risk assessments are adequate to fulfil EFSA's mission to protect public and environmental health and that they are conducted transparently. The possible alternative outputs of the risk assessment should be defined.

Scientific guidance documents for the risk assessment should be reviewed by the risk managers for adherence to the risk regulation policy, and also by a panel of high level, actively publishing scientists who are independent from industry. The scientists should screen the guidance documents for bias, non-scientific and outdated assumptions, and violations of the precautionary principle, and should revise them independently of the regulatory authorities.

It is also essential to revisit the "legacy" of risk assessment methods developed by industry-funded and industry-linked projects and experts and revise them according to the above principles and procedures.

³⁰ E Millstone et al, *Risk-assessment policies: differences across jurisdictions*, Institute for Prospective Technological Studies, Seville, Spain, EUR Number: 23259 EN, April 2008, available at <http://ipts.jrc.ec.europa.eu/publications/pub.cfm?id=1562>

³¹ Codex Alimentarius Commission (2018). Procedural Manual, 26th edition, pp 124-130. <http://www.fao.org/publications/card/en/c/l8608EN>

1.6. There is a reported shortage of independent experts to carry out risk assessment

EFSA reports to have difficulty³² in attracting enough external experts for its panels and working groups who are independent from the industry sector to fulfil regulatory roles. This is certainly due to inadequate financial compensation for their work at EFSA, considering the demands of such a role. But it is also a consequence of the EU and national research policies incentivising academia to collaborate more and more with industry (for instance, via public-private partnerships). This trend drives scientists' work towards industrial priorities and limits their freedom to explore research questions that could produce results that undermine commercial interests (see also point 1.8).

Similarly, Member States, either in their role as RMS or as providers of comments during consultations, often lack the human resources to carry out the thorough review that the dossiers require.

Proposed solutions

EFSA should actively recruit independent experts, who should be adequately recompensed. EFSA's budget should include fair compensation for experts and, when needed, their employers. The recent EC proposal foresees a 75% budget increase for EFSA³³. A proportion of these funds could be used for this purpose.

EU and national research policies should allocate sufficient funding for public research projects to evaluate the possible risks from pesticide products and develop methodologies for their safety assessment, without any industry involvement (see 1.8), and establish public sector capacity and expertise in these fields.

Member States should give incentives to academia, including recompense for time spent, to make sure that it can fully contribute to the work of EFSA and its risk assessments.

³² EU Commission (2018). Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the transparency and sustainability of the EU risk assessment in the food chain amending Regulation (EC) No 178/2002 [on general food law]... <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1523604766591&uri=COM:2018:179:FIN>

³³ EU Commission (2018). Ibid.

1.7. Current risk assessment policies prioritize industry interests, rather than human and animal health, and the environment

The Commission is tasked with the role of risk manager. As such, it should provide EFSA and other risk assessment agencies in Member States with a clear mandate to deliver a risk assessment that would provide a high level of protection for human and animal health and the environment, and that honours the precautionary principle, as stipulated in the EU pesticide Regulation (EC) 1107/2009.

Instead, the Commission has in some cases become an obstacle to achieving these goals. It often operates unaccountably and non-transparently, prioritising the interests of industry over the public interest.

For example, the Standing Committee on Plants, Animals, Food and Feed (SCoPAFF), which deals with the authorization of pesticides, is composed of representatives of all Member States and presided over by the European Commission's DG SANTE. SCoPAFF approved a set of criteria that were supposed to identify pesticides that are endocrine disruptors (EDCs). But those criteria were criticised by experts in the field of endocrinology for demanding too high a level of proof³⁴. Consequently they would fail to identify pesticides that are EDCs and fail to protect people and the environment from the adverse effects of these substances – protection that is required by the pesticide regulation^{35,36}. The actions of the Commission in its role as risk manager therefore compromise the risk assessments of pesticides that have endocrine disrupting properties.

Many risk assessments are carried out on the basis of unacknowledged presuppositions that prioritise the interests of industry and the agribusiness lobby over human and animal health and the environment. For example, evidence of harm from industry-commissioned animal tests is routinely played down, ignored, or discounted by risk assessors and risk managers as not sufficiently strong to justify a ban or restrictions in the use of a substance. This tendency arises in part from a lack of an explicit interpretative risk

³⁴ Endocrine Society (2017). Joint letter to EU Member State ministers. June 15. https://www.edc-eu-tour.info/sites/edc-eu-tour.info/files/field/document_file/joint_ese_espe_es_statement_on_edc_criteria.pdf

³⁵ EDC Free Europe (2017). EDC-Free campaigners criticize vote on first ever EDC criteria. July 10. <http://www.edc-free-europe.org/edc-free-campaigners-criticize-vote-on-first-ever-edc-criteria/>

³⁶ PAN Europe (2017). Endocrine disrupting pesticides in European food. <https://bit.ly/2KEQ2A1>

assessment policy that is strongly protective of health and the environment being established in advance of the risk assessment.

There is also a tendency for EFSA to embed political decisions in its own guidance documents or for EFSA's opinions to be uncritically adopted into policy – but this should not be EFSA's role. EFSA's role should be to deliver scientific risk assessments that meet the mandate given to it, to provide a high level of protection for human and animal health and the environment.

Proposed solutions

Risk assessment policy should be established by risk managers (i.e. the Commission and in some cases also the Council of Ministers) in advance of risk assessment.

While the pesticide regulation assumes an implicit risk assessment policy that prioritises a high level of protection for public health and the environment, this aspect of the regulation has not been fulfilled in practice. Risk managers have failed to impose this legislative mandate on the risk assessors and the risk assessors have failed to consistently deliver opinions that respect the EU's chosen level of protection. Consequently risk assessment policy should be made more explicit and precautionary.

With this in mind, all risk assessment policy documents should be developed, decided and applied in accordance with the provisions of Codex Alimentarius on risk assessment policy.³⁷ We apply these provisions to the case of pesticide risk assessment and management as follows:

- Determination of risk assessment policy should be included as a specific component of risk management that should take place prior to the risk assessment.
- The Commission should take explicit responsibility for providing risk assessment policy to EFSA, and should do so transparently and accountably, with the oversight of the Parliament and the Council of Ministers. The benchmarks that it sets should not be 'invisible' and negotiated in secret between government and industry. Instead they should be established in open consultation with risk assessors and all other interested

³⁷ Codex Alimentarius Commission (2018). Procedural Manual, 26th edition, pp 124-126. <http://www.fao.org/publications/card/en/c/18608EN>

parties. All decision-makers should be identified and held accountable for their choices. This procedure aims at ensuring that the risk assessment is systematic, complete, unbiased, and transparent.

- Only if and when the above conditions are met and the Commission operates transparently and accountably, adheres to the relevant guidance, and fully accepts its legislative obligation to prioritise public health and the environment, should it be given the authority to set the mandate for the risk assessors. We firmly oppose the Commission's being given any authority or public mandate in the absence of these conditions being met.
- The mandate given by the Commission as risk manager to the risk assessors should clearly prioritise a high level of protection for public health and the environment, as well as adherence to the EU's formal policy on precaution.
- Where necessary, risk managers should ask risk assessors to evaluate the potential changes in risk resulting from different risk management options.

1.8. Industry evaluates and prepares its own risk assessment methodologies

Many risk assessment methods are evaluated or prepared in EU research programmes like FP7 and Horizon 2020 in public-private partnerships. Examples include:

- ACROPOLIS, a programme funded under FP7 that developed methodologies for assessing the cumulative risk assessment of pesticides.³⁸ The project coordinator, Jacob van Klaveren, acknowledged that the objective of the project was to “alleviate consumer concerns” and “to prove that pesticide use is safe” – although the objective should have been to determine *whether* their use is safe. Key people involved in the project, including van Klaveren, had interests in the pesticide industry, such as links with the industrial lobby group ILSI. Such interests conflict with the interests of consumer and environmental protection. The project promoted a probabilistic risk assessment (PRA) tool to try to give quantitative answers in conditions of considerable uncertainty. PAN EU stated that PRA was invoked “to allow a certain

³⁸ PAN EU (2014). A poisonous injection. <https://www.pan-europe.info/old/Resources/Reports/PANE%20-%202014%20-%20A%20Poisonous%20injection.pdf>

level of health damage to people in an attempt to ‘neutralise’ the coming policy on [cumulative risk assessment]”, which industry was unable to stop³⁹.

- SEURAT⁴⁰, another EU-funded program, argued for use of a risk assessment methodology called AOP, or adverse outcome pathway. AOP is a “mode of action” approach that industry has promoted for years, notably as an alternative to animal testing. Scientists apply AOP to guess whether adverse effects will develop in the body following chemical exposure, and if so, how. PAN EU stated in a report that AOP should not be used as a final decision-making method because it provides “an unknown level of prediction and cannot guarantee the high level of protection that is required by EU law”. It is speculative, not empirical. People involved in this project had links with ILSI⁴¹.

Collaboration between industry and regulators to prepare or evaluate the rules for industry constitutes a clear conflict of interest because the pesticides industry is able to choose the standards against which its own ‘homework’ is to be ‘marked’. There is a fundamental and irreconcilable conflict between the interests of the companies trying to place those products on the market and the public interest in health and environmental protection. In the area of tobacco, such irreconcilable interests are recognized by the WHO Framework Convention on Tobacco Control, which was designed to protect public health policies from commercial and other vested interests of the tobacco industry⁴².

Proposed solutions

When the EU and Commission fund research projects that work on risk assessment methods, the experts involved should NOT be employed by, or otherwise linked to, the regulated companies, as is often the case currently. EU research programmes should

³⁹ van Klaveren J (2011). Pesticide assessment. ACROPOLIS. https://acropolis-eu.com/object_binary/o4422_ACROPOLIS_03.pdf

⁴⁰ SEURAT-1 (2018). Welcome. <http://www.seurat-1.eu/>

⁴¹ PAN EU (2016). AOP: The Trojan horse for industry lobby tools? <https://www.pan-europe.info/sites/pan-europe.info/files/public/resources/reports/pan-europe-aop-report-8.8-dec-16.pdf>

⁴² FCTC – WHO Framework Convention on Tobacco Control (2008). Guidelines for implementation of Article 5.3. Protection of public health policies with respect to tobacco control from commercial and other vested interests of the tobacco industry. Adopted by the Conference of the Parties at its third session (decision FCTC/COP3(7)).

http://www.who.int/fctc/treaty_instruments/Guidelines_Article_5_3_English.pdf

fund independent academics without conflicts of interest with industry to inform policy-makers' decisions about risk assessment guidelines and methods.

Regulators should decide on the rules for risk assessment independently of industry through a transparent decision-making process. Risk managers should take explicit and accountable responsibility for setting fundamental guidelines, to which risk assessors should conform (or give reasons for not conforming). Those guidelines should not be invisible and negotiated in secret between government and industry but should be decided by risk managers in open meetings, in deliberations with all interested parties, in order that decision-makers can be made democratically accountable for their choices.

In the interim, while industry-linked people are still involved in EU-funded programmes, the scope of industry's involvement should be fully disclosed, clearly defined, and limited. Industry should have no role in setting risk assessment policies, beyond that of a stakeholder that can respond to public consultations in the same way as a concerned NGO. Industry should not participate in decision-making or in selecting or providing members of expert panels.

1.9. There is no meaningful post-authorisation monitoring

Despite the provisions of Regulation (EC) 1107/2009, there is hardly any post-authorisation monitoring of the impact of pesticide use in the EU member states to ensure that the rules and their implementation are adequate to protect humans, animals, and the environment. Examples of the monitoring that should be routinely carried out (but often is not) include the volume and type of pesticides used by farmers, the location, and what restrictions were applied; environmental levels of pesticides; and exposure levels of farm animals and humans, including bystanders and residents living near sprayed fields. Moreover, there is a trend in EU Member States' governments to cut the workforce of environmental policing agencies, which makes the situation worse.

Proposed solutions

- Each Member State should implement routine national monitoring for human, farm animal, and environmental levels of pesticides and outcomes. Protection goals should be established to determine when exposures exceed health targets. On a case-by-case basis, epidemiological studies should be commissioned. Industry should pay the

costs of both monitoring and testing but these should be managed and conducted by independent bodies.

- Routine national inspections of farmers' pesticide use should be carried out.
- Data on pesticide use in the EU as a whole, and at the level of each Member State, should be publicly available. These data should include the names of pesticides used, as well as volumes, locations, and frequency. National authorities should set up a central register to receive complaints by citizens and farmers on pesticide exposure, relating to pesticide drift, illegal or even legal uses, driven by health or other concerns. If complaints reveal a negative impact upon health or the environment related to the use of certain pesticides, then national authorities are currently legally obliged to review such authorisations and notify the Commission and the other Member States⁴³.

⁴³ See Regulation 1107/2009: for formulations, see Article 44, "Withdrawal or amendment of an authorisation"; for active substances, see Article 21, "Review of approval".

2. Methodological shortfalls – Evidence generation and analysis

2.1. Test methodologies are outdated and testing is incomplete

Some of the current regulatory testing protocols are conceptually and technically out of date and therefore not sensitive enough. This increases the potential for serious adverse effects of pesticides to go undetected. In addition, even the available regulatory safety tests for pesticides on endocrine disruption, immunotoxicity, and developmental neurotoxicity are seldom applied. For example, in the data requirements for pesticides with endocrine disrupting properties, additional assessment of neurotoxic or immunotoxic effects in long-term life-cycle experiments that cover potential harm from exposure during sensitive periods of life remains optional.

Proposed solutions

- Data requirements should be modernised to establish regulatory safety testing of sufficient sensitivity. Major adverse health effects that are currently not sufficiently covered (e.g. endocrine disruption, developmental neurotoxicity and immunotoxicity, adipogenicity and metabolic disorders, and epigenetic effects) should be included. New and/or additional test protocols will be needed in order to form a complete toxicity assessment.
- A protocol covering most of the adverse outcomes at once in a single experiment could save testing time and spare animals, as compared to existing guidelines where different endpoints are tested in separate studies (e.g. Manservigi et al. 2017)⁴⁴.
- For pesticides already on the market, endpoints that are missing from older test guidelines should be addressed before approvals can be renewed.
- Sufficient flexibility must be built into the process so that new insights into serious adverse effects on health can promptly be taken into consideration, even when they are not specifically covered by regulatory data requirements (e.g. epigenetic changes and behavioural effects and disorders).

⁴⁴ Manservigi F, Babot Marquillas C, Buscaroli A, Huff J, Lauriola M, Mandrioli D, Manservigi M, Panzacchi S, Silbergeld EK, Belpoggi F (2017). An integrated experimental design for the assessment of multiple toxicological end points in rat bioassays. *Environ Health Perspect* 125:289–295. <http://dx.doi.org/10.1289/EHP419>

2.2. Incomplete dossiers and assessment reports are wrongly accepted

Currently the Rapporteur Member States illegally approve the admissibility of incomplete dossiers/applications. Common data gaps include the adverse effects of metabolites, impurities, effects on non-target organisms (e.g. birds, fish, and frogs).

It is EFSA's role to identify these data gaps, along with any areas of concern. However, the EU Commission (DG SANTE) and Member States often do not wait for the missing information to be supplied but approve the authorisation of the substance in question, requesting the missing information to be submitted at a later date as "confirmatory information" (within a period of several months, depending on the missing data). In some cases, even after this period has elapsed, the applicant asks for further extensions or delivers confirmatory information that is incomplete.

Regulation (EC) 1107/2009 Article 6(f) indicates that "derogations" should only be allowed in exceptional circumstances (in cases where new data requirements were adopted during the evaluation or for information considered confirmatory in nature) – but currently derogations are applied on a large scale, allowing chemicals market access even when they do not comply with the legal requirements.

Proposed solutions

- Completeness of the dossiers should be ensured by a single body (e.g. EFSA), in a standardised way.
- The Rapporteur Member State must comply with its obligations under EU law and reject applications (dossiers) that do not include all the data required by Regulation (EC) 1107/2009 from the start, following the principle, "No data, no market". At a later stage in the application procedure, the EU Commission is also obliged by Reg. (EC) 1107/2009 to refuse the authorisation of pesticides with data gaps or areas of concern identified by EFSA.
- Pesticides that were previously authorised with outstanding data gaps and lack of confirmatory data should be immediately re-evaluated.

2.3. Harmful pesticides continue to be authorised in the EU without restrictions

Pesticides for which the body of evidence indicates certain harmful effects to humans, animals, or the environment, or for which EFSA identifies areas of concern that remain unresolved, continue to be approved and used, against the provisions of Regulation (EC) 1107/2009 and the Sustainable Use of Pesticides Directive (2009/128/EC). Member States argue that the pesticide in question is too important for agriculture and will impact the competitiveness of the EU in the international market, as foreign exporters may request an 'import tolerance' for active substances in their food products that are not in use in EU. Such pesticides are often authorised together with recommendations to restrict certain uses or apply mitigation measures (e.g. to set buffer zones), but the implementation and effectiveness of these measures are never verified. The precautionary principle enshrined in EU law is not applied.

Proposed solutions

- All pesticides for which the body of evidence indicates any harmful effects to humans, animals, or the environment, or for which EFSA indicates areas of concern, should be banned, or their use restricted. In case of uncertainty, the precautionary principle should be applied.
- In all cases the risk assessor and the risk manager (RMS, EFSA and the Commission) should ensure that Member States fully comply with the Sustainable Use of Pesticides Directive 2009/128/EC, under which farmers should:
 - Use synthetic chemical pesticides only as a last resort, giving preference to non-chemical alternatives or to pesticides of low risk
 - Implement strict mitigation measures (e.g. buffer zones)
 - Reduce volumes of pesticide use, and
 - Explicitly adopt and implement a policy of substituting less safe compounds with safer ones.
- The Commission should ensure that each Member State has a Farm Advisory Service (FAS), with the expertise to inform farmers on pest management methods other than the use of pesticides.
- EU farmers should be motivated to improve their practices without being 'punished' by markets. Thus, the Commission should ban imported products that contain residues

of non-approved pesticides, or that contain residues of any pesticide exceeding the EU's permitted maximum residue levels, with no exceptions.

2.4. In some cases, the RMS takes the applicant's assessment of the evidence at face value

In some cases, the RMS takes the applicant's assessment at face value and/or limits the remit of its assessment to the applicant's assessment. For example, in the glyphosate assessment, the BfR (German health institute) missed significant increases in tumours in glyphosate-exposed animals⁴⁵ as a result of initially relying on industry's own evaluation of the studies without performing the necessary check of comparing the summaries with the original studies⁴⁶.

Proposed solutions

All RMS must be mindful of their legal obligations under Regulation 1107/2009:

- According to Article 11.2: *"The rapporteur Member State shall make an independent, objective and transparent assessment in the light of current scientific and technical knowledge"*
- The assessment itself should not be of the industry assessment but of (Article 11.1) *"whether the active substance can be expected to meet the approval criteria"*.

2.5. Peer-reviewed scientific literature is used in a limited, biased, and unintegrated way

The application dossier for a pesticide active substance must by law include independent scientific peer-reviewed open literature⁴⁷. However, the literature reviews carried out by industry often omit large numbers of academic studies⁴⁸. The few academic studies that

⁴⁵ GMWatch (2017). EU authorities broke their own rules and brushed aside evidence of cancer to keep glyphosate on the market. July 13. <https://gmwatch.org/en/news/latest-news/17724>

⁴⁶ Clausing P (2017). Glyphosate and cancer: Authorities systematically breach regulations. GLOBAL2000. https://gmwatch.org/files/GLO_02_Glyphosat_EN.pdf (p.3).

⁴⁷ Regulation 1107/2009, Article 8(5) and EFSA (2011). Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009.

⁴⁸ PAN Europe (2014). Missed and Dismissed. <https://www.pan-europe.info/old/Resources/Reports/PANE%20-%202014%20-%20Missed%20and%20dismissed.pdf>

are found are then either excluded from the evaluation as non-relevant for reasons that do not relate to their scientific relevance to the question at stake (e.g. the Klimisch criteria⁴⁹ are used to exclude results originating from non-GLP or OECD-protocol studies) – or they are given very limited weight as a source of information about the toxicity of chemicals.

In contrast, studies compliant with GLP (Good Laboratory Practice) and OECD test guidelines are by default accepted as being reliable, relevant, and adequate for the risk assessment, even when the results are poorly reported. There is almost no integrated assessment of regulatory and scientific studies; instead, industry regulatory studies are played off against studies conducted by researchers who are independent from industry.

Proposed solutions

The Rapporteur Member State (RMS) and the Commission must ensure that the applicant complies with its obligation to submit all published and unpublished literature on the active substance being considered for authorisation renewal, using the fundamental principles of systematic review^{50,51}. If properly applied, systematic review methods provide objectivity and transparency to the process of collecting and synthesizing scientific evidence in a strategic manner, enabling unbiased conclusions to be reached on the impact of pesticides on human and environmental health.

In systematic reviews, relevance should be defined in terms of the extent to which the outcomes, exposures, and (where applicable) the population studied are informative of potential health risks in humans or non-target organisms. For a fully transparent and systematic review of the scientific literature, the following points should be taken into consideration:

⁴⁹ The “Klimisch criteria” are named after the employee of BASF who published them in a journal. They evaluate the relevance and reliability of studies based on whether they conform to OECD test guidelines and are GLP compliant. However, adherence to OECD test guidelines and GLP does not mean that a study is better than a non-OECD/GLP study published in a peer-reviewed journal, neither does it guarantee the quality of interpretation of the findings. And the “Klimisch criteria” are not a scientifically valid standard for evaluating the quality of a study from the independent peer-reviewed literature.

⁵⁰ Rooney AA et al (2014). Systematic review and evidence integration for literature-based environmental health science assessments. *Environmental Health Perspectives* 122(7).
<https://ehp.niehs.nih.gov/1307972/>

⁵¹ EFSA (2010). Application of systematic review methodology to food and feed safety assessments to support decision making. *EFSA Journal*.

- It is scientifically unacceptable to dismiss studies simply because they do not adhere to OECD protocols and GLP rules, which are designed for industry studies. OECD/GLP studies and academic studies should be considered to be complementary in identifying the potential and actual effects of pesticides. Academic studies that are not constrained by OECD guidelines or GLP protocols – since they are not performed for regulatory purposes – may be more informative on potential unanticipated adverse effects, as that they may test for effects beyond what is foreseen in the OECD test guidelines.
- Just because a scientific study is not OECD/GLP compliant does not mean that an endpoint within the study is irrelevant to risk characterisation. Studies reporting adverse effects other than those examined in official regulatory testing are relevant for regulatory purposes and must be considered in risk assessments.
- Studies of pesticide formulations, studies of isolated active ingredients, and studies using different routes of exposure than those described in guidelines, should be included in a systematic review and weighed for relevance. For example, evidence about the toxicity of whole formulations is more directly relevant than studies of isolated active ingredients, as it reflects the use of the pesticide in the field once authorisation has been granted.
- Industry-sponsored evaluations of the scientific evidence must be considered as having a risk of bias since they are financed by the industry that has a commercial interest in placing the chemicals on the market (see 1.1 for the proposed solution to this problem).

2.6. Scientific evidence for adverse effects is frequently dismissed for unscientific and non-transparent reasons

Invalid reasons for dismissing scientific evidence for adverse effects include (but are not limited to⁵²) claims that the observed effect(s) is:

- within the range of historical control data and therefore spontaneously occurring. The cited historical control data is generally unpublished and unavailable to the public.
- a secondary effect to overall toxicity
- non-relevant for humans (or to wildlife populations in cases of non-target organisms), in cases when species other than the standard species of regulatory toxicity studies were used
- inconsistent with data from other studies.

Proposed solutions

The above arguments should be accepted as valid only when a scientific evidence-based justification is provided. Otherwise they are purely speculative and should be deemed unacceptable.

Adverse effects observed in animal studies should be evaluated and given weight according to explicit and consistent scientific criteria, established by a panel of independent scientists and applied in a systematic review.

Historical control data must not be used to dismiss significant effects found in treated animals following comparison with concurrent control of non-exposed animals. Studies and risk assessments should follow the OECD Guidance Document 116 *on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies*, which stipulates that the concurrent control data provide the most valid comparison. The Guidance imposes stringent restrictions on the type and source of historical control data that may be used, as well as on how these data are used.

⁵² Clausing et al (2018). Pesticides and public health: An analysis of the regulatory approach to assessing the carcinogenicity of glyphosate in the European Union. *Journal of Epidemiology and Community Health*. Mar 13. <http://jech.bmj.com/content/early/2018/03/06/jech-2017-209776>

In the analysis and interpretation of results from laboratory studies, the analysis should match the design. If animals are exposed to different concentrations of the substance, a trend analysis should be mandatory.

2.7. Toxicity of pesticide formulations is not addressed

Decisions on pesticide authorisations are made based on an assessment of the toxicity of the declared “active ingredient” of the pesticide product. Co-formulants⁵³ and adjuvants⁵⁴ are considered secondary and the toxicity of the whole mixed formulated pesticide products – which are the actual exposures experienced by humans – is not evaluated. Frequently, academic studies on effects of formulated products are dismissed completely from the assessments and are not taken into consideration at all, even in the overall evaluation of the active substance. Moreover, most co-formulants are considered to be proprietary secrets and remain undisclosed.

Proposed solutions

A worst-case reference formulation containing the highest concentration of active substance(s) and adjuvants that the applicant would consider marketing should be defined. Dilutions of this formulation should be tested in long-term *in vivo* studies to try to identify a no-observed-adverse-effect level (NOAEL).

All pesticide ingredients should be assessed in a tiered approach, alone and in combination (formulation). In the first tier, substances should be tested *in vitro* in high-throughput assays to assess endpoints such as endocrine disruption, neurotoxicity, or genotoxicity. When an active ingredient, adjuvant, or formulation leads to a positive result in a bioassay, this should trigger higher-tier animal testing for the specific endpoint, using realistic levels of exposure in sensitive *in vivo* tests. This would be in agreement with the opinion on the risk assessment of chemical mixtures from EFSA, which recommends a whole mixture approach to encompass any unidentified materials

⁵³ Co-formulants are substances or preparations which are used or intended to be used in a plant protection product or adjuvant, but are neither active substances nor safeners or synergists.

⁵⁴ Adjuvants are defined as mixtures or preparations which are marketed separately and are mixed with a plant protection product before use to increase the product's efficacy.

in mixtures and interactions between mixture components⁵⁵.

Despite the shortcomings of tests performed in animals and the frequently expressed desire to minimise such testing, *in vivo* toxicological studies on rodents are still necessary to assess endpoints that *in vitro* toxicity assays cannot assess.

Non-regulatory studies on formulated products containing the primary pesticide active ingredient in the risk evaluation should be included in the risk assessment by taking them into consideration in the weight of evidence approach.

Information on adjuvants and co-formulants should be published, notwithstanding industry pleas for commercial confidentiality. Adjuvants, as much as active ingredients, must be considered as “emissions into the environment”. According to Article 4.4(d) of the Aarhus Convention on public access to documents and Article 6 (1) of the Aarhus Regulation EC No 1367/2006 on the application of the provisions of the Aarhus Convention, information relating to emissions into the environment has to be disclosed since there is an overriding public interest (Article 4.2; Reg. EC 1049/2001).

2.8. Toxicity of pesticide mixtures is not addressed

In real-life conditions, people are always exposed to several chemicals (including pesticides) at the same time. These chemicals may work through similar and/or interacting mechanisms, with both options bringing additional risks. In fact, farmers often use cocktails of pesticide products on their crops. Despite the political decisions (enshrined in Reg. EC 296/2005 and EC 1107/2009) to take combination effects into account, the potential effects of chemical mixtures are still ignored in risk assessment and in risk management policy-making. This is also the case for the assessment of chemicals across the board. These omissions create a dangerous blind spot and prevent public authorities from regulating real-life exposures to mixtures of chemicals.

⁵⁵ EFSA (2013). Scientific report of EFSA: International frameworks dealing with human risk assessment of combined exposure to multiple chemicals EFSA Journal 11(7):3313. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2013.3313>

Proposed solutions

- Prioritise the testing and evaluation of mixtures in the following order: (1) co-formulated products; (2) products approved to be mixed prior to application; (3) based on post-approval monitoring, pesticide ingredients that are frequently encountered simultaneously in residue analyses.
- The identity of all components of pesticide mixtures must be disclosed. A full set of toxicological data must be made available for all these components in order to facilitate a transparent risk assessment.
- The possible combination effects of chemicals should be evaluated by an overarching risk assessment of the toxicological data of all components of the mixtures (including adjuvants of formulations), with a consideration of common mechanisms. Tailored testing should be performed that would enable toxicity to be evaluated from interactions with receptors as well as toxicokinetics and metabolism.
- Currently the NOAEL taken from an animal study is divided by an uncertainty or safety factor of 100, in order to extrapolate from animal studies to the exposed human population and set a “safe” dose (acceptable daily intake or ADI). This factor supposedly accounts for potential differences in response across species (e.g. rats and humans), as well as across individuals of the same species: a 10-fold factor is used for inter-species variability and a 10-fold factor for intra-individual variability, even though evidence suggests that variability can be greater than implied by those figures. Where a combination analysis is not carried out, an extra safety factor of at least 10 should be applied to address potential mixture toxicity, resulting in a total safety factor of at least 1000.

2.9. Weight of evidence is misused

The variability of biological responses, as well as differences in study methods and statistical power, can result in individual studies producing “contradictory” results (e.g. an observed effect can be statistically significant in some studies, but not in other similar ones).

Risk assessors often claim to use an approach called “weight of evidence” (WoE) to reconcile such contradictions. However, WoE is currently inadequately formalized as a methodology and is not documented in sufficient detail to provide transparency of

approach when used. Relevant results are dismissed, outcomes of the assessments seem flawed, and it is not possible to determine if disagreement is due to misapplication of methods, genuine scientific uncertainty, or biased processes.

Proposed solutions

Use of WoE must be transparent and should include explicitly systematic approaches. The common practice of simply stating that a WoE approach was followed is insufficient. It needs to be specified which (of many) criteria have been used to select relevant studies and how they have been weighed.

Furthermore, an integrated approach should be mandatory (Rooney et al, 2014)⁵⁶. For instance, if evidence comes from both animal studies and epidemiology, and both lines of evidence are limited but point in the same direction, their mutual support must become part of the WoE. Assessing and dismissing them separately because evidence from each area was “too light” is not a scientifically valid approach.

⁵⁶ Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA (2014). Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect* 122:711–718. <http://dx.doi.org/10.1289/ehp.1307972>

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