IMPROVING AUTHORISATION PROCESSES FOR PLANT PROTECTION PRODUCTS IN EUROPE

A scientific perspective on the assessment of potential risks to human health

SAPEA

Science Advice for Policy by European Academies

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Informs the European Commission Group of Chief Scientific Advisors Scientific Opinion No. 5

About SAPEA

Spanning the disciplines of engineering, humanities, medicine, natural sciences and social sciences, SAPEA - Science Advice for Policy by European Academies - brings together outstanding knowledge and expertise from over 100 academies, young academies, and learned societies in over 40 countries across Europe.

SAPEA is part of the European Commission's Scientific Advice Mechanism (SAM), which provides independent, interdisciplinary, and evidence-based scientific advice on policy issues to the European Commission. SAPEA works closely with the European Commission Group of Chief Scientific Advisors.

This Evidence Review Report informed the European Commission Group of Chief Scientific Advisors Scientific Opinion on 'Authorisation processes of plant protection products in Europe from a scientific point of view', which is available here: http://ec.europa.eu/research/sam/pdf/sam_ppp_report.pdf

Funded through the EU's Horizon 2020 programme, the SAPEA consortium comprises Academia Europaea (AE), All European Academies (ALLEA), the European Academies' Science Advisory Council (EASAC), the European Council of Academies of Applied Sciences, Technologies and Engineering (Euro-CASE), and the Federation of European Academies of Medicine (FEAM).

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Foreword

Producing enough food for the human population whilst also maintaining a clean and safe environment to ensure effective delivery of ecosystem services is a key challenge for humanity. The side effects of intensive agriculture, and particularly the use of plant protection products (PPPs), are often directly or indirectly harmful to human health and frequently affect common goods like clean water and air, and ecosystem services like pollination. Produce resulting from commercial agriculture is traded worldwide, exposing consumers to residues of pesticides that may have been applied half a world away. Recognising these cross-border threats to human and environmental health, the Member States of the European Union (EU) have relinquished national remits in the joint endeavour of creating a safer, cleaner, and healthier Europe: in the EU's 'dual system' of pesticide authorisation, PPPs have to be authorised at EU level before Member States can authorise them at the national level. To ensure that the legislation governing the EU's PPP authorisation processes achieves its objectives and is efficient and effective, it is regularly evaluated and updated with the latest scientific findings and developments.

SAPEA was asked to provide scientific input on how to make the EU's current PPP authorisation processes more effective, efficient, and transparent. SAPEA is an integral part of the European Commission Scientific Advice Mechanism (SAM) and provides a direct link between the scientific expertise contained in the European academies, and policy makers in the European Commission. We assembled an international Working Group of experts that provided specialist knowledge on subjects ranging from the assessment of pesticide-induced risks to various aspects of human health, epidemiology, and exposure assessment, to toxicology, the latest methods for understanding and assessing toxicity, and regulatory processes. The resulting SAPEA Evidence Review Report (ERR) 'Improving authorisation processes for plant protection products in Europe: a scientific perspective on the assessment of potential risks to human health' demonstrates not only the outstanding knowledge of the experts nominated by European academies, learned societies, and academy networks, but also the experts' exemplary commitment to the voluntary task of bringing the best and newest scientific knowledge into policy making.

This ERR is also a product of SAPEA's continued collaboration with the Group of Chief Scientific Advisors and informs the Group of Chief Scientific Advisors' Scientific Opinion on the topic. In addition to this ERR, a workshop on risk perception and acceptability of human exposure to pesticides was organised in collaboration with the Institute for Advanced Sustainability Studies (IASS), to broaden the evidence base provided

to the Group of Chief Scientific Advisors Opinion. SAPEA's reports and the Group of Chief Scientific Advisors' Opinion are published together and aim to make important contributions to the European Commission's policy making in a broad range of areas, as well as the planning of the EU's future priorities and corresponding resource allocation.

On behalf of SAPEA, I would like to thank everyone involved in successfully completing this project, and particularly the Working Group members for their hard work and unstinting dedication to the goal of making Europe a healthier and safer place for all its citizens.

Prof. Bernard Charpentier, Chair, SAPEA Board & President of FEAM 2015-2018

SAPEA Executive Summary

Could the current EU dual system for approval and authorisation of plant protection products (PPPs) be rendered more effective, efficient, and transparent, and if so, how could this be achieved?

1. This question was put to the European Commission Scientific Advice Mechanism (SAM) by Commissioners Vytenis Andriukaitis (Health and Food Safety) and Carlos Moedas (Research, Science, and Innovation). It was taken up by the Group of Chief Scientific Advisors, which provides independent scientific advice to the College of European Commissioners to support their decision-making. The SAPEA Consortium, an integral part of SAM, was asked to produce an Evidence Review Report to support the production of a Scientific Opinion by the Group of Chief Scientific Advisors. A Working Group of international experts was asked to **focus on methods and procedures for assessing potential harmful effects on human health from the use of PPPs, to report on both the current scientific state-of-the-art and the potential for future developments in toxicity assessment, and to identify ways in which the existing authorisation processes for PPPs might be improved from a scientific perspective** (these being presented as "Options" for the Group of Chief Scientific Advisors to consider when formulating its recommendations).

2. Regulatory risk assessment for PPPs in the European Union (EU) aims to ensure a high level of protection of human and animal health and the environment. Among other things, it entails checks that the highest exposures which could realistically occur when products are used as authorised, are well below the level at which potential toxic effects might be expected to occur. Parts of the risk assessment (particularly relating to the toxicity of active substances) are coordinated centrally by the European Food Safety Authority (EFSA) and agreed by all EU Member States, while other elements (mostly relating to formulated products) are conducted at Member State level (in what is known as a "dual system"). **Although the system is precautionary, there is scope for further improvement in: the scientific data that underpin risk assessments; the methods by which such data are analysed; and the ways in which assessment procedures are organised and tasks allocated. Importantly, regulatory risk assessment must be fair, consistent, transparent, and communicated effectively so as to maintain public trust.**

3. Improvements to the range and quality of data informing risk assessment could come from advances in: toxicology, where newly emerging methods should enable the collection of data more directly relevant to human toxicity; **epidemiology**, where the development of new biomarkers for pesticide exposure and new study designs

could improve surveillance for unanticipated adverse effects of PPPs once products have been approved for sale and use; and **exposure sciences**, where there is scope for refining information on the distribution and determinants of personal exposures to pesticides in different circumstances.

4. **Improvements to the methods of risk assessment** could be made through a range of measures: there is a need to **reassess several data requirements** for (re-)approval of PPPs and the guidelines and evidence informing assessment of potential toxicity. **Post-marketing surveillance of approved PPPs** could be improved through systems at Member State level which register all cases of acute illnesses associated with PPPs, and by periodically monitoring the scientific literature for evidence of human health effects from PPPs. When assessed at review, previously approved active substances should be **grouped according to their pesticidal mode(s) of action** to facilitate consistency of approach and highlight compounds of potential concern. Toxicology assessments of co-formulants and of formulated products should be more extensive and rigorous, taking into account **constituent concentrations and the potential for additive or synergistic toxic effects in mixtures**. Co-formulants and products deemed suitable for use in/as PPPs should be publicly listed. The risk of **combined effects from exposure to multiple active substances**, either simultaneously or in sequence, could be considered in more depth than at present. Empirical data on exposures resulting from the most common combined-exposure scenarios would help to **develop standardised methods for authorisation of common combinations and/or application sequences of PPPs**. Some active substances in PPPs also have uses in biocides and medicines and the health risks from **aggregate exposures across different uses** should be accounted for. Novel '**nanopesticides**' and '**biopesticides**' require the development of relevant and standardised risk-assessment procedures. Differences in handling of scientific uncertainty may cause inconsistencies in decisions on (re-)authorisation of PPPs in the EU, but the introduction of **formal quantitative uncertainty analysis as a routine part of risk assessment** could reduce inconsistencies and increase the transparency of risk assessments.

5. **Improvements to the organisation of risk assessment** could be achieved by **revising the current division of labour between EFSA (European Food Safety Authority) centrally and regulatory authorities in individual EU Member States**. To increase efficiency, and improve scientific rigour, consistency and transparency, EFSA could take responsibility for all aspects of risk assessment that are common to all EU Member States, and maintain published databases setting out EU-agreed end-points for risk assessment on approved active substances, co-formulants, and products, as well as generic methods for Member States to use when conducting risk assessments for specific uses of products. In addition, **formal mandatory training for**

staff undertaking risk assessments should be instituted to ensure that risk assessors can correctly apply new and emerging methods in their work. Lastly, **creation of an independent, international centre for PPP-related research** could provide invaluable services in method development, primary research, evidence evaluation, and training.

6. Based on the above considerations, the Working Group has identified **26 Options to improve PPP authorisation processes in Europe**. See page 79 for a list of Options.

7. Both this Evidence Review Report and the Group of Chief Scientific Advisors' Scientific Opinion were published in June 2018. They **inform the REFIT Evaluation of the EU Regulations (EC) No 1107/2009 and No 396/2005[a] on plant protection products and pesticides residues and thus contribute to the implementation of a more effective, efficient and transparent authorisation system for plant protection products that incorporates the latest scientific developments and discoveries.** In addition, both reports aim to make important contributions to the planning of the EU's future political priorities and corresponding resource allocation.

[a] The Evaluation and Fitness Check Roadmap for the REFIT Evaluation of Regulations (EC) No 1107/2009 and No 396/2005) is available for download here: http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_197_ealuation_plant_protection_products_en.pdf

SAPEA Extended Summary

Could the current EU dual system for approval and authorisation of plant protection products (PPPs) be rendered more effective, efficient, and transparent, and if so, how could this be achieved?

1. This question was put to the European Commission Scientific Advice Mechanism (SAM) by Commissioner for Health and Food Safety, Vytenis Andriukaitis, via the Commissioner for Research, Science and Innovation, Carlos Moedas, on behalf of the European Commission. It was taken up by the European Commission Group of Chief Scientific Advisors. which provides independent scientific advice to the College of European Commissioners to support their decision-making. The SAPEA Consortium, an integral part of the Scientific Advice Mechanism, was asked to produce an Evidence Review Report (ERR) to support the production of a Scientific Opinion by the Group of Chief Scientific Advisors.

2. The SAPEA Working Group was asked to **focus on methods and procedures for assessing potential harmful effects on human health from the use of PPPs, and to report on both the current scientific state-of-the-art and the potential for future developments**. The report does not address other aspects of risk assessment for PPPs (e.g. environmental impacts) or the assessment of their efficacy, although these are considered by the Group of Chief Scientific Advisors. It identifies various **ways in which the existing authorisation processes for PPPs might be improved from a scientific perspective**, presenting them as "Options" for the Group of Chief Scientific Advisors to consider when framing its recommendations.

3. The Working Group based its assessment on the knowledge and experience of individual members, supplemented by targeted searches of the scientific literature in relation to specific questions. In addition, to guard against imbalance and important omissions, a preliminary draft of the ERR was circulated to a wider group of scientists with relevant expertise, who provided comments, both in writing, and in discussion, at a one-day workshop held in October 2017. A workshop in December 2017 examined the proposed Options from an ecotoxicological perspective, and concluded that their adoption would not reduce levels of environmental protection. The ERR was peer-reviewed in December 2017, and revisions were made in response to the feedback.

4. The ERR starts with a brief **overview of the aims and methods of human health risk assessment as part of the EU's regulation of PPPs**, highlighting a number of limitations. Next, it **identifies various recent or ongoing scientific advances that might enhance the evidence underpinning human health risk assessment for PPPs**

in the near- or longer- term future. It then considers **ways in which current methods of risk assessment might be improved, and how delivery of the risk assessment could best be organised from a scientific perspective**.

5. Regulatory risk assessment for PPPs in the EU aims to ensure a high level of protection of human and animal health and the environment. **To maintain public trust, its methods must be open, transparent, internally consistent, and reflect the current state of scientific knowledge.** Moreover, the scientists conducting risk assessments should be suitably experienced and manifestly free from potential conflicts of interest. Outputs should be clearly communicated to risk managers and to the public.

6. The assessment of risks to human health starts by determining the potential adverse effects of active substances (the components of PPPs that are principally responsible for their intended beneficial effects), and levels of exposure to those substances at which there is high confidence that adverse effects will not occur ("toxicological reference values"). In addition, a more limited assessment is made of the toxicity of the chemicals with which active substances are formulated in PPPs (co-formulants), and of formulated products per se. A check is then made that the highest human exposures that might reasonably be expected to occur when a product is used according to the conditions of its approval, are below the relevant toxicological reference values. Parts of this risk assessment (particularly relating to the toxicity of active substances) are coordinated centrally by EFSA and agreed by all EU Member States, while other elements (mostly relating to products) are conducted at Member State level (in what is known as a "dual system").

7. This system appears to work well, but it has a **number of limitations**. While the approach is precautionary, and has become more so over time, it is possible that some **more complex human health outcomes are not adequately addressed by the standard toxicity tests that are currently available**. Also questionable is the adequacy with which risk assessment addresses the **toxic potential of co-formulants,** alone and in combination with active substances, and there is a possibility of **aggravated toxicity from combined exposure** to active substances and co-formulants in different PPPs. There is a need to **improve the methods of risk assessment for PPPs based on microorganisms, and for PPPs that exploit new nanotechnologies.** Moreover, in recent years, **apparent inconsistencies** with evaluations by other respected scientific bodies have been a **cause of confusion, and threatened public trust**. Finally, current approaches to the **assessment and communication of scientific uncertainties** are imperfect.

8. The scope to improve the current system is limited by certain **practical constraints:**

standards and control measures must be enforceable; funding must be adequate and used efficiently; and unnecessary use of laboratory animals should be avoided.

9. Nevertheless, there are **opportunities for improvement**, both in the **data that underpin the risk assessment** (which come mainly from the scientific disciplines of toxicology, epidemiology and exposure sciences), and in the **way in which the assessment is organised and conducted.**

10. Currently, the potential toxicity of chemicals in PPPs is determined largely by looking for the occurrence and frequency of adverse effects when they are administered to experimental animals at different dose levels. However, a **new approach** is now emerging, which instead focuses on the **detailed mechanisms by which chemicals interact with the body, and the biochemical pathways through which they might cause harm**. This is informed by experiments using cells (often derived from humans), which are grown in culture. Recently developed techniques for automated high-throughput testing enable screening for changes in a wide range of biological processes that underlie the function of cells, and in the future, information generated in this way may be further enhanced through the development of new cell lines and methods of cell culture. Understanding is supported also by computerised mathematical modelling of relationships between the molecular structures of chemicals and their biological activity.

11. In some areas, such as the evaluation of potential to cause skin allergy, **this new approach is already beginning to impact on methods of risk assessment,** although much work will be needed before it can completely **replace standard testing in animals.** In the shorter term, it is more likely to find application in **complementing and augmenting traditional methods of testing**, especially for hazards that currently are not so well addressed (e.g. hormonal disruption and effects on the developing nervous system). Before they can be used, the **suitability of new methods for evaluating toxicity needs to be established**. However, the validation processes that are currently followed are not ideally suited to the process-focused approach, and there is a need to agree on new methods and criteria by which to determine whether methods are fit for purpose. Regulatory agencies such as EFSA could play a leading role in **developing new approaches to the validation of mechanistically-based methods for the assessment of toxicity.**

12. Another development that might **reduce the use of experimental animals** without compromising the robustness of risk assessment could be to carry out tests on two or more substances simultaneously, using the same group of unexposed "control" animals for each chemical.

13. **Epidemiology** contributes to risk assessment for PPPs once they have been approved for use, and human exposure has occurred. The body of relevant epidemiological evidence is increasing rapidly, and there is therefore a **growing need to consider such data when reviewing approvals for products that are already on the market.** The information can usefully complement that from toxicology, but care is needed in its interpretation which should take into account the methodological limitations of the assessed epidemiological studies. Particularly challenging is the reliable ascertainment of exposure when carried out retrospectively, relying on the recall of study participants. **Measurement of chemical markers for exposure** in body tissues or fluids (e.g. blood or urine) may be more accurate, but few such "biomarkers" are currently suitable for use.

14. In the future, various **methodological developments** may improve the scope and quality of epidemiological data on PPPs. These include the use of: hypothesis-free, environment-wide association studies (EWAS), which simultaneously **assess the relationships of health outcomes to a wide range of pesticides;** Mendelian randomisation studies, which explore the **associations of health outcomes with genes that modify the body's metabolism of specific pesticides** in a way that would be expected to make a given exposure more toxic; **pooling of data from multiple existing studies** so that conclusions can be drawn with greater statistical confidence; and using **markers of disease processes as an outcome** rather than the development of clinically overt disease.

15. In addition, there could be benefits from **wider use of epidemiological methods to explore the distribution and determinants of personal exposures to pesticides** in different circumstances. This information could be used to check that the modelling of potential exposures as part of regulatory risk assessment is sufficiently precautionary, and might also point to effective ways of reducing people's exposures.

16. **Exposure sciences contribute to regulatory risk assessment for PPPs** both in the generation of epidemiological data, and in the modelling of potential exposures that will be set against toxicological reference values to determine their acceptability (see above). Dietary exposures to residues of PPPs and their metabolites in food have been relatively well studied, but there is a **need for further research on the potential exposures** of operators who apply PPPs, bystanders who are nearby when PPPs are applied, residents who live near treated areas, and particularly workers who enter crops after they have been treated and who experience amongst the highest exposures.

17. **Exposures to PPPs during their application can be usefully reduced** by good

engineering (e.g. through use of low-drift nozzles or intelligent spraying equipment that automatically complies with regulatory requirements) and by maintaining buffer zones around treated crops. However, the **efficacy of such measures depends on their correct implementation**. More information is needed about the "real life" behaviours of operators regarding the use of such equipment and application techniques (which may vary between Member States), and about the efficacy of mitigation measures. Moreover, there is a need to improve and harmonise definitions of drift-reducing capability across Member States.

18. Alongside improvements in the scientific evidence to inform regulatory risk assessment for PPPs, it is important to **ensure that available data are evaluated optimally**. One way of improving the methods of risk assessment could be to allow **greater flexibility in data requirements, particularly for the re-evaluation of PPPs that are already approved**. A more flexible approach might, for example, allow read-across between chemicals that cause toxicity through similar biochemical mechanisms, and could exploit new developments in toxicology as they emerge, in some cases reducing the use of laboratory animals. There could also be benefits from more frequently **targeting re-evaluations to particular aspects of the risk assessment,** which the assessor considers to be of greatest concern. In addition, the routine requirement for a mouse carcinogenicity study (testing potential to cause cancer) as part of the evaluation of active substances could usefully be reassessed, since it is of questionable value. And there is a case that **reports of toxicological investigations submitted in support of applications for approval should include all relevant historical control data** that meet specified criteria, rather than leaving the applicant to decide what should be presented. Records of these data could then be maintained by a public statutory body.

19. Assessments of potential toxicity could be improved through wider application of statistical modelling when deriving toxicological reference values from experimental data, and consideration should be given to study designs that are better suited to this approach.

20. Strategies for the **assessment of toxic effects on the development of the nervous system** might be usefully refined by incorporating mechanistically-informed tests on tissues or cells in addition to studies on whole animals.

21. When approvals are reviewed for **PPPs that are already on the market**, relevant information may be available from toxicological and/or epidemiological reports in the peer-reviewed scientific literature, as well as from the standard investigations that are required to support new approvals. There is a need to **develop and refine methods**

for quantitative and qualitative synthesis of evidence from non-standardised toxicological and epidemiological studies. Moreover, applications for (re-)approval of active substances should **routinely include a systematic review of the published literature** to identify all evidence that might be relevant to the risk assessment.

22. Post-marketing surveillance of PPPs approved for commercial use is necessary to check that they do not cause unanticipated human health problems. This is partly the responsibility of the approval holder. However, Member State governments could contribute by maintaining schemes that **systematically ascertain cases of acute illnesses suspected of being caused by PPPs**, and transmit the data to EFSA for central analysis. In addition, a system could be established to **monitor the peer-reviewed literature** at appropriately frequent intervals for epidemiological papers and case reports concerning human health effects of PPPs.

23. When reviews are conducted of previously approved active substances, compounds should be **grouped according to their pesticidal mode(s) of action** to facilitate consistency of approach and to help **highlight compounds of potential concern.**

24. In addition to their active ingredients, PPPs contain a wide range of **co-formulants with varying chemical properties and potential for toxicity.** Current requirements for toxicological assessment of co-formulants are much more limited than those for active substances, but some co-formulants could pose health risks, either in their own right or in combination with the active substance and other constituents of the formulated product. It would be desirable to develop a **positive list of chemicals that can be considered for inclusion as co-formulants in PPPs**, supported by a **more rigorous system for tiered assessment of the toxic potential of chemicals intended for use as co-formulants in PPPs.**

25. Once separate assessments have been made of the active substance(s) and co-formulants that are contained in a PPP, there is a need to determine the **toxicity characteristics of the mixture as a whole**, taking into account constituent concentrations and potential for toxic interaction. It would be desirable to develop an efficient system that assesses products **grouped according to the concentration ranges of the co-formulants**, taking into account the properties of the active substance and individual co-formulants as already determined, and paying special attention to any potential for additivity or synergy in toxic effects. Products deemed **potentially suitable for use as PPPs should be publicly listed.**

26. PPPs are authorised only when there is adequate confidence that their use will not

cause adverse health effects. However, for a given use, the **confidence of safety** may be greater for one product than another. **Making information available to consumers** about levels of confidence, to be considered in conjunction with, for example, potential for adverse environmental impacts, possible between-product differences in efficacy, and potential for pest resistance, could **promote the use of products offering greater reassurance of safety and might encourage manufacturers to develop products with better safety profiles.**

27. Current regulation requires consideration of the **risks from exposure to multiple active substances in combination**, either simultaneously or in sequence (cumulative risk assessment). When a PPP containing more than one active substance is assessed, the potential for combined effects is considered through a simple tiered approach, but this is not harmonised across the EU, and more complex scenarios, such as the use of tank mixes (mixtures of different PPPs and/or other agrochemicals in a spray tank) and sequential applications to the same crop over the course of a season, receive less attention. A **standardised method should be developed for the authorisation of tank mixes** by EU Member States, and in the longer term, methods should be developed to assess risks to operators and workers from sequential use of different PPPs on the same crop, and perhaps the health risks from sequential use of combinations of PPPs on neighbouring crops.

28. Some active substances in PPPs also have uses in biocides and human or veterinary medicines and the potential for harm to health from **aggregate exposures across different uses** can and should be accounted for in risk assessment across EU regulations.

29. Nano-sized active ingredients and formulations have the potential to enhance the delivery and efficacy of PPPs (thus potentially reducing the quantities used), to improve the stability of chemical mixtures, and to allow slow- or controlled-release of active ingredients. However, such nanopesticides may pose greater risks to human health and the environment. Before nanomaterials are approved for pesticide-related use in the EU, the definition of the term 'nanopesticide' should be reviewed, and a standardised risk assessment procedure developed for such products.

30. Biopesticides encompass three different types of active substance: microbial organisms, non-toxic pheromones and attractants, and natural extracts mostly from plants. While it is appropriate to conduct chemical risk assessment for pheromones and natural extracts, risk assessment of microbial active substances needs input from microbiology as well as toxicology, and there is a need to **review and revise the data requirements for such substances.**

31. The handling of scientific uncertainty is a possible source of inconsistency in decisions on the authorisation of PPPs in the EU. Risk assessors may differ in their evaluation of whether available data give adequate reassurance of safety, either because they have differing confidence in the conclusions that can be drawn from the findings, or a divergent understanding of the level of confidence that risk managers require. The potential for inconsistency in assessments is greater during review of approved products than during assessment of new products because reviews are informed by a wider range of non-standardised evidence. EFSA has recently instituted **formal, preferably quantitative, uncertainty analysis with pre-determined protection goals and levels of confidence as a routine part of risk assessment.** Given that numerical levels of confidence partly reflect the subjective opinions of risk assessors, and cannot be empirically validated, the main values of formal uncertainty analysis are likely to lie in promoting consistency between risk assessments, in identifying causes for diverging assessments, and in increasing the transparency of risk assessment. As formalised quantification of uncertainty is introduced, its benefits and costs should be evaluated.

32. To improve the organisation of risk assessment it would be desirable to **resolve the currently unsatisfactory division of labour** between EFSA centrally and regulatory authorities in individual EU Member States, which may contribute to inconsistencies in the assessment and management of risks from PPPs in the EU. **Ideally, EFSA would be responsible for organising all aspects of risk assessment that could be common to all EU Member States**, including:

- the evaluation and interpretation of relevant scientific studies on active substances, co-formulants, and products;
- the setting of key endpoints used in risk assessments;
- the standardisation of generic methods.

As an outcome of this process (which would be conducted in close collaboration with Member States), **EFSA would publish: lists of active substances and co-formulants** that could be included in PPPs submitted for approval within the EU for use on specified crops; **a list of products based on the listed active substances and co-formulants,** which could be considered for authorisation by individual EU Member States; and **dossiers of generic methods/models/tools** to be applied when individual EU Member States conduct risk assessments for specific uses of products on the EFSA lists. Individual EU Member States would then consider applications for specified uses of listed products within their jurisdiction, taking into account local circumstances and relevant aspects of national law. In coming to decisions, they would apply EFSA-standardised generic methods and use EU-agreed key endpoints and conclusions for the active substance(s), co-formulants, and products. This approach would **increase efficiency for regulators and applicants, improve scientific rigour and consistency,**

provide transparency, and eliminate the potential for bias in the selection of rapporteur Member States for the assessment of active substances.

33. It is important that the personnel undertaking risk assessments continue to have the necessary **training to apply correctly new and emerging methods of risk assessment, including methods of systematic review and meta-analysis.** A formal mandatory training scheme could be organised and maintained for staff undertaking risk assessments for PPPs in the EU, including those employed in the regulatory bodies of EU Member States.

34. In view of the growing volume and importance of research on pesticide risk assessment, and the ever-increasing complexity of the science that it entails, it is worth considering the scope for **an independent, international centre for PPP-related research.** This could serve as a major resource worldwide by helping to develop methodology, conducting primary research, carrying out independent evaluations of published evidence, and contributing to training.

35. Based on the above considerations, the Working Group identified **26 Options that might improve PPP authorisation processes in Europe.** See page 79 for a list of those Options.

36. The policy recommendations of the Group of Chief Scientific Advisors and the evidence-based Options set out in this Evidence Review Report were examined at a stakeholder workshop of representatives from industry, policy, and civil society in February 2018.

37. Both this Evidence Review Report and the Group of Chief Scientific Advisors' Scientific Opinion were published in June 2018. They are designed to be considered in tandem, to **inform the REFIT Evaluation of the EU legislation on plant protection products and pesticides residues[b]**, and thus contribute to the implementation of a **more effective, efficient, and transparent authorisation system for plant protection products that incorporates the latest scientific developments and discoveries**. In addition, both reports aim to make important contributions to the planning of the EU's future political priorities and corresponding resource allocation, including the preparation of the Commission's post-2020 Multi-Annual Financial Framework (MFF).

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[b] The Evaluation and Fitness Check Roadmap for the REFIT Evaluation of Regulations (EC) No 1107/2009 and No 396/2005) is available for download here: http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_197_ealuation_plant_protection_products_en.pdf.

1. Introductory note

This report was produced by a Working Group of the Scientific Advice for Policy by European Academies (SAPEA) Consortium in response to a request from the European Commission (EC) for a rapid evidence review to inform the deliberations of its Group of Chief Scientific Advisors. Among other topics, the Group of Chief Scientific Advisors had been asked to consider whether the current dual system for approval and authorisation of plant protection products (PPPs) in the European Union (EU) could be rendered more effective, efficient and transparent, and if so, how this could be achieved. The SAPEA Working Group (Annex 1) was asked to focus on methods and procedures for assessing potential harmful effects on human health from the use of PPPs, and to report on both the current scientific state-of-the-art and the potential for future developments. The report does not address other aspects of risk assessment for PPPs (e.g. environmental impacts) or the assessment of their efficacy, although these are considered by the European Commission Group of Scientific Advisors.

In the limited time that was available for completion of the report, it was not possible to carry out a formal systematic review of all potentially relevant scientific evidence. Instead, the Working Group based its assessment on the knowledge and experience of individual members, supplemented by targeted searches of the scientific literature in relation to specific questions. In addition, to guard against imbalance and important omissions, a preliminary draft of the report was circulated to a wider group of scientists with relevant expertise, who provided comments, both in writing and in discussion, at a one-day workshop. The names and affiliations of those external experts are listed in Annex 2[c]. We are most grateful to them for their input, and at the same time emphasise that they are not responsible for the final content of the report, which was agreed only by members of the Working Group. We are also thankful to the SAPEA Board for the provided editorial assistance.

The report starts with a brief overview of the aims and methods of human health risk assessment as part of the EU's regulation of PPPs, highlighting a number of limitations. Next, it identifies various recent or ongoing scientific advances that might enhance the evidence underpinning human health risk assessment for PPPs in the near- or longer-term future. It then considers ways in which current methods of risk assessment might be improved, and how delivery of the risk assessment could best be organised from a scientific perspective.

At a number of points the report identifies "Options" for the potential consideration of the Group of Chief Scientific Advisors when formulating their recommendations to the EC. These Options, which emerged during either the Working Group meetings or at a one-day workshop with additional experts, are not necessarily supported unanimously by members of the Working Group. They are presented to assist the Group of Chief Scientific Advisors in their deliberations, and in some cases, where it might be helpful to the Group of Chief Scientific Advisors, are accompanied by a short discussion of their possible advantages and disadvantages.

2. Regulatory risk assessment for plant protection products in the EU

2.1. AIMS

Regulatory risk assessment for PPPs in the EU aims to ensure a high level of protection of human and animal health and the environment, while safeguarding the competitiveness of agriculture in the EU. Before PPPs are placed on the market, it should be demonstrated that they will not have any harmful effect on human or animal health, including that of vulnerable groups, or any unacceptable effects on the environment, when products are used as authorised (Directorate General for Health and Food Safety, 2016; European Commission - Legislation on Plant Protection Products). However, because of unavoidable scientific uncertainty, zero risk can never be guaranteed. Therefore, in practice the requirement regarding human health is for a high level of confidence that harmful effects will not occur (see 2.2 Overview of methods). Moreover, minor adverse effects (e.g. skin sensitisation in professional spray operators) may sometimes be tolerated if the risk is sufficiently small.

In addition, it is important that the regulatory system should be trusted by, and fair to, stakeholders. To this end, its methods should be open, transparent, internally consistent, and reflect the current state of scientific knowledge. Also, the scientists conducting risk assessments should be suitably experienced and manifestly free from potential conflicts of interest. And finally, the outputs of risk assessment should be clearly communicated to risk managers and to the public.

2.2. OVERVIEW OF METHODS

The methods by which regulatory risk assessments for PPPs are currently carried out in the EU are complex and for a detailed account, readers are referred to the website of the European Food Safety Authority (EFSA) (http://www.efsa.europa.eu/en/science/pesticides).

In broad terms, the human health risk assessment entails first determining the potential adverse effects of active substances, and levels of exposure (toxicological reference values) below which there is high confidence that those effects will not occur, even in individuals who are relatively sensitive (e.g. because of genetic predisposition or their age). For new active substances, this is done principally from data generated through a prescribed set of standardised toxicological tests in laboratory animals, which usually

have been conducted or commissioned by a sponsoring company that is applying for approval. However, particularly when approvals are reviewed for pesticides that are already on the market, relevant data may be available also from other toxicological research (e.g. conducted by academic institutions), human health surveillance, and epidemiological investigations. In contrast to the standardised experimental designs that are required for the approval of new substances, the studies in this auxiliary evidence base may vary in their design, sample size, and quality. In addition to the potential for harm from active substances, a more limited assessment is made of the toxicity of the chemicals with which active substances are formulated in PPPs (co-formulants), and of formulated products per se.

Confidence in the absence of potential adverse effects stems from the use of a wide range of tests and a wide range of outcomes in those tests. Moreover, toxicological reference values aimed at preventing all toxic effects are specified through the application of assessment factors ("uncertainty factors") to "points of departure"[d] derived from toxicological studies. The points of departure are chosen to reflect doses at which relevant studies indicate no or only minimal toxicity, and the assessment factors (most often 100[e]) are chosen to allow for possible differences in susceptibility within and between species. Confidence that toxic interactions will not occur when active substances are mixed with co-formulants derives in part from the limited empirical assessment of toxicity that is carried out for the formulation as a whole. This is supported by the application of more generic evidence on the nature of toxic interactions between chemicals and the circumstances in which they occur, to what is known about the toxicity of the active substance and its co-formulants individually.

Alongside this assessment of toxicity, reasonable upper limits are estimated for the levels of human exposure to the active substance that might occur by different pathways if a product were used according to the proposed conditions of approval (including Good Agricultural Practice, GAP) (Poisot, 2003). The pathways considered include (but are not limited to) exposures of: operators when applying the product; workers who enter treated crops; bystanders who are nearby when application takes place; residents who live close to treated crops; and consumers who eat foods derived from treated crops or other crops grown on the same land subsequently, and from animals that have fed on treated crops. A check is then made that such exposures would not exceed relevant toxicological reference values.

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[d] A point on a toxicological dose–response curve established from experimental or observational data generally corresponding to an estimated low effect level or no effect level.

[e] i.e. the reference value is set at one hundredth of the point of departure.

Parts of this risk assessment (particularly relating to the toxicity of active substances) are coordinated centrally by EFSA and agreed by all EU Member States, while other elements (mostly relating to products) are conducted at Member State level in what is known as a "dual system".

2.3. LIMITATIONS OF CURRENT APPROACH

As already mentioned, no system of regulatory risk assessment can provide a complete guarantee against harmful effects in humans. Historically, there have been examples of PPPs approved for use in European countries, which subsequently were shown to cause serious disease, even when used according to the terms of approval. For example, the nematicide 1,2-dibromo-3-chloropropane (DBCP, see https://toxnet. nlm.nih.gov) was used before it was established that it had deleterious effects on human male reproductive health.

To reduce the chance of such outcomes, regulatory risk assessment has evolved over time, becoming more precautionary, and this is reflected in a significant drop in the number of approved active substances. Of about 1,000 active substances on the market in at least one Member State before 1993, only 26% (corresponding to about 250 substances) passed the harmonised safety assessment completed in December 2008 (Karabelas, Plakas, Solomou, Drossou, & Sarigiannis, 2009); and at present there are roughly 500 approved active substances[f] . Nevertheless, it remains possible that some adverse effects in humans have not been predicted by regulatory toxicity testing, and have subsequently gone undetected because epidemiological surveillance has been insufficient or too insensitive. In particular, some more complex human health outcomes may not be adequately addressed by the standard toxicity tests that are currently available. These include immunotoxicity, childhood leukaemias (Pelkonen et al., 2017), developmental neurotoxicity (EFSA Panel on Plant Protection Products and their Residues (PPR), 2013), chronic neurological diseases such as Parkinson's disease (Choi, Polcher, & Joas, 2016), neuropsychological effects and mental illnesses, as well as endocrine disorders such as some hormonal cancers, endometriosis, metabolic syndrome, type-2 diabetes, and reproductive senescence (OECD, 2014b). And even where more extensive investigation might be carried out (e.g. for developmental neurotoxicity), the thresholds for doing so may currently be too high (Fritsche et al., 2017; Bal-Price et al., 2015).

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[f] Pesticides Database of the European Commission: http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN, accessed 4 Feb. 2018.

Also questionable is the adequacy with which the risk assessment addresses the toxic potential of co-formulants, alone and in combination with active substances (Di Mare, Garramone, Rubbiani, & Moretto, 2017). Currently, systematic testing of products as formulated is limited to acute systemic toxicity (oral, dermal, and inhalational), and possible irritant and sensitising effects, leaving open the possibility that some synergic toxic effects might be missed. Regulation (EC) No 1107/2009 promotes the provision of a published 'negative list' of co-formulants that cannot be included in PPPs, but no substances have been listed yet, and the criteria for doing so are still to be finalised.

As well as concerns about chemicals that are co-formulated in the same PPP, there is a possibility of additive or even aggravated toxicity from combined exposure to active substances and co-formulants in different PPPs (Hernández, Gil, & Lacasaña, 2017). This could occur through their simultaneous application in tank mixes[g] , through sequential applications by the same spray operator or to the same crop, or from dietary consumption of foods containing a mix of residues. There is evidence that tank-mixing is a frequent practice (Glass et al., 2012; Luttik et al., 2017; Fryday, Thompson, & Garthwaite, 2011), and that for certain crops the sequential use of different PPPs over the course of a growing season is extensive (Garthwaite et al., 2015). Efforts to address this complex aspect of risk assessment, for example in relation to setting maximum residue levels (MRLs), have started (EFSA Panel on PPR, 2014), but the problem could usefully be explored further.

Another facet of risk assessment for PPPs that has been challenged is the assessment of potential exposures, particularly to residents and bystanders (Deziel et al., 2015; EFSA Pesticides Unit, 2014). Recent research by the Institute of Occupational Medicine (UK) suggests that methods of modelling residents' exposure are sufficiently conservative, urinary excretion of relevant pesticide metabolites being generally much lower than that predicted by the models (Galea et al., 2015). However, more research on this would be helpful (see below).

A further challenge is to improve the methods of risk assessment for PPPs based on microorganisms. In comparison with chemical agents, bio-pesticides have potential advantages in being more targeted, environmentally friendly, and sustainable (Glare et al., 2012). However, current data requirements for regulatory risk assessment of PPPs were largely framed in relation to products based on specific chemicals, and are not well suited to some biopesticides (Chandler et al., 2011).

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[g] i.e. where the operator mixes two or more PPPs in a spray tank before they are applied

Similarly, the toxicity of PPPs that contain nanoparticles[h] , some of which are probably now in development, should be carefully assessed. A biocide formulation incorporating nanomaterials has already been approved for use, and according to an Australian Government Report, 3,000 patent applications for nanopesticides were lodged in the decade leading up to 2015 (Australian Pesticides and Veterinary Medicines Authority 2015). The toxicity of some nanopesticides may not depend simply on their chemical content, but also on the shape and size of the constituent particles, and thus may require new approaches to the assessment of risk. There are many toxicokinetic[i] differences between nanoformulations and conventional products. For example, some particles slow the release of active substances over time, minimising peaks of exposure and thus potentially reducing the risk of acute toxicity[j] . These concerns could extend to particles smaller and slightly larger than the nano-size range in current definitions (Kookana et al., 2014).

As well as providing adequate protection against harmful effects, regulatory risk assessment should be fair, consistent, and transparent (Wilks et al., 2015). However, in recent years, apparent inconsistencies in evaluations between respected scientific bodies have been a cause of confusion and threatened public trust in the regulatory system. A notable example is the herbicide glyphosate, which has been classed as a probable human carcinogen by the International Agency for Research on Cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2017). In contrast, EFSA and the European Chemicals Agency (ECHA) have concluded that glyphosate is unlikely to be a human carcinogen (EFSA, 2015) and its continued use in Europe has recently been approved for a further five years (European Commission, Approval of active substances – Glyphosate, 2017). Use of different datasets, particularly on long-term toxicity and carcinogenicity in rodents, may partially explain the divergent conclusions, but methodological differences in the evaluation of the available evidence have also been identified (Tarazona et al., 2017). Apparent discrepancies of this sort indicate a need for better communication with decision-makers and the public regarding the purpose and methods of risk assessment, the interpretation of its findings, and the justification for its conclusions.

[h] Particles in the nanoscale have dimensions of 1-100 nanometers. A nanometer is a billionth of a meter.

[i] Relating to the processes by which potentially toxic substances are taken up and handled in the body.

[j] Toxicity that develops soon after exposure.

There is also the possibility of internal inconsistency, both in the evaluation of one PPP in comparison with another, and in decisions made for the same PPP by different EU Member States. These problems will be influenced by the design of the regulatory system, and in particular the division of work between EFSA and ECHA centrally, and individual EU Member States (see section on improving the organisation of risk assessment).

Finally, all risk assessments should include consideration of possible sources of uncertainty in the information underpinning the evaluation (Kennedy et al., 2015). Although the current regulatory assessment of PPPs contains elements that are intended to address uncertainty, and a framework and principles for uncertainty analysis have recently been finalised by EFSA (EFSA Scientific Committee, 2018), the current process falls short of the standards set by the Codex Alimentarius[k], compromising transparency regarding the level of certainty that is achieved, and whether it reaches the level envisaged by PPP legislation (Secretariat of the Joint FAO/WHO Food Standards Programme, 2013).

2.4. CONSTRAINTS ON IMPROVEMENT

Limitations of the type that have been discussed are an encouragement to explore ways in which risk assessment for PPPs might be improved. However, any changes that are proposed should have regard to several practical constraints:

- Standards and control measures that are mandated must be enforceable.

- The system requires sufficient funding to achieve the declared aims efficiently. If scientific resources are restricted, they must be applied on the basis of appropriate cost-benefit assessments.

- Unnecessary use of laboratory animals should be avoided.

[k] The Codex Alimentarius, or «Food Code» is a collection of standards, guidelines and codes of practice adopted by the Codex Alimentarius Commission, which is the central part of the Joint FAO/WHO Food Standards Programme and was established by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) to protect consumer health and promote fair practices in food trade.

3. Improving the scientific data that inform risk assessment

In exploring ways in which regulatory risk assessment for PPPs might be improved, we first consider recent and ongoing scientific advances that might improve the range or quality of data on which to base evaluations of risk.

3.1. TOXICOLOGY

3.1.1 Toxicity pathways

Most of the toxicological studies that are required to support regulatory approval of PPPs use experimental animals, and thus are not sensitive to the full range of possible adverse effects in humans. However, advances in science and technology are now providing opportunities to develop in-vitro test methods that are human-based and hence should avoid some of the limitations that are inherent in extrapolation between species.

An emerging philosophy has been most clearly set out in the United States National Research Council's (NRC) report entitled "Toxicity Testing in the 21st Century: A Vision and a Strategy" (National Research Council, 2007), which served as a catalyst for several major publicly-funded initiatives in the USA, such as the Environmental Protection Agency's (EPA) Toxicity ForeCaster (ToxCast) and Toxicology Testing in the 21st Century (Tox21) programmes (Richard et al., 2016). In parallel, the EU also undertook work in this area where authorities, agencies and research institutions have also endorsed the regulatory use of New Approach Methods (NAMs) (Worth et al., 2014) and produced partnerships such as the SEURAT-1 programme (Safety Evaluation Ultimately Replacing Animal Testing: http://www.seurat-1.eu) (Gocht et al., 2018) and currently EU-ToxRisk (Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century: http://www.eu-toxrisk.eu) (Daneshian, Kamp, Hengstler, Leist, & van de Water, 2016), a programme which strives towards a toxicological assessment based on human cell responses and a comprehensive mechanistic understanding of cause-consequence relationships of chemical adverse effects.

Central to the NRC's approach was the concept of a toxicity pathway, a series of biological processes that, when affected by the action of a chemical, lead to an adverse effect. This thinking closely mirrors that underpinning work by the WHO International Programme on Chemical Safety (IPCS) (and others) on mode of action (MOA), and more recently by the Organisation for Economic Co-operation and Development (OECD) (in

collaboration with EFSA and others), on adverse outcome pathways (AOPs) (Vinken et al., 2017). These all envisage toxicity (adverse outcomes or effects) resulting from the interaction of a chemical with a critical molecular target in a molecular initiating event (MIE), leading to progressive changes at the cellular and tissue level (key events). Adversity results only when homeostatic and protective mechanisms at the level of each of the key events are overwhelmed. The level at which a key event is triggered is affected both by intrinsic factors (e.g. sex, genetic variation, tissue) and by exogenous influences (e.g. diet, environmental exposures, disease), which will vary within and between individuals. Application of molecular and computer-based approaches pertinent to this paradigm has potential to increase the relevance, predictability, and timeliness of safety evaluations for pesticides, while reducing the need for animal studies. However, for a method to be usable, its validity and fitness-for-purpose must be established (Whelan & Eskes, 2016).

For many years, efforts focused on developing "one-for-one" replacements for existing tests in experimental animals – for example, an in-vitro method that would enable developmental toxicity to be assessed. However, it is now recognised that, with few exceptions, this is not realistic or feasible. Biology and pathophysiology are too complex for apical effects[l] , which themselves may reflect a multiplicity of disease processes, to be captured through a single in-vitro assay. The evolving understanding is that a suite of assays will be needed to address the multiple pathways that can lead to end-organ effects. Its key concept is that most xenobiotic toxicities are related to effects on a limited number of physiological pathways required for normal cellular maintenance, regulation, or adaptation (Piersma et al., 2014; Daston et al., 2015; ICCVAM, 2018). Defining these AOPs will allow toxicologists to move away from investigating apical endpoints towards an approach in which effects are mechanistically understood, and will assist prevention and monitoring. For some organ-specific toxicities, a strategy has already been proposed. For example, a set of in-vitro test methods has been identified, which might be used to cover the different pathways that could lead to toxic effects on the thyroid gland (Browne, Noyes, Casey, & Dix, 2017).

The toxicity of a given dose of a pesticide will depend on both the toxicokinetics and the toxicodynamics of the compound – i.e. what dose of the active moiety (parent or metabolite) is achieved at the target tissue, and the sensitivity of the molecular

[l] An apical effect (or endpoint) is an observable outcome in a whole organism, such as a clinical sign or pathological abnormality that is indicative of a disease state that can result from exposure to a toxicant. When it is the most sensitive, relevant effect observed, it often serves as the basis for establishing a reference value, and it is then known as the critical effect.

target(s) to the substance. The suitability of any new method needs to be evaluated with respect to these two determinants. In terms of toxicodynamics, use of human-based or human-derived in-vitro test systems will eliminate inter-species differences (Knasmüller et al., 2004). However, many of the test systems use cells that differ, sometimes substantially, from the target cell in vivo. For example, most immortal cell lines (which are used in toxicology for their convenience and consistency) are currently derived from tumours and have a transformed phenotype (the characteristics of the cell are different from those of the cell of origin due to acquired genetic changes). This phenotype usually differs quantitatively and sometimes qualitatively from the cell of interest. Hence, the cell line needs to be characterised with regard to features that might modify its response to toxicants as compared with the target tissue (Schmidt et al., 2017; Horvath et al., 2016). In addition, the biological origin of the cell line should be verified, as appropriate (Coecke et al., 2005).

With respect to toxicokinetics, a major limitation of almost all current in-vitro test systems is that they lack, or are substantially deficient in, many of the enzymes (and transporters) involved in the disposition of xenobiotic substances. When the parent compound is directly responsible for toxicity, this limitation can be overcome by suitable extrapolation of the active-site concentration in vitro to the concentration at the active site in vivo (Kramer, Di Consiglio, Blaauboer, & Testai, 2015). This is usually achieved through some form of physiologically-based toxicokinetic (pharmacokinetic) modelling, which can range from relatively simple approaches using only a measure of metabolic clearance and plasma protein binding (both determined in vitro), to a fully-parameterised, multi-tissue model. However, where the toxic moiety is a product of metabolism (an active metabolite), a failure of in-vitro models to account for toxicokinetics could lead to some toxicity being completely overlooked. Currently, efforts are underway to introduce metabolic activity into some assays, but no general solution is yet available (Mekenyan, Dimitrov, Pavlov, & Veith, 2004).

It is anticipated that many of the non-animal methods that will be developed will represent MIEs or key events in AOPs (or modes of action; Lalone et al., 2013). This would have considerable advantages. The toxicological consequence would be known, as

[m] Weight of evidence is a process in which all of the evidence considered relevant for a risk assessment is evaluated and weighted within a prescribed framework. A tailored weight of evidence approach has been developed to support adverse outcome pathways based on the modified Bradford-Hill Considerations (biological plausibility, essentiality and empirical support of linkage, quantitative understanding of the linkage, evidence supporting taxonomic applicability and evaluation of uncertainties and inconsistencies).

AOPs represent chemically-agnostic pathways leading to adverse outcomes (when sufficiently perturbed). Hence, any pesticide that modulates key events to a sufficient extent would be expected to cause the adverse outcome associated with the AOP. Whilst AOPs are chemically-agnostic and hence represent biological processes, the linkage between key events and adverse outcomes is established by example – i.e. one or more chemicals is shown, using a weight of evidence approach[m] , to cause toxicity through the AOP (Gross, Green, Weltje, & Wheeler, 2017; EFSA Scientific Committee, 2017a; Meek et al., 2014). One result of this is the concept of grouping or category-formation of chemicals. Chemicals that are sufficiently similar, as judged by chemometric analysis, would be expected to share one or more AOPs. For example, many organophosphate and carbamate pesticides act through inhibition of the enzyme acetylcholinesterase (AChE). Potency ranking of such chemicals could then be achieved, initially using appropriate key-event assays in vitro (e.g. inhibition of AChE), and perhaps eventually by in-silico assessment (computer modelling and simulations) of the molecular determinants of the interactions governing MIEs (see below) (Allen, Liggi, Goodman, Gutsell, & Russell, 2016).

3.1.2 High throughput screening and high content analysis

The pace of method development is currently very rapid, and several strategies are being pursued. Amongst these is high throughput screening, using robotic methods to test many chemicals across a concentration range for a variety of endpoints. The most extensive effort of this sort is the US EPA's ToxCast program, which screens around 800-900 different toxicity endpoints (including short-term and long-term systemic toxicity, cancer, reproductive toxicity, and developmental toxicity) and has evaluated 2,000 chemicals to date (Clarke, Connolly, Frizzell, & Elliott, 2015). The US Tox21 program has broader chemical coverage (10,000 chemicals to date), but covers fewer endpoints (~150). An alternative approach is high content analysis, either by chemical assays or by imaging (Cole, Madren-Whalley, Li, Dorsey, & Salem, 2014.). Cells are assessed as broadly as possible for changes in biological processes underlying cell functions. Foci of investigation include mRNA species (transcriptomics), proteins (proteomics), low molecular weight organic products of intermediary metabolism (metabolomics), and cell signalling processes (high-content imaging). However, this is a rapidly developing field and technological advances are leading to analysis of an ever-increasing range of cell contents (e.g. phosphorylated proteins, sugars, histone modifications, DNA methylation, miRNAs and other non-coding RNA species) (Rezvanfar, Hodjat, & Abdollahi, 2016). Whilst so far these two broad approaches have largely been applied independently, there are initiatives to combine elements from each to enable a more holistic assessment of chemical toxicity. They may be of most value in risk assessment for pesticides when they are linked to adverse-outcome pathways.

3.1.3 New cell lines

The phenotypic limitations of many of the cell lines most readily available has led to a search for more representative alternatives. Whilst primary cells often remain well differentiated in vitro, their useful lifetime in culture is usually short (sometimes only 24 hours, depending on cell type) before they lose key functions. Moreover, they are limited in supply. Derivation from stem cells offers a means of overcoming these limitations, and for some cell types this has proved successful (Pamies & Hartung, 2017). However, for others, most notably hepatocytes, development of cells with a mature phenotype is proving elusive. Thus, for some applications, cell lines from animals may currently provide the best available option.

3.1.4 New methods of cell culture

All of the systems described involve monoculture of cells, i.e. culture of cells of one type, in a two-dimensional layer. However, the phenotype of cells in-vivo often depends importantly on cell-cell or cell-matrix signalling, and a number of toxic responses involve cell-cell interactions. Hence, several groups have developed three-dimensional culture systems and/or multi-cell systems comprising cells of different types (Grego et al., 2017; Lelièvre, Kwok, & Chittiboyina, 2017). These have advantages over simpler cell models, maintaining differentiated functions for longer, and exhibiting toxicological responses closer to those observed in-vivo.

3.1.5 Microphysiological systems

Related to these approaches are microphysiological systems – so-called "organs-on-a-chip". These use a number of different cell types, some or all of which may be derived from stem cells, which are integrated in a matrix that allows communication between cells (e.g. the vascular blood supply, endocrine system, and inflammatory system), through the architecture of the device (Jones, 2016). However, these multi-cell models are all more complex than two-dimensional single cell systems, and their use can be more time-consuming. Also, they are generally not amenable to high throughput applications. Hence, choice of system will depend on the needs of the assessment (Buschmann, 2013).

3.1.6 In-silico approaches

The identification of molecular initiating events through work on adverse-outcome pathways provides a critical focus for the development of Quantitative Structure Activity Relationships (QSARs). Using chemical descriptors, it is possible to identify the key molecular parameters that determine interaction with (and perhaps activation of) a molecular target (e.g. a receptor, enzyme or ion channel) and the intensity of this interaction (affinity and perhaps also potency). Many other in-silico approaches

(i.e. based on computer modelling and simulations) are available and being further developed, which might aid in assessing the toxicity of PPPs. These include molecular docking, which enables assessment of the three-dimensional interactions of chemicals with conformational targets, chemometric-based grouping and category formation, and virtual organs or tissues, either alone or in combination (Cronin et al., 2017; Committee on Incorporating 21st Century Science into Risk-Based Evaluations, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, & National Academies of Sciences, Engineering, and Medicine, 2017; Wittwehr et al., 2017).

As quantitative information is obtained on the key events leading to adverse outcomes, this can be combined with fundamental knowledge of the underlying biology to develop a quantitative biodynamic model in a systems-based approach (Coecke et al., 2013). Analogous to physiologically-based toxicokinetic models, these have the advantage that they can be extended to human sub-populations and scenarios for which data do not exist. If the biological parameterisation is appropriate, quantitative biodynamic models can reliably predict outcomes in data-deficient situations (Miller, McMullen, Andersen, & Clewell, 2017; Wathieu, Ojo, & Dakshanamurthy, 2017; Bloomingdale et al., 2017).

3.1.7 Potential for practical application

Regulatory agencies from across the world have had a leading role in efforts to move beyond traditional empirical assessment of apical toxic endpoints in laboratory animals, to evaluations of toxicity based on an understanding of toxic pathways with quantitative determination of relevant parameters through in-vitro studies. In some areas, this paradigm shift is already beginning to impact on methods of risk assessment. For example, a new strategy is being introduced for the assessment of potential to cause skin sensitisation, which will reduce the need for animal testing, and it is called for in read-across[n] scenarios for toxicological assessment of pesticide metabolites in relation to dietary risk assessment (EFSA Panel on PPR, 2012a; 2016).

In the future, it may prove possible to extend applications to more complex domains of toxicology such as developmental toxicity, carcinogenicity, neurotoxicity and, perhaps most demanding, systemic toxicity. However, before standard testing in

[n] Use of toxicological information for one chemical (the source chemical) to predict the same toxicological effect for another chemical (the target chemical), which is considered to be «similar» in some way (usually on the basis of structural similarity or the same mode or mechanism of action).

animals can be replaced, it will be necessary to identify and characterise all relevant adverse outcome pathways within the domain of interest, which begs the question of how many AOPs would be needed to cover a domain. One way of addressing this would be to construct biological ontologies for the domains – i.e. "maps" of all the biological processes that could lead to a toxic effect. It would then be possible to determine coverage by existing AOPs and systematically fill any gaps with additional AOPs. Whilst this is a substantial undertaking, in the long term it will be necessary if work on AOPs is to realise its full potential. An example of this approach can be seen in ongoing work on developmental toxicity (Baker et al., 2018; ECETOC, 2016).

In the shorter term, the new methodology is more likely to find application in complementing and enhancing traditional methods of testing, especially for hazards that currently are not so well covered (e.g. endocrine disruption, immunotoxicity, and developmental neurotoxicity).

3.1.8 Assessing fitness for purpose

Before they can be used, the suitability of new methods for evaluating toxicity needs to be established according to agreed criteria. For regulatory risk assessment, the agreement of standardised experimental methods by the OECD serves as a basis for the mutual acceptance of data by OECD Member States and often others as well (EFSA Panel on PPR, 2016). To date, very few non-animal methods have been approved by OECD for stand-alone use. To determine the suitability of alternative methods that do not use animals, the European Union Reference Laboratory for Alternatives to Animal Testing (EURL-ECVAM) in Europe and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICVAM) in the US (amongst others) have established a rigorous validation procedure. This is a lengthy process and to date few methods have attained validation. There is growing recognition that such a validation process is unable to keep pace with the rate of methodological advances, and further that the objective has shifted from one-to-one replacement to a process-focused approach. Hence, it should now perhaps be sufficient to demonstrate the fitness for purpose of new methods using other suitable criteria, which could be specified according to the proposed application. Key to regulatory use is to know the limitations of the assays by means of performance characterisation, analogous to that in analytical chemistry, and model prediction, both qualitatively and quantitatively, as already in use for in-silico approaches such as physiologically-based pharmacokinetic (PBPK) modelling. In this way, methods can be developed for assessing key events in the AOP for a toxic outcome of concern, and their performance characterised. Regulatory agencies such as EFSA should play a leading role in developing new approaches to the validation of mechanistically-based methods for the assessment of toxicity.

Option 1. Regulatory agencies (including EFSA) should work with OECD in developing new approaches to the validation of mechanistically-based methods for the assessment of toxicity, focusing on their fitness for purpose.

3.1.9 Scope to reduce the use of animals

Non-animal methods for assessing toxicity have great potential to reduce animal testing. However, at present it is not possible to avoid the use of in-vivo studies if toxicity evaluations are to be as reliable as possible, using methods that are internationally accepted. Currently, mechanistically based approaches are perhaps of most value when integrated with traditional test methods to enable more hypothesis-based assessments and focused evaluations relating to effects of particular concern.

It should be noted that whilst it is necessary to generate large amounts of (in-vivo) toxicity data for the regulatory assessment of a new pesticide (active ingredient), for some aspects of the evaluation data may be much more limited. This includes the potential for toxicity from some plant-specific metabolites or degrades of pesticide active ingredients. In such circumstances, non-animal methods such as structure-activity analysis° and read-across may be of considerable value and have been incorporated in the recent guidance on the residue definition for dietary risk assessment of pesticides (EFSA Panel on PPR, 2016). In the assessment of modes of action for cancer and non-cancer end-points using the IPCS mode of action/human relevance framework, the results from new, non-animal methods can be invaluable. In addition, in-vitro-, and increasingly in-silico methods are of considerable value in the qualitative and quantitative assessment of many aspects of Absorption, Distribution, Metabolism, and Excretion (ADME), e.g. comparative human or livestock activity (Dalgaard, 2015).

Scientific developments and understanding are currently not sufficient to enable the complete replacement of in-vivo testing with in-vitro methods to predict hazards and potency for systemic toxicities. However, new approaches can be used to complement traditional testing, start to replace some aspects of in-vivo testing, and immediately inform read-across scenarios. In the long term they may well provide alternative approaches in the assessment of toxicity for PPPs.

Even where in-vivo testing is essential, it might be possible to reduce the numbers of animals used without compromising statistical power or scientific validity. In particular,

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° Use of the chemical or 3D structure of a molecule to infer its possible toxicological activity, based on information from other molecules containing the same structural motifs.

there may be scope sometimes to carry out toxicity studies on two or more chemicals in parallel, using the same contemporary control group for all of them. Where this is possible, the data generated should be admissible for regulatory risk assessment.

Option 2. Allow the use of data from shared contemporary control groups in risk assessment for plant protection products.

3.2. EPIDEMIOLOGY

Epidemiology contributes to risk assessment for PPPs once they have been approved for use, and human exposure has occurred. The body of epidemiological evidence concerning PPPs is growing rapidly, with more than 600 reports published in the peer-reviewed literature between 2006 and 2012 (Ntzani, Chondrogiorgi, Ntritsos, Evangelou, & Tzoulaki, 2013). Thus, there is a growing need to consider epidemiological data when reviewing approvals for pesticides. With appropriate care, useful conclusions can be drawn (EFSA Panel on PPR, 2017), but epidemiological studies also have limitations which must be taken into account.

Most epidemiological investigations are observational rather than experimental and, as such, they are liable to "confounding"[p] and subject to various forms of "bias"[q]. In addition, the associations that are observed may be unrepresentative as a consequence of random sampling variation, especially when studies include only small numbers of people who have both experienced the exposure of interest and subsequently developed the health outcome. Depending on the exact circumstances, confounding, bias and chance may cause the health effects of a pesticide to be under- or over-estimated, and findings should therefore be interpreted with caution. Nevertheless, epidemiological studies have successfully identified several adverse effects of pesticides, including hazards of skin cancer from arsenical compounds (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012), and of male infertility from dibromochloropropane (Goldsmith, 1997).

[p] Confounding occurs when the exposure of interest is statistically associated with other factors ("confounders"), which independently determine risk of the health outcome.

[q] Bias is a systematic tendency to underestimate or overestimate a parameter of interest because of deficiency in the design or execution of a study.

3.2.1 Assessment of exposures

The biggest challenge in pesticide epidemiology is the assessment of exposures.

Sources of exposure

The highest exposures to pesticides are mainly occupational, occurring in spray operators and in workers who enter crops after they have been treated (e.g. for harvesting). Because of good occupational hygiene, exposures in the manufacture and formulation of pesticides tend to be lower (although historically that was not always the case). In EU countries, exposures from non-professional use (e.g. in the home and garden) are also generally lower, both because of the way in which non-professional products are formulated and packaged, and because the scale of their use is more limited. Exceptions occur where products are intentionally misused (usually for deliberate self-harm), but such exposures are normally one-off rather than sustained or repeated. Evidence from biomarker studies indicates that exposures from non-occupational proximity to spraying, including from residence near treated crops, is much lower than that which can occur in professional spray operators (Sleeuwenhoek, Cocker, Jones, & Cherrie, 2007). Dietary exposure from consumption of treated crops and their derivatives is generally lower than occupational exposures (González-Alzaga et al., 2017), although historically, potentially significant exposures to bioaccumulative pesticides, such as organochlorine insecticides, have occurred through dietary consumption (Simmonds & Johnston, 1994).

For most important health outcomes, the relevant timing of exposure will be months or years before the onset of disease. Adverse effects on neurocognitive development can result from a short exposure at a critical period during pregnancy, infancy or early childhood, when the brain is still developing (Rice & Barone, 2000). In addition, acute toxicity from one-off high exposures at any age may sometimes be followed by long-term adverse effects (e.g. subtle long-term cognitive impairment following acute organophosphate poisoning) (Chen, 2012). However, in most cases, risk is likely to depend on exposure accumulated over months or years (Takahashi & Hashizume, 2014).

Ascertainment of exposure

Many published epidemiological findings concern associations with exposure to pesticides in general, rather than to specific compounds or groups of compounds, and are of little value for regulatory risk assessment, other than perhaps pointing to particular health outcomes that merit further investigation. To impact more directly

on regulatory decisions, studies must provide information about associations with a specific active substance, or with a class of compounds that are thought to act through a similar toxic mode of action. Quantification of exposures (according to a relevant metric) may allow conclusions about the relationship of risk to level of exposure, but even where the classification of exposure is only crude (e.g. higher than background levels in the general population vs. not), a study may highlight an important hazard.

Exposures are often ascertained retrospectively through the personal recall of participants, or even their next of kin. However, this presents challenges, especially when interest extends to events many years in the past (as for example, in case-control studies of cancer or chronic neurological disease). Reports of previous work with pesticides may be reasonably accurate, but reliable determination of exposure to specific compounds is more difficult. As an alternative, information may be collected on the types of crop that were treated (which may be better remembered), and likely exposures then inferred indirectly by application of a crop-exposure matrix (based on data from other sources).

Personal recall has provided useful information about occupational exposure to pesticides, but recall of non-professional use can be seriously misleading. For example, the ALSPAC survey (Avon Longitudinal Study of Parents and Children) asked pregnant women and their partners how frequently they had used (i) pesticides; and (ii) "weed killers" during the pregnancy, and a validation study was then carried out on a subsample of the 13,433 women who had answered the questionnaire. On detailed questioning, 90% of those who had originally stated that they did not use pesticides, were in fact found to have done so (Nieuwenhuijsen, Grey, & Golding, 2005). The ALSPAC investigators found that more than 85 different pesticide products were stored in the targeted homes, with 76 different active ingredients (Grey, Nieuwenhuijsen, & Golding, 2006). Many pesticides for home use have similar names, and distinguishing between them is not easy.

Biomarkers of exposure

An alternative to personal recall of exposures may sometimes be the use of biomarkers in body fluids or tissues (e.g. blood, hair, urine or adipose tissue). Examples include the measurement of organochlorine compounds or their metabolites, and of dioxins (some of which have contaminated chlorophenols and phenoxy herbicides). However, this is only appropriate where the biomarker reflects the relevant measure of exposure. Modern pesticides have short biological half-lives, and therefore do not give rise to long-term residues in tissues that persist following cessation of exposure, although this may be less of a problem in prospective studies of pregnancy when exposures

during a critical interval may have important long-term impact on the development of the offspring (Engel et al., 2016).

Attempts are now being made to identify new long-term biomarkers for past exposure to pesticides, based on patterns of DNA methylation. The potential for this approach has been demonstrated in relation to cigarette smoking, for which characteristic methylation signatures have been identified that are evident even after an individual has stopped smoking for many years (Ambatipudi et al., 2016). Moreover, there is a specific signature indicative of pre-natal exposure from maternal smoking (Richmond et al., 2015), which persists through to adulthood (Richmond & Joubert, 2017). There is evidence that some pesticides may be associated with unique and specific epigenetic markers of this sort. For example, significant associations have been reported between serum levels of persistent organic pollutants and DNA methylation at a number of sites in the genome (van den Dungen et al., 2017). However, research in this field is in its infancy, and although there have been some promising studies, it is not yet clear whether markers will be found that provide relevant measures of exposure to specific pesticides (or classes of pesticide) with sufficient accuracy to be used in regulatory risk assessment.

Prospective assessment of exposures

Determination of exposures can be easier and more valid when carried out prospectively in cohort studies. Recall of recent exposures should be more reliable than that of exposures many years earlier, and may be amenable to verification by, for example, checking the labels on products. Moreover, shorter-term biomarkers are available for a wider range of pesticides than long-term biomarkers (although currently still only for a minority – e.g. Egeghy et al., 2011). However, the assessment of exposure needs to be repeated regularly over many years (human biomonitoring) to obtain a reliable measure of long-term cumulative exposure. Furthermore, unless the health outcomes of interest are common, the cohorts followed have to be large enough to give adequate numbers of cases for statistically meaningful estimates of risk.

Few such studies have looked at exposure to pesticides, but blood, urine, and breast milk samples are often still available for detailed analysis of pesticide exposure. A small number of cohorts have been devised to look specifically at effects of pesticides (Eskenazi et al., 2003; Robinson et al., 2015; Agricultural Health Study, 2018; Levêque et al., 2015). These have naturally tended to focus on agricultural workers because they have the highest exposures. However, individual agricultural workers are frequently exposed to many different pesticides, which can then make it difficult to relate health outcomes to any one compound. The method has worked best for the

investigation of developmental effects following exposures during pregnancy, where the relevant period of exposure is shorter, the scope for multiple exposure less, and the outcomes of interest can be assessed soon after the exposure. For example, in one study, prenatal exposures to organophosphates and pyrethroids were assessed prospectively through measurement of urinary metabolites, and related to child neurodevelopment at three months of age (Fluegge, Nishioka, & Wilkins, 2016).

3.2.2 Assessment of health outcomes

Approaches to the assessment of health outcomes in epidemiological studies of pesticides are much the same as in other areas of epidemiology, and do not pose any unique challenges. As in other epidemiological research, it is important that health outcomes are clearly and unambiguously specified. In addition, it may assist interpretation if case definitions are harmonised with those used in other investigations.

Historically, many studies of occupationally exposed individuals have focused on cancer, which can be ascertained from cancer registrations as well as from death certificates and hospital records. In addition, because many widely used insecticides are neurotoxic, there has been substantial research on neurological and neuropsychological outcomes in adults such as neuropathy and aspects of cognitive function (Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment 2014). Congenital developmental abnormalities and deficits in neurodevelopment, cognition and behaviour in childhood have been another focus, because the fetus and infant are particularly vulnerable to toxic effects of some chemicals (García et al., 1998; Shi & Chia, 2001; Grandjean & Landrigan, 2014; Martin-Reina et al., 2017). Other potential health outcomes have received less attention, often because toxicological evaluation suggests that they are less likely to be a problem (Ntzani et al., 2013). There could, however, be benefit from more epidemiological research on some less serious health effects such as contact dermatitis and acute irritancy.

In addition, greater use could be made of validated intermediate outcome measures (surrogate outcomes) that indicate an increased risk of harmful health effects (e.g. low birth weight for gestational age, which is predictive of disease not only in infancy but also in adult life) (Godfrey & Barker, 2001).

Recent research in rodents (Klengel, Dias, & Ressler, 2016) and in humans (Pembrey, Saffery, & Bygren, 2014) has suggested that environmental exposures, including to pesticides, may have transgenerational effects (possibly through inheritance of epigenetic changes). There is a need for further investigation of this phenomenon, which might indicate an increased risk of adverse health outcomes in the descendants of those who have been exposed.

3.2.3 New developments in study design

Several new developments in epidemiological study design and analytical techniques could lead to improvements in the evidence that supports risk assessment for PPPs (EFSA Panel on Plant Protection and their Residues, 2017).

Hypothesis-free environment-wide association studies

By analogy to hypothesis-free Genome-Wide Association Studies (GWAS), it has been proposed that Environment-Wide Association Studies (EWAS) could be useful to screen for unsuspected environmental causes of disease (Manolio et al., 2012). This would entail characterisation of each individual's "exposome", which is a measure of multiple exposures that they have experienced (Wild, 2012). The method has been applied in a study of type 2 diabetes using biomarker data from the National Health and Nutrition Examination Survey (NHANES) in the United States, which identified a possible association with the pesticide derivative heptachlor epoxide (Patel, Bhattacharya, & Butte, 2010). Exposomes can be determined using information not only from biological assays, but also from questionnaires or environmental measurements. For example, the ALSPAC study has assembled exposomes for its participants using biological and non-biological, environmental data collected from conception onwards, including from parents and grandparents (Golding et al., 2014).

Like GWAS studies, EWAS studies must be interpreted with caution. When large numbers of mutually independent associations are assessed, it can be expected that some will be statistically significant by chance, even if there are no true causal relationships. Moreover, exposure to a chemical varies over time, and can therefore be characterised in many ways. In the absence of a prior hypothesis, there is no basis for assuming that one exposure metric will be more relevant than another. Although the studies are, by their nature, only hypothesis-generating, they can provide an indication of possible effects or lack of effects. Where associations are found, other cohorts can be examined, and/or corroborative evidence sought from elsewhere.

Mendelian randomisation

As already described, confounding is one of the major challenges in observational epidemiology. To finesse this problem, Mendelian randomisation studies assess the association of disease with genes that modify the metabolism of chemicals of interest (Smith et al., 2007). For a given exposure, such genes may alter the internal dose of a chemical, and therefore the risk that it will cause adverse effects (Smith & Ebrahim, 2003). Moreover, the genes are fixed throughout life, and generally are unlikely to influence, or be statistically associated with, the extent to which individuals are

exposed externally (ibid.). Thus, an association between a disease and a gene which increases internal levels of a chemical may be a strong indication that the chemical causes the disease.

In theory, Mendelian randomisation studies might be used to explore possible hazards of pesticides. In any such study, the relationship between genotype and phenotype should be known or established. In addition, detection of an effect will require an adequate prevalence within the study sample, both of the relevant gene, and also of sufficiently high exposure to cause effects in those who have the genetic susceptibility (Costa, Giordano, Cole, Marsillach, & Furlong, 2013). In practice these conditions may not often be met, and as yet there are no examples of such studies on pesticides that have been telling. A further problem is ensuring that the genetic marker does not also indicate differences in other aspects of metabolism, which independently influence the outcome under study. That may require assessment of its association with the health outcome in the absence of exposure to the pesticide (or at least with exposure below some threshold level), and therefore a need to determine exposures reliably.

Cohort studies in the general population

A point of debate is whether, given recent advances in techniques for the measurement of biomarkers, greater resources should now be invested in cohort studies in the general population. Although the highest exposures to pesticides are generally occupational, those involved represent a relatively small proportion of the general population, and are likely to be less susceptible to some adverse effects than, for example, the very young and the elderly.

There are currently a large number of cohort studies in Europe, which were designed to assess the influences of environmental factors on health and well-being over time (Vrijheid, 2015). Many have collected and stored biological samples (often with repeat samples from the same individuals), and with advances in biomarker technology, it is possible that these could be used to assess pesticide exposures (Burton, Fortier, & Knoppers, 2010). One way forward could be to bring together a team of scientists to collate material from a number of such studies, and organise appropriate biological and statistical analyses, looking at the relationship between different markers of the various modes of exposure to pesticides and a range of health outcomes

Advantages of using cohort studies in this way would include:
- the use of prospectively collected data and samples, making it less prone to bias;
- the use of uniform analytical methods for biological measurements;
- all results could be published electronically, obviating any bias from selective

publication;

- greater statistical power and opportunities to assess the consistency of findings across different studies;
- the potential to investigate gene-environment interactions and interactions between environmental factors, which might explain differences in results between cohorts.

Given that the data and samples have already been collected, this exercise could be relatively inexpensive and could provide valuable feedback to inform the design and conduct of new studies, although it would depend heavily on the validity of available assays for relevant metrics of exposure. Furthermore, even with the inclusion of multiple cohorts, statistical power for many disease outcomes would still be rather limited. However, there could be greater scope to assess effects on parameters indicative of disease processes. For example, in adults an effect on bone mineralisation might point to an increased risk of pathological osteoporosis; higher levels of depressive symptoms could indicate a greater risk of clinical depression; and an overall reduction in measures of cognitive function might be paralleled by an increased risk of dementia. In children, higher mean Body Mass Index (BMI) could indicate a greater risk of clinical obesity, and effects on measures of hyperactive behaviour might point to increased risk of frank Attention Deficit Hyperactivity Disorder (ADHD). It would also be possible to examine biomarkers such as telomere length and epigenetic age, which may reflect propensity to disease outcomes (see Annex 4 section 5 for further details).

3.2.4 Other uses of epidemiology

While most epidemiological research on pesticides focuses on their associations with illness and disease, epidemiological methods can also contribute to regulatory risk assessment in other ways. For example, with biomarkers as outcome measures, they can be used to explore the distribution and determinants of personal exposures to pesticides in different situations (for an example see Castorina et al., 2010). The potential for future developments in this area is discussed further in the section on exposure sciences that follows.

3.3. EXPOSURE SCIENCES

Exposure sciences contribute to regulatory risk assessment for PPPs both in the generation of epidemiological data, and in the modelling of potential exposures that will be set against toxicological reference values to determine their acceptability. Potential advances in exposure assessment for epidemiological research have already been discussed, but there is also scope for improvement in exposure modelling.

3.3.1 Modelling of exposures

Much work has been done in recent years on the assessment of dietary exposures to pesticides, in particular through the ACROPOLIS project (Aggregate and Cumulative Risk Of Pesticides: an On-Line Integrated Strategy; EFSA Panel on PPR, 2012a). However, more effort is needed in relation to other exposure pathways.

Modelling the potential exposures of consumers, operators, workers, bystanders, and residents entails application of standardised algorithms to relevant parameters (EFSA, 2014). In some cases, the parameters are determined empirically from ad-hoc studies, but more often default values are used according to the nature of the product and the way in which it will be used. The default values are themselves derived empirically, often from multiple studies, but there is a need for further research to refine those that are less well supported, and to test the overall validity of the modelling method. Examples of this are investigations carried out by the Institute of Occupational Medicine (UK), which used biomarkers to assess the exposures of operators and residents to various pesticides (Sleeuwenhoek, Cocker, Jones, & Cherrie, 2007; Galea et al., 2015). A particular priority is the exposure of workers, which can sometimes be relatively high, and which to date has been studied less than that of operators.

Option 3. Further investigation is needed on the levels and determinants of exposure in workers who enter crops that have been treated with PPPs to support refined modelling in risk assessment.

3.3.2 Scope for mitigation measures

Exposures to PPPs during their application can be reduced by good engineering. For example, levels of exposure in operators of boom sprayers who handle concentrated formulations can be lowered through use of low-level filling systems or closed-transfer systems. Spraying systems with low-drift nozzles have been developed, which reduce the quantities of airborne spray by more than 75%, and in many cases can be used without substantially reducing product efficacy (Butler Ellis, Miller, & Orson, 2008). And the development of sensors and computer-based control systems as part of precision-farming approaches means that it is now possible to design and construct spraying equipment that automatically complies with regulatory requirements relating to wind speed and direction. Prototypes of such equipment are currently being developed. While technology of this sort can be recommended as best practice, it is unclear how much reliance could be placed on its correct use to mitigate potential risks to health that would otherwise be unacceptable.

The same applies to other measures such as buffer zones. It is unclear how closely operators comply with specified buffer zones, and therefore whether buffering could confidently be used to support an authorisation of a product that would not otherwise be possible. Currently, some EU Member States allow the use of buffer zones as a prescribed measure to protect human health, while others do not.

To resolve this uncertainty, more information is needed about the "real life" behaviours of operators regarding the use of equipment and application techniques. And because there could be major differences across the EU, this needs to be examined at Member State level. Several surveys have already been conducted within and across EU Member States, but these have mainly been based on questioning of operators/owners rather than direct observation of practice (Butler Ellis et al., 2017; Glass et al., 2012).

In addition, more clarity is needed on the efficacy of mitigation measures. Where buffer zones have been required by EU Member States (e.g. for environmental protection), the widths specified have mainly been based on data from studies conducted in Germany (Ganzelmeier et al., 1995; Rautmann, Streloke, & Winkler, 2001), but this has recently been called into question by new research from the Netherlands showing very different results (van de Zande, Rautmann, Holterman, & Huijsmans, 2015). Also, while a number of EU Member States (including the UK, Netherlands, Germany, France, Sweden, and Belgium) now have schemes for classifying the drift-reducing capabilities of application systems (mainly based on nozzle specifications that are used in adjusting buffer zone distances), there are differences between them, and there is no agreed approach to classification. There is a need, therefore, to improve and harmonise definitions of drift-reducing capability.

Option 4. EU Member States should conduct studies to explore the "real life" behaviours of operators regarding the use of equipment and application techniques and the extent to which such approaches can be used to manage or reduce exposures.

4. Improving the methods of regulatory risk assessment

Alongside improvements in the scientific evidence to inform regulatory risk assessment for PPPs, it is important to ensure that available data are evaluated optimally. In this section we consider various ways in which the methods of risk assessment might be enhanced.

4.1. DATA REQUIREMENTS

4.1.1 Flexibility

To support the evaluation of PPPs, applicants for approval are required to submit a dossier for each active substance, covering a standard list of data requirements. There could, however, be advantages in allowing greater flexibility, particularly when previously approved pesticides are re-evaluated for continued approval, with the requirements for, and sufficiency of, data being decided more by the risk assessor. A more flexible approach of this type might, for example, allow read-across between chemicals with similar toxic mode of action, and could exploit new developments in toxicology as they emerge, in some cases reducing the use of laboratory animals. There might also be benefits from more frequently targeting re-evaluations to those aspects of the risk assessment that the assessor considers to be of greatest concern (e.g. when new epidemiological evidence suggests a possible risk to health).

In applying a more flexible approach, however, care would be needed to avoid unjustifiable inconsistencies in the treatment of different chemicals.

Option 5. At the discretion of the risk assessor, allow more flexibility in the scope of re-evaluations for continued approval of active substances, and in the data that are required to support them.

4.1.2 Mouse carcinogenicity study

Currently, one of the standard data requirements for active substances is a mouse carcinogenicity study, which rarely, if ever, provides information of value in the risk assessment of the compound (Billington, Lewis, Mehta, & Dewhurst, 2010; Osimitz, Droege, Boobis, & Lake, 2013). There is a case for reviewing whether this requirement is justified and, if not, whether any alternative test should replace it.

Option 6. Based on current evidence, the routine requirement for a mouse carcinogenicity study to support the approval of active substances should be reassessed.

4.1.3 Historical controls

The evaluation of toxicological studies in animals may sometimes be assisted by consideration of historical control data, in particular where there is concern that the incidence of an outcome in contemporary controls may be unrepresentative because of random sampling variation. Although current regulation sets certain criteria for the use of historical control data, it also allows applicants to submit such data at their discretion from an unknown number of control datasets. Therefore, the submission of historical control data tends to be limited to circumstances in which it could improve the case for approval.

Option 7. Require that reports of toxicological investigations submitted in support of applications for approval include all relevant historical control data that meet specified criteria.

Option 8. Place maintenance of historical control data records in the hands of a public statutory body.

4.2. ASSESSMENT OF POTENTIAL TOXICITY

4.2.1 Points of departure from toxicological studies

Currently, the points of departure used to derive toxicological reference values are normally No Observed Adverse Effect Levels (NOAELs)[r]. However, this has several drawbacks, including a failure to reflect statistical uncertainties (which will vary according to sample sizes in the studies considered for NOAEL identification, dose spacing, sensitivity of the endpoint being measured and the shape of the relevant dose-response curve) (EFSA Scientific Committee, 2017b). An alternative is to use the corresponding Benchmark Dose (BMD)[s] . To derive the reference point for establishing a health-based reference value, the lower bound of a BMD confidence interval (BMDL) is used (EFSA Panel on PPR, 2014). This approach has lately been recommended

[r] The No Observed Adverse Effect Level (NOAEL) is the highest dose level in an in-vivo toxicity study at which, based on statistical comparison with unexposed contemporary controls, together with any other relevant considerations (e.g. findings at higher doses), there is judged to be no clear evidence of any treatment-related adverse effect

[s] The Benchmark Dose is an estimate of the dose that causes a low but measurable effect (e.g. a 5% reduction in body or organ weight or a 10% increase in the incidence of kidney toxicity), referred to as the Benchmark Response (BMR). The BMD is usually determined by computational fitting of a series of empirical dose-response curves (mathematical relationships between the two variables, dose and response) and selecting those that provide statistically satisfactory fits to the data.

by EFSA (EFSA Scientific Committee, 2017b) and, although the current international guidelines for study design have been developed with the NOAEL approach in mind, they do not preclude application of the BMD approach.

Option 9. Where appropriate, BMDs should be used in preference to NOAELs for establishing toxicological reference values. To support this, consideration should be given to study designs that are better suited to estimation of BMDs than those currently employed.

4.2.2 Developmental neurotoxicity

Currently, two study guidelines (Test Guidelines TG 426 and TG 443) are internationally accepted for the direct assessment of developmental neurotoxicity by chemicals. While neither investigation is routinely required for all active substances, their conduct can be triggered by the observation of neurotoxic effects in standard repeat-dose testing, a known neurotoxic mode of action, or a molecular structure suggestive of neurotoxic potential. In practice, however, this does not often happen. Thus, out of 450 pesticides that have been approved in the EU, 35 were tested by TG426, and none by TG443 (which is a relatively new guideline; OECD, 2017). A group of regulators, academic scientists and scientists from industry recently agreed that there is a need for a better testing strategy for developmental neurotoxicity of chemicals, based on mechanistically-informed, fit-for-purpose in-vitro batteries of tests, which could be applied more widely than the testing that is currently employed, and used to trigger more targeted in-vivo studies (EFSA Panel on PPR, 2013; Bal-Price et al., 2015; Tyl et al., 2008; Fritsche et al., 2017).

Option 10. Regulators should refine strategies for the assessment of developmental neurotoxicity, incorporating mechanistically-informed in-vitro tests.

4.2.3 Integration of data from different sources

When new active substances are first considered for approval, the data used to assess toxicity generally come only from toxicological tests performed in accordance with published guidelines. However, when extant approvals are reviewed, relevant information may be available also from less standardised toxicological studies and/or epidemiological investigations reported in the peer-reviewed scientific literature (Committee on Endocrine-Related Low-Dose Toxicity, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, & National Academies of Sciences, Engineering, and Medicine, 2017). In these circumstances, the determination of toxicological reference values is less straightforward because the weight that can be given to each study will depend on its quality and the nature of any inherent biases.

Traditionally, the approach has been to evaluate each of the available investigations separately, and then to establish each reference value using the single study that is judged to provide the most relevant point of departure. There is a need, therefore, for better methods of integrating data on toxicity from multiple studies of varying design and quality. As well as accounting for the strengths and limitations of each study individually, these should address the possibility of publication bias, which reflects a tendency for positive findings to be submitted and accepted for publication preferentially.

Current regulation (EU) No 1107/2009 mandates that epidemiological evidence should be used for risk assessment where available from studies conducted in accordance with recognised standards and supported by data on levels and duration of exposure. However, it is unclear to what recognised standards for the conduct of epidemiological research this refers, and what level of information is required regarding levels and duration of exposure. It is easy to conceive circumstances in which epidemiological results could be telling even though there was only minimal information about levels of exposure. For example, the demonstration of an extremely high relative risk of angiosarcoma of the liver among chemical operatives exposed to vinyl chloride monomer did not require information on levels of exposure to establish that there was a hazard (Fox & Collier, 1977). In theory, a similar scenario could occur for a pesticide.

Applicants submitting dossiers for approval of active substances are obliged to provide any relevant peer-reviewed and publicly available scientific literature, and guidance for this exists for approval of active substances (EFSA, 2011). However, there is no explicit framework for searching, summarising, and evaluating the published literature. Methods have long been developed for the formal synthesis of epidemiological evidence, and are now widely used in published systematic reviews and meta-analyses (Cooper, Hedges, & Valentine, 2009). These include a structured step-wise approach implementing standardised methods for: defining eligibility criteria for the evidence base under study; searching for the totality of the evidence across multiple databases; retrieving the available evidence; extracting detailed study-level information including study design characteristics, point estimates and measures of uncertainty; assessing heterogeneity (between-study variation); grading the quality of individual studies; assessing risk of bias at the individual study level; assessing reporting bias (including publication bias); performing sensitivity analyses; and finally calculating summary estimates for the parameters of interest under different assumptions (Higgins & Green, 2011). From the stages briefly cited above, it is evident that for a systematic review and meta-analysis to be included in the risk assessment process, it should have been conducted with rigour and its methods should be reported fully (Moher, Liberati, Tetzlaff, & Altman, 2009). Selective inclusion of evidence in a systematic review and

meta-analysis at the discretion of those conducting or commissioning the evidence synthesis can lead to spurious results and misleading conclusions.

It should be possible to apply similar methods in the review of toxicological evidence. More challenging is how best to weigh toxicological results alongside those from epidemiology when drawing overall conclusions (Moher et al., 2009). There are no simple means by which this can be achieved, but approaches have recently been suggested that may lead to guidance. Certainly, the risk assessors who undertake the task should have a good understanding of both disciplines. For practical reasons, the approach adopted may need to vary according to the nature and extent of evidence that is available and the level of scientific and public concern about a pesticide.

Option 11. Further development and evaluation of methodologies for quantitative and qualitative synthesis of evidence from non-standardised toxicological and epidemiological studies should be encouraged.

4.3. POST-MARKETING SURVEILLANCE

Once a PPP has been approved for commercial use, a system of post-marketing surveillance is needed to check that it does not cause unanticipated human health problems, and to pick up any evidence of such problems at an early stage. Part of the responsibility for this rests with approval holders, who are legally required to notify the regulator if adverse information comes to their attention (Ayres & PAHES Working Group, 2012). However, governments can add usefully to this in two ways.

4.3.1 Reporting systems for acute health effects
Possible acute health effects are best monitored through reporting schemes, the assumed link to a PPP depending on their nature and their timing in relation to exposure. To be of most value, it is helpful if notifications include information about: the identity of the PPP that is suspected of causing the health problem; the circumstances and extent of exposure (which could be through normal use, accidental misuse or intentional misuse); and the nature of the health problem, including its timing in relation to exposure. However, it is worth recording suspected cases even where full information is not available. The best methods for collecting such information will vary by EU Member State depending on the organisation of health care systems. However, there is a case that each Member State should have some scheme for systematic ascertainment of acute illness that is suspected of being caused by PPPs, and that data obtained should be transmitted to EFSA for collation with those from other Member States, and central analysis. As far as possible "toxidrome"[t] diagnostic criteria should be EU-wide, and any improvements in medical education (especially

doctors' training in toxicology) that are needed to support this should be encouraged (EFSA Panel on PPR, 2017; Ayres & PAHES Working Group, 2012; Thundiyil, Stober, Besbelli, & Pronczuk, 2008).

Option 12. Each EU Member State should have a scheme for systematic ascertainment of acute illness that is suspected of being caused by PPPs, and the data obtained should be transmitted to EFSA for collation with those from other EU Member States, and central analysis.

4.3.2 Periodic monitoring of the peer-reviewed literature

Unlike acute toxicity, chronic health effects can rarely be ascribed to a chemical exposure with confidence in the individual case (exceptions occur when the relative risk is high or there are particular clinical features which establish the link with exposure), and therefore cannot be monitored adequately through reporting schemes. However, indications of unrecognised hazards may emerge from controlled epidemiological studies. In addition, cases of sensitisation to PPPs are from time to time reported in scientific papers (e.g. Guo, Wang, Lee, & Wang, 1996.). It is important, therefore, to monitor the published scientific literature at regular intervals to check for case reports and epidemiological studies that might have implications for the regulation of PPPs (as has been done for some years in the UK by the Health and Safety Executive's Medical and Toxicology Panel). Relevant publications can then be collated in a central database.

Option 13. A system should be established to monitor the peer-reviewed literature at appropriately frequent intervals for epidemiological papers and case reports concerning human health effects of PPPs.

4.4. GROUPING OF ACTIVE SUBSTANCES AT REVIEW

In general, review of previously approved active substances will work best if they are grouped according to their pesticidal mode(s) of action (e.g. looking at cholinesterase-inhibiting organophosphates as a group). This will facilitate a consistency of approach, and highlight compounds for which the risk assessment may be less reassuring. This is an area of active progress for EFSA in the EU, and the EPA in the United States of America (EFSA Panel on PPR 2014; EPA, 2016).

[t] Toxic syndrome or toxidrome is a constellation of toxic effects comprising a set of clinical fingerprints for a group of toxic chemicals.

Option 14. When reviews are conducted of previously approved active substances, compounds with the same pesticidal mode of action should be assessed in one process.

4.5. TOXICITY OF CO-FORMULANTS

In addition to their active ingredients, PPPs contain a wide range of co-formulants with varying chemical properties and potential for toxicity. Currently, the toxicological assessment that is required for co-formulants is much more limited than for active substances, which are designed to be biologically active, and therefore tend to be intrinsically more hazardous. Nevertheless, some co-formulants could pose risks to health, either in their own right, or in combination with the active substance and other constituents of the formulated product (Cox & Surgan, 2006; Eddleston et al., 2012). There is provision currently for a published list of chemicals that may not be included as co-formulants in PPPs, but so far, no compounds have been placed on the list.

A preferable approach might be to develop a positive list of chemicals that could be considered for inclusion as co-formulants in PPPs, supported by a more rigorous system for their toxicological evaluation. For reasons of efficiency, the methods used could start with a preliminary assessment based on molecular structure and any readily available information about the safety of the chemical when used for other purposes (including from the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) database) (Dobe et al., 2017). Those that were judged to be of greater toxicological concern could then be subject to more detailed evaluation, with data requirements determined by the risk assessor (care would be needed to ensure a consistency of approach). This evaluation, including outcomes such as potential for irritancy and sensitisation, could then be placed in a published database, and available for use when assessing the safety of products that included the chemical. Care would be needed to ensure that the evaluations were consistent with those published by other agencies such as ECHA, any discrepancies being resolved by discussion.

Option 15. A more rigorous system should be developed for tiered assessment of the toxic potential of chemicals intended for use as co-formulants in PPPs, with a published list of those deemed potentially suitable, and a published database summarising their toxicological characteristics.

4.6. TOXICITY OF FORMULATED PRODUCTS

Once separate assessments have been made of the active substance(s) and co-formulants that are contained in a PPP, there is a need to determine the toxic characteristics of the mixture as a whole, taking into account their concentrations and potential for toxic interaction. To avoid unnecessary duplication of activities, it would be sensible if this were carried out with products grouped according to concentration ranges of the co-formulants. For example, one might consider a suspension concentrate with a 1-5% content of emulsifier A, 1-3% of antifoam agent B, etc. The assessment would take into account the properties of the active substance and individual co-formulants as already determined, and would pay special attention to any potential for additivity or synergy, either because of shared toxic modes of action, or through toxicokinetic effects.

Those products that were deemed potentially suitable for use as PPPs could then be included in a published list, along with a summary of their evaluations.

Option 16. A uniform system should be developed for the assessment and public listing of formulated products (containing specified active substances and co-formulants in specified concentration ranges) that have been accepted as potentially suitable for use as PPPs.

4.7. COMPARATIVE RISK ASSESSMENT

PPPs are authorised only when there is adequate confidence that their use will not cause adverse health effects. However, even where this applies, for a specified use, the ratios of exposures to relevant toxicological reference values may be lower for one product than another. There is a case that this information should be considered when choosing between products, along with other factors such as the potential for adverse environmental impacts, possible between-product differences in efficacy, and potential for pest resistance. The information is not currently made available to purchasers and their advisors, but if it were, other things being equal, it might promote the use of products offering the greater reassurance of safety.

To add this refinement would entail little extra work for the assessor. Moreover, it might encourage manufacturers to develop products with a better safety profile. However, it would only be worthwhile if it had impact on the choices made by users, and there is a danger that it could cause confusion by suggesting that some products were safer than others (strictly the difference would be in reassurance of safety rather than level of risk). It should be noted that this idea goes beyond the current substitution

principle, which has been an element of regulation for PPPs since 2009, and is based more on hazard than on the reassurance of safety when products are used according to conditions of authorisation.

Option 17. Develop a simple scheme that would help users in choosing between PPPs for a specified application, by indicating those with smaller margins between exposures and relevant reference values.

4.8. MIXTURES

Current regulation requires consideration of the risks from exposure to multiple active substances in combination, either simultaneously or in sequence (cumulative risk assessment). Ways of addressing this in relation to dietary exposures and the setting of maximum residue levels are being developed and will soon be implemented (Kennedy et al., 2015; EFSA Panel on PPR, 2014). At present, however, cumulative risk assessment for operators, workers, bystanders, and residents is only conducted to a limited extent. When a PPP containing more than one active substance is assessed, the potential for combined effects is considered through a simple tiered approach. However, this is not harmonised across Europe, and the North and the Central zones have developed their own separate guidance. More complex scenarios, such as the use of tank mixes and sequential applications to the same crop over the course of a season, are considered even more rarely (in the UK, a methodology has been applied to common tank mixes) (Boobis et al., 2008).

The main obstacle to cumulative risk assessment for these non-dietary exposures is the lack of data on patterns of exposure to different PPPs over time in the same individual. One possible approach would be to develop a landscape-based assessment of the probability of exposure across space and time, integrating information on patterns of use and market penetration (including that submitted under Directive 2009/128/EC on establishing a framework for Community action to achieve the sustainable use of pesticides, under Regulation EC 1907/2006 on Registration, Evaluation, Authorisation and Restriction of Chemicals, or by applicants and other stakeholders), and on field structure and placement within the landscape. This would give a probability of exposure to a given PPP for any specified location and time. A drawback, however, is that the levels of exposure could vary widely, according to exactly what the individual was doing and where (a distance of only a few metres could make a large difference to levels of exposure, as could barriers such as hedges and walls).

An alternative option would be to start by focusing on the situations in which combined exposures are most likely to occur (e.g. from use of tank mixes and products that

are often used in sequence on the same crop), and to collect empirical data on the patterns of exposure in samples of operators and workers (evidence from biomarker studies suggests that the exposures of residents will be difficult to distinguish from background levels (Galea et al., 2015)). This could help to inform the development of a standardised method for the authorisation of tank mixes by EU Member States. The main concern is exposure to multiple active substances with similar toxic mode of action, and to co-formulants in one product that might modify the uptake of an active substance that was present in another product from the same tank mix.

Option 18. A standardised method should be developed for the authorisation of tank mixes by EU Member States. In the longer term, methods should be developed to assess risks to operators and workers from sequential use of different PPPs on the same crop, and perhaps the health risks from sequential use of combinations of PPPs on neighbouring crops.

4.9. AGGREGATE EXPOSURES

Some active substances in PPPs also have other uses, and it is therefore possible that a person could be exposed to the same substance from multiple sources. For example, many of the pesticidal fungicides and insecticides are also used in biocides and in some veterinary (and human) medicines. The potential for harm to health from aggregate exposures across different uses is not currently considered in regulatory risk assessment in the EU, despite the availability of both developed and emerging methodologies on aggregate exposure pathways (Teeguarden et al., 2016; van der Voet et al., 2015). The relevance of aggregate exposures to decisions in risk management will depend on the relative contributions from different sources. If, in a given scenario, one source is strongly predominant, then the potential contributions from the other sources will be of little consequence.

Option 19. Aggregate exposure to chemicals should be accounted for in risk assessment across EU regulations where relevant.

4.10. NANOPESTICIDES

Development of nano-sized active ingredients and formulations[u] has potential to

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[u] Materials that meet the criteria for a nanomaterial are defined in the Novel Food Regulation (EU) No 2015/2283 and Regulation on the Provision of Food Information to Consumers Regulation (EU) No 1169/2011. In addition to the nanomaterials that have particle sizes in the defined nanoscale (1-100 nanometers), other very small particles in size classes just above or below this band may be produced that also have properties which stem from their size. "Nano tails" in the size range of interest are already present to an undefined extent as components of existing products (e.g. following milling).

enhance the delivery and efficacy of pesticides and other agrochemicals (Kah, 2015). It is claimed that nanopesticides will reduce the overall use of PPPs through enhanced efficacy and better control of applications in the field. Other projected benefits include better stability of dispersions, and slow- or controlled-release of the active ingredients. Enhancement of efficacy might, however, be accompanied by increased risks to human health and the environment (ibid.).

Currently no nanomaterial-based PPPs are approved for use in the EU, although the first US-approved nanopesticide (HeiQ AGS-20) is under consideration at ECHA as a biocide. In the USA, HeiQ AGS-20, a nanosilver for use on textiles to suppress bacteria that cause odours and stains, was submitted to a lengthy approval process that was extended and required accompanying consultation with the Science Advisory Panel. Further data and worker-protection measures were required for the product registration. Standardised protocols do not exist for several of the studies that were asked of the nanosilver registrants, these included studies on particle-size distribution and leaching.

Nanomaterials can also be used as PPP co-formulants. However, since there is no database centrally registering PPP formulations, it is not clear if any nanomaterials are already approved in the EU for such use. One relevant study concerns amorphous silica nanoparticles as a co-formulant for pesticide-related use (Mei-Rong, Shu-Min, Fei, Yu-Ru, & Cai-Ling, 2012.); synthetic amorphous silica (CAS No 112926-00-8) has already been approved as an existing active substance for use in insecticides.

Option 20. Definition of the term "nanopesticide" should be reviewed to ensure that it comprehensively includes all relevant microformulations that are engineered to confer greater efficacy and enhanced safety.

Option 21. Development of a standardised risk-assessment procedure for the approval of PPP nano-components (active substances and co-formulants).

4.11. BIOPESTICIDES

Biopesticides encompass three different types of active substance: microbial organisms, pheromones and attractants (chemicals with no direct toxic action on the pest), and natural extracts mostly from plants (botanicals). Pheromones and natural extracts are chemicals, and therefore from a scientific perspective the chemical risk assessment process and data requirements are appropriate. Risk assessment for microbial active substances follows different principles and should involve other scientific disciplines. For microbials acting through the production of metabolites,

a combination of microbiology and toxicology is needed. A number of guidance documents have been produced, mostly under the auspices of the OECD (OECD, 2014a), to address this problem, and these could be integrated into the PPP data requirements to make them more relevant, unambiguous, and flexible.

Option 22. Revision of the microbial data requirements for active substances and for plant protection products.

4.12. ASSESSMENT OF UNCERTAINTY

One possible source of inconsistency in decisions on the authorisation of PPPs is the handling of scientific uncertainty. Risk assessors may differ in their evaluation of whether available data give adequate reassurance of safety, either because they have differing confidence in the conclusions that can be drawn from the findings, or a divergent understanding of the level of confidence that risk managers require (reflecting ambiguity in the qualitative expressions that are currently used to express levels of confidence).

The problem is less for new active substances, evaluation of which is normally based on a standard set of toxicological and other studies that have been carried out in accordance with internationally agreed protocols. Toxicological reference values are largely established according to well-recognised principles, with application of standard assessment factors, and potential exposures are calculated by following standardised methods, based on known distributions of exposure. However, the level of confidence achieved by these procedures is generally expressed in qualitative rather than quantitative terms. Furthermore, assessors sometimes differ in the point of departure that they choose when establishing a reference value, or opt to apply a non-standard assessment factor.

There is much greater potential for inconsistency in assessments when approvals for products are reviewed, because the weight that is given to results from non-standard studies may vary substantially. Moreover, it may not be obvious whether the reassurance of safety is greater or less than that which would be required for first approval.

In response to this challenge, it is now the policy of EFSA that formal uncertainty analysis be conducted as part of risk assessment. As a starting point, risk managers indicate their protection goal and the required level of confidence that it will be achieved (EFSA Scientific Committee, 2018). Risk assessors then determine whether the standard approaches for risk assessment provide the required level of confidence,

and adjust them if necessary. This done, the standard approaches can be applied in the normal manner. Further de-novo evaluation of uncertainty is needed only in assessments that are subject to non-standard uncertainties (e.g. missing or poor-quality data, or special considerations). When non-standard uncertainties are present, there is a range of options for addressing them, depending on what is proportionate for the case at hand. In all cases, the conclusions of the process may be expressed in the same manner as at present. However, they will be underpinned by more rigorous and transparent assessment of uncertainty, which should clarify the level of confidence for risk managers and help them to understand and resolve the reasons for diverging assessments. A draft guidance document has been subject to public consultation, and the technical report on this consultation published (EFSA, 2016). A revised draft of the guidance was published in March 2016 and tested in pilot studies in each area of EFSA's work, including PPPs. This led to a final version published in January 2018 (EFSA Scientific Committee, 2018).

A systematic approach of this sort does not exclude expert judgement, but ensures that the uncertainties affecting different parts of the risk assessment process are not overlooked, and is therefore seen as more secure. It increases the workload of risk assessors when non-standard uncertainties are present, but it is anticipated that this can be managed through an iterative approach starting with simple procedures, and only proceeding to greater levels of scrutiny where it is warranted. Methods such as sensitivity analysis may be deployed to distinguish sources of uncertainty that are particularly of concern.

Wherever possible, assessors are expected to quantify uncertainties when they find them, and procedures for combining the quantitative elements are being tested in different settings. In an emergency there may not be time for a full uncertainty assessment, but for most assessments a standardised uncertainty protocol is expected to evolve, becoming more routine and less burdensome. More consistent formal reporting of uncertainty should make it easier to repeat and check assessments.

There is a danger, however, of spurious precision in quantitative expressions of confidence, although EFSA's guidance is designed to avoid this. A risk manager might for example seek 99% confidence that his/her protection goals will be achieved (i.e. that on average the protection goal will be achieved in 99% of assessments). However, while evidence may sometimes emerge that a protection goal of zero risk has manifestly not been achieved (through demonstration that adverse effects had occurred), there is no way of ever being certain that a zero-risk protection goal has been attained. There will always be a possibility of unrecognised adverse effects. With a less stringent protection goal (e.g. risk less than 1%), one cannot even be certain that

it has not been achieved because the proportion of PPPs with documented adverse effects will be subject to statistical uncertainty. Thus, numerical levels of confidence cannot be empirically validated. In large part, they reflect the subjective opinions of risk assessors, which may differ importantly from one to another.

The main value of formal uncertainty analysis may therefore lie in promoting consistency between risk assessments (by ensuring that individual sources of uncertainty are explicitly identified and evaluated consistently), in identifying reasons for any major differences between risk assessors in their confidence that a protection goal will be achieved, and in increasing the transparency of risk assessment.

Option 23. As formalised quantification of uncertainty is introduced, its benefits and costs should be evaluated to identify where it is of most value, and how it can be made most efficient.

5. Improving the organisation of risk assessment

One of the factors that may contribute to inconsistencies in the assessment and management of risks from PPPs in the EU is an unsatisfactory division of labour between EFSA centrally and regulatory authorities in individual EU Member States (Annex 3). The optimal allocation of tasks will depend in part on practical and political considerations that lie outside the remit of this report. However, we can make observations from a scientific perspective.

Ideally, EFSA would be responsible for all aspects of risk assessment that could be common to all EU Member States. This would include:

- The evaluation and interpretation of scientific studies on active substances, co-formulants, and products that were submitted in support of approval, or were identified from other sources as being relevant to approval.

- Setting key endpoints that would be used in risk assessment, such as those relating to chemical properties, toxicological reference values, and maximum residue levels for specified crops.

- Standardisation of generic approaches that would be used in risk assessment – for example, in estimating the potential exposures of applicators, workers, bystanders, residents, and consumers, and when considering potential toxicity from multiple chemicals in combination and/or aggregate exposures.

Representatives of Member States should have the opportunity to comment on and discuss draft findings before they were finally agreed so that a harmonised regulation is developed.

As an outcome of this process, EFSA would publish:

- Lists of active substances and co-formulants that could be included in PPPs submitted for approval within the EU for use on specified crops, together with associated endpoints (e.g. relating to chemical properties, toxicological reference values, maximum residue levels).

- A list of products based on the listed active substances and co-formulants, which

could be considered for authorisation by individual EU Member States, together with associated key parameters (e.g. relating to chemical stability, acute toxicity, skin sensitisation).

- Generic methods, to be applied when individual EU Member States conduct risk assessments for specific uses of products on the EFSA list (e.g. for estimating potential exposures of operators and consumers).

Individual EU Member States would then consider applications for specified uses of listed products within their jurisdiction, taking into account local circumstances (e.g. agricultural practices, climate, pest pressures, pesticide resistance) and relevant aspects of national law (e.g. environmental regulations). In coming to decisions, they would apply the generic methods that had been standardised by EFSA centrally, and use the EU-agreed endpoints and conclusions that had been derived by EFSA in relation to the active substance(s), co-formulants, and the products themselves.

The advantages of this approach would be:

- Efficiency, both for regulators and applicants – it would avoid unnecessary duplication of activities.

- Scientific rigour and consistency – it would make it easier to ensure input from scientists with appropriate expertise (this would be particularly useful for areas of science in which national regulatory bodies have less expertise, such as epidemiology and because the work (or at least its oversight) was centralised, it would be easier to ensure that different chemicals were assessed to similar standards.

- Transparency – EU-agreed endpoints, the basis on which they were derived, and agreed generic methods for further evaluation of specific products could be published in a way that made the information readily accessible to applicants, national regulators, and other stakeholders.

- Avoidance of potential for bias – it would remove the possibility of bias from applicants selecting particular EU Member States as rapporteurs when submitting active substances for approval.

Unlike at present, it would be possible to list an active substance without there necessarily being any authorised uses of products that contained it. The fact of listing would merely indicate that the substance had been assessed as a necessary step

before products containing it could be considered for use in the EU. In practice, however, it is unlikely that many companies would apply for assessment of an active substance if they did not intend simultaneously or soon after to apply for authorisation of one or more PPPs that contained it. Moreover, a note could still be added to the list to indicate whether any product based on an active substance was currently authorised for use.

Option 24. Reorganise the arrangements for risk assessment of PPPs such that EFSA is responsible for all aspects of the process that are common to all EU Member States, and that public databases are available of end-points relevant to risk assessment for active substances, co-formulants, and products based thereon, which have been evaluated as potentially suitable for use in the EU.

5.1. TRAINING FOR RISK ASSESSORS

However the tasks of risk assessment are distributed between EFSA and EU Member States, it will be important that the personnel undertaking the work continue to have the necessary training (including, but not limited to, training on systematic reviews and meta-analyses). Part of that training will be acquired in obtaining external academic qualifications, and through working in teams alongside more experienced colleagues. In addition, the centrally organised training that is currently provided by EFSA could be further enhanced as part of a formal mandatory training scheme that also provided opportunities for bidirectional transfer of knowledge on emerging topics (e.g. training risk assessors on epidemiology and epidemiologists on risk assessment).

Option 25. A formal mandatory training scheme should be organised and maintained for staff undertaking risk assessment for PPPs in the EU, including those employed in the regulatory bodies of EU Member States.

5.2. AN INTERNATIONAL CENTRE FOR PESTICIDE RESEARCH

In view of the growing volume and importance of research on pesticide risk assessment, and the ever-increasing complexity of the science that it entails, it is worth considering the scope for an independent, international centre for PPP-related research. This could serve as a major resource worldwide, helping to develop methodology, conducting primary research (especially using innovative methods), carrying out independent evaluations of published evidence, and contributing to training. One member of the Working Group has set out further thoughts on this in Annex 4.

Option 26. Establish a new international centre for pesticide research.

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7. List of Options

To improve the scientific data that inform risk assessment: p.

Option 1. Regulatory agencies (including EFSA) should work with OECD in developing new approaches to the validation of mechanistically-based methods for the assessment of toxicity, focusing on their fitness for purpose.   35

Option 2. Allow the use of data from shared contemporary control groups in risk assessment for plant protection products.   36

Option 3. Further investigation is needed on the levels and determinants of exposure in workers who enter crops that have been treated with PPPs to support refined modelling in risk assessment.   44

To improve methods of regulatory risk assessment:

Option 4. EU Member States should conduct studies to explore the "real life" behaviours of operators regarding the use of equipment and application techniques and the extent to which such approaches can be used to manage or reduce exposures.   43

Option 5. At the discretion of the risk assessor, allow more flexibility in the scope of re-evaluations for continued approval of active substances, and in the data that are required to support them.   44

Option 6. Based on current evidence, the routine requirement for a mouse carcinogenicity study to support the approval of active substances should be reassessed.   46

Option 7. Require that reports of toxicological investigations submitted in support of applications for approval include all relevant historical control data that meet specified criteria.   47

Option 8. Place maintenance of historical control data records in the hands of a public statutory body.   48

Option 9. Where appropriate, BMDs should be used in preference to NOAELs for establishing toxicological reference values. To support this, consideration should be given to study designs that are better suited to estimation of BMDs than those currently employed.

Option 10. Regulators should refine strategies for the assessment of developmental neurotoxicity, incorporating mechanistically-informed in-vitro tests.

Option 11. Further development and evaluation of methodologies for quantitative and qualitative synthesis of evidence from non-standardised toxicological and epidemiological studies should be encouraged.

Option 12. Each EU Member State should have a scheme for systematic ascertainment of acute illness that is suspected of being caused by PPPs, and the data obtained should be transmitted to EFSA for collation with those from other EU Member States, and central analysis.

Option 13. A system should be established to monitor the peer-reviewed literature at appropriately frequent intervals for epidemiological papers and case reports concerning human health effects of PPPs.

Option 14. When reviews are conducted of previously approved active substances, compounds with the same pesticidal mode of action should be assessed in one process.

Option 15. A more rigorous system should be developed for tiered assessment of the toxic potential of chemicals intended for use as co-formulants in PPPs, with a published list of those deemed potentially suitable, and a published database summarising their toxicological characteristics.

Option 16. A uniform system should be developed for the assessment and public listing of formulated products (containing specified active substances and co-formulants in specified concentration ranges) that have been accepted as potentially suitable for use as PPPs.

Option 17. Develop a simple scheme that would help users in choosing between PPPs for a specified application, by indicating those with smaller margins between exposures and relevant reference values.

Annex 1. Working Group Members

Evangelia Ntzani, Associate Professor of Epidemiology, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine (Greece); Center for Evidence Synthesis in Health, Brown University School of Public Health (USA). Chair.

David Coggon, Emeritus Professor of Occupational and Environmental Medicine, Medical Research Council Lifecourse Epidemiology Unit, University of Southampton (United Kingdom). Deputy Chair.

Susanne Hougaard Bennekou, Senior Advisor, Toxicologist, Danish Environmental Protection Agency (Denmark).

Alan Boobis, Professor of Toxicology, Centre for Pharmacology and Therapeutics, Imperial College London (United Kingdom).

Jean Golding, Emeritus Professor of Paediatric and Perinatal Epidemiology, Centre for Child and Adolescent Health, Public Health Sciences, Bristol Medical School, University of Bristol (United Kingdom).

Dr Paul Miller, Director, Silsoe Spray Applications Unit Ltd. (United Kingdom).

Colin Ockleford, Emeritus Professor of Anatomy, Lancaster Medical School (United Kingdom).

Annex 2. External experts

The experts listed below attended an expert workshop on 26 October 2017 in Brussels and provided written and verbal feedback on a preliminary draft of the SAPEA Evidence Review Report.

Professor Thomas Backhaus, University of Gothenburg (Sweden).

Dr Hubert Deluyker, retired from the European Food Safety Authority (Italy).

Professor Damjana Drobne, University of Ljubljana (Slovenia).

Paul Hamey, Chemicals Regulation Division, Health & Safety Executive (HSE) (United Kingdom).

Professor Antonio Hernandez Jerez, University of Granada (Spain).

Dr Malyka Galay Burgos, independent scientist at Galay Biosciences (Spain).

Professor Andy Hart, Visiting Professor at Newcastle University, (UK).

Dr Marie-Odile Rambourg, French Agency for Food, Environmental and Occupational Health and Safety (ANSES) (France).

Dr Wolfgang Reinert, DG Santé (European Commission) (Belgium).

Professor Michael K. Skinner, Washington State University (USA).

Dr Roland Solecki, German Federal Institute for Risk Assessment (BfR) (Germany).

Dr Kurt Straif, International Agency for Research on Cancer (IARC) (France).

Dr Jose Tarazona, European Food Safety Authority (Italy).

Dr Guy Van Den Eede, Joint Research Centre (European Commission) (Belgium).

Professor Maurice Whelan, Head of Unit, Directorate General Joint Research Centre (Italy).

Annex 3. A proposal for an effective, efficient, and transparent approval system for plant protection products in the European Union
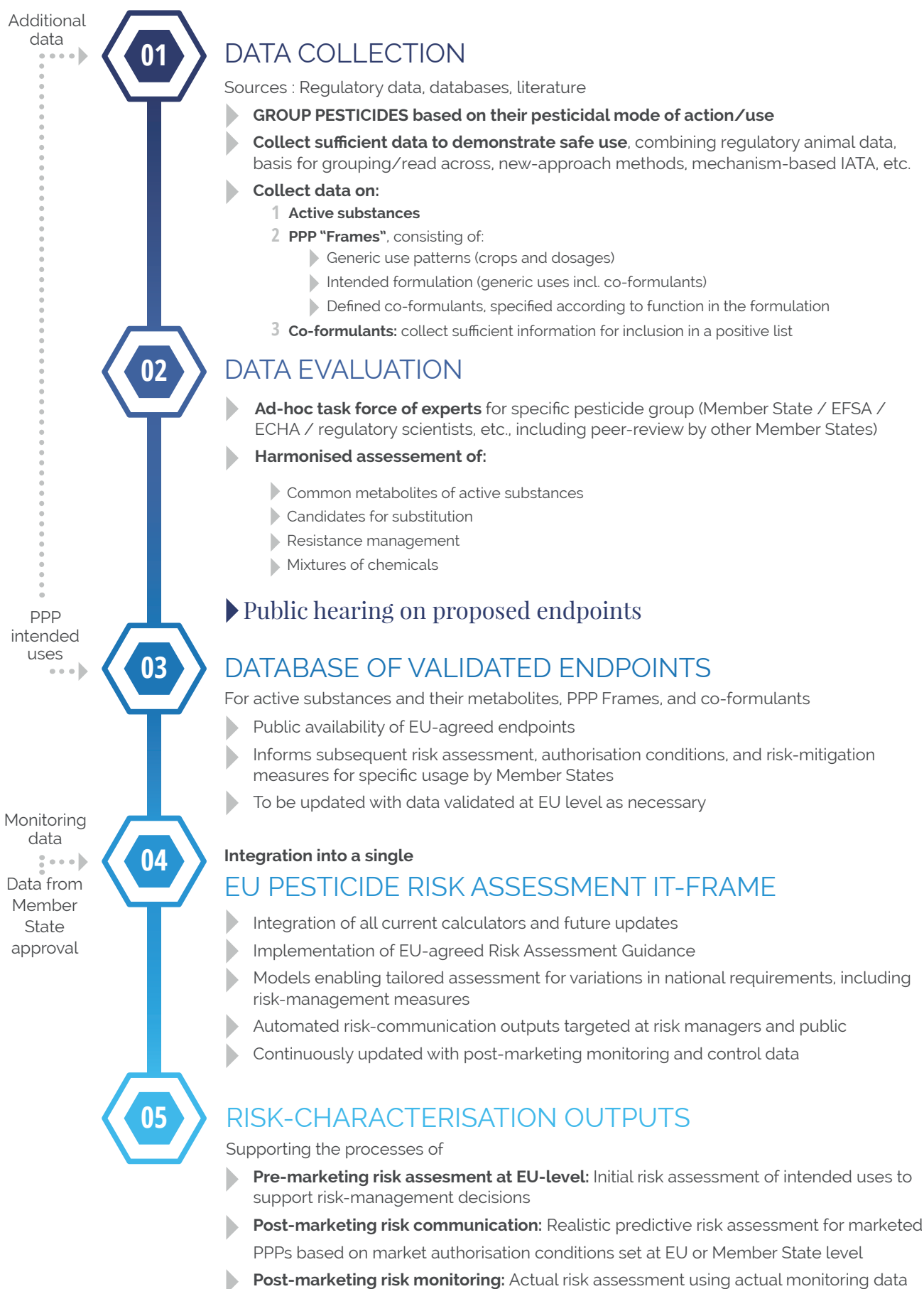
A proposal of the ideal system that would achieve safety for humans and the environment, availability of all relevant data, and a harmonised evaluation system/ process is depicted in Figure 1. The proposal has incorporated some of the suggestions elaborated by EFSA in the Technical Report "Scientific risk assessment of pesticides in the European Union (EU): EFSA contribution to on-going reflections by the EC", (2018) [v].

1. DATA COLLECTION

We propose that groups of pesticides with shared pesticidal mode of Action (MoA)/ use should be assessed in one process to make efficient use of data and resources of evaluators/experts, fulfil the needs for scientific competence of experts, and ensure a harmonised evaluation of different endpoints. Dossiers should contain sufficient data to demonstrate safe uses. The "sufficiency" of data should be decided by the risk assessor, which would allow a tailored and flexible evaluation that could use existing regulatory animal data, grouping/read-across approaches, new approach methods, mechanisms-based IATA (Integrated Approaches to Testing and Assessment), etc., thus allowing the system to make the best use of the newest scientific developments in chemical safety assessment.

For PPPs, it is proposed that a "PPP frame" be evaluated. A "frame" is to be understood as a combination of generic use patterns (crop and dosages), intended formulations that would cover the generic uses, and a range of defined co-formulants according to their function in the specific intended formulations. For example, a suspension concentration with an emulsifier frame from 1-5% of emulsifier A, B, C, or D; 1-3% of antifoam A, B, or C, etc. for other co-formulant

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[v] European Food Safety Authority, (2018). Scientific risk assessment of pesticides in the European Union (EU): EFSA contribution to on-going reflections by the EC. EFSA supporting publication 2018: EN-1367; https://doi.org/10.2903/sp.efsa.2018.EN-1367

01 DATA COLLECTION

Sources : Regulatory data, databases, literature

▶ **GROUP PESTICIDES based on their pesticidal mode of action/use**

▶ **Collect sufficient data to demonstrate safe use**, combining regulatory animal data, basis for grouping/read across, new-approach methods, mechanism-based IATA, etc.

▶ **Collect data on:**
  1 **Active substances**
  2 **PPP "Frames"**, consisting of:
    ▶ Generic use patterns (crops and dosages)
    ▶ Intended formulation (generic uses incl. co-formulants)
    ▶ Defined co-formulants, specified according to function in the formulation
  3 **Co-formulants:** collect sufficient information for inclusion in a positive list

02 DATA EVALUATION

▶ **Ad-hoc task force of experts** for specific pesticide group (Member State / EFSA / ECHA / regulatory scientists, etc., including peer-review by other Member States)

▶ **Harmonised assessement of:**

  ▶ Common metabolites of active substances
  ▶ Candidates for substitution
  ▶ Resistance management
  ▶ Mixtures of chemicals

▶ Public hearing on proposed endpoints

03 DATABASE OF VALIDATED ENDPOINTS

For active substances and their metabolites, PPP Frames, and co-formulants

▶ Public availability of EU-agreed endpoints

▶ Informs subsequent risk assessment, authorisation conditions, and risk-mitigation measures for specific usage by Member States

▶ To be updated with data validated at EU level as necessary

04 **Integration into a single**

EU PESTICIDE RISK ASSESSMENT IT-FRAME

▶ Integration of all current calculators and future updates

▶ Implementation of EU-agreed Risk Assessment Guidance

▶ Models enabling tailored assessment for variations in national requirements, including risk-management measures

▶ Automated risk-communication outputs targeted at risk managers and public

▶ Continuously updated with post-marketing monitoring and control data

05 RISK-CHARACTERISATION OUTPUTS

Supporting the processes of

▶ **Pre-marketing risk assesment at EU-level:** Initial risk assessment of intended uses to support risk-management decisions

▶ **Post-marketing risk communication:** Realistic predictive risk assessment for marketed PPPs based on market authorisation conditions set at EU or Member State level

▶ **Post-marketing risk monitoring:** Actual risk assessment using actual monitoring data

Additional data

PPP intended uses

Monitoring data

Data from Member State approval

Figure 1. Schematic representation of the proposed effective, efficient, and transparent approval system for plant protection products (PPPs) in the European Union. IATA: Integrated Approaches to Testing and Assessment; EFSA: European Food Safety Authority; ECHA: European Chemicals Agency.

function groups. Sufficient data should be collected to include the co-formulants in a "positive list" of co-formulants (instead of the "negative list" of the current regulation, which is not motivating generation of relevant data). This would allow harmonisation of endpoints when the co-formulants have been allocated to the positive list, but at the same time maintain some room for manoeuvre regarding the intellectual property rights of petitioners.

2. EVALUATION OF THE DATA

Since a group of specific active substances and PPPs is to be evaluated in terms of mode of action/use, an ad-hoc task force of experts familiar with the specific group of pesticides/modes of action/uses should be assembled to fit the need of the specific "bulk evaluation". Such experts could come from EU Member States, regulatory bodies and authorities, etc., or might be independent scientists. Such an approach could achieve harmonised assessment, for example in terms of common metabolites of active substances in ground water and/or in food and feed. In addition, the evaluation of "candidates for substitution" would be based on a holistic evaluation of up-to-date endpoints. Furthermore, if relevant, considerations with regard to management of resistance could be integrated in the assessment. Risk assessment of mixtures of chemicals could also be addressed, as the system would make the relevant data available. Once endpoints have been proposed by the ad-hoc group, there should be a public hearing involving experts outside the ad-hoc group as well as the public.

3. DATABASE OF VALIDATED ENDPOINTS

EU-agreed validated endpoints for the active substances, co-formulants, and PPP frames should be deposited in a public database to make them readily available to all EU Member States for subsequent risk assessment of specific intended uses of PPPs. During the process of national authorisation of PPPs, the compatibility of the PPP application with the EU database can be checked at Member State level. If the PPP is confirmed to be within the evaluated PPP-frame, and if safe uses can be demonstrated based on the EU-validated endpoints, then the Member State decides the authorisation conditions and risk mitigation measures as needed. In cases where new data are needed to support the intended use, these should be submitted and validated at EU level before being included into the EU database.

4. INTEGRATION INTO AN EU PESTICIDE RISK ASSESSMENT IT-FRAME

It would be highly desirable to create a single IT-frame, integrating all current calculators and future updates, and implementing EU-agreed guidance documents. Risk-assessment models should support tailored assessments fitting national requirements in terms of (agri)cultural variabilities, integrating landscape and climate, and risk mitigation measures. Furthermore, to facilitate transparency, risk assessment communication tools should be established that automatically generate risk assessment outputs targeted at risk managers and the public.

IT-tools should be continuously updated with actual risk assessment data (i.e. post-marketing monitoring and control data), thus enabling a broader application of monitoring data equivalent to the existing maximum residue-level monitoring program. These data could, if needed, refine the exposure and hazard assessments from the realistic predictive risk assessments and enable conclusions about an actual risk assessment.

5. RISK CHARACTERISATION OUTPUTS

The described system would produce three complementary risk-characterisation outputs that support three distinct processes:

Pre-marketing risk assessment at EU level: initial EU risk assessment for pre-assessment of the intended uses of each active substance, relevant co-formulants, and PPP to support risk management decisions.

Post-marketing risk communication: realistic predictive risk assessment for marketed PPPs based on market authorisation conditions decided by risk managers at EU or Member State level. Cumulative risk assessment considering several substances (active substances and/or co-formulants) and PPPs will be performed when the respective methodology is available.

Post-marketing risk monitoring: actual risk assessment, refined by actual monitoring data according to "post-marketing vigilance principles".

6. SUMMARY

The proposed system will allow a science-based, effective, efficient, transparent, and dynamic pesticide risk assessment system in Europe that will
- make efficient use of expert knowledge resources and data,
- be agile in regard to incorporating new science and data into risk assessment,
- support risk management decisions and provide transparency to the public,
- maintain a high level of Member State influence,

- address co-formulants in PPPs,
- address risk assessment for mixtures and candidates for substitution,
- integrate post-marketing data (monitoring) into risk assessment,
- support a harmonised system based exclusively on EU-agreed endpoints but still maintain freedom of manoeuvre with regard to intellectual property.

Annex 4. Long–term strategy for the creation of a dedicated independent Institute to develop methodologies for the assessment of the safety of pesticides and herbicides – a personal view

CONTENTS

1. SUMMARY

Biological understanding has progressed rapidly in the past decade and consequently new strategies are warranted to improve the identification of beneficial and adverse effects of pesticides PPPs and herbicides. Based on (a) the duplication of animal experiments worldwide, (b) the lack of consistency in regard to consideration

of epidemiological outcomes, and (c) the failure to take advantage of data already available, this paper suggests that an independent scientific Institute be created as a repository of information and expertise, answerable to a completely independent body such as the World Health Organization. This brief paper outlines the tasks that could be undertaken by such an Institute to create a resource for use by regulatory bodies.

2. THE DEFECTS IN THE CURRENT SYSTEM

Although countries and/or areas may have regulations in place to protect human health in regard to plants grown under their jurisdiction, pesticide use is worldwide and contaminated products may be imported without oversight of all possible effects that may be harmful to human health. Therefore, it is vitally important to ensure that appropriate procedures are in place to protect the health and well-being of the public worldwide.

For example:

i. There is no consistent method of evaluation across the world. Consequently, although a chemical may be banned in one jurisdiction (K say) it may still be used freely in another and contaminated products may not be banned from importation into jurisdiction K.

ii. The current system is open to many biases from the industries involved in manufacture and distribution of chemicals, with consequent possibility of dangers to health of the population at large.

iii. Experimental evaluation of the products is partly in the hands of the manufacturers, with their reports then being evaluated by each jurisdiction.

iv. There are major expenses (to both the manufacturers and the authorities) in similar assessments being undertaken by numerous jurisdictions in regard to the same chemical.

v. Initial evaluations for a new product are based on animal experiments, and unsurprisingly involve little, if any, human evidence.

vi. Animal evidence is based on crude disease outcomes and may not take note of epigenetic, neurocognitive or other biological effects. In addition, account may not be taken of the fact that outcomes are likely to be strongly influenced by the genetic make-up (or sex) of the animal.

vii. Renewal of a licence includes the examination of the peer-reviewed papers published concerning the major chemical concerned (but not necessarily the co-formulants or the complete product). The papers that are published have no rationale to them – they are often undertaken on the whim of the academic or of the funder. As far as I am aware, there is no consistency in regard to chemicals

examined or outcomes to be addressed in the epidemiological literature.

viii. Although there are some national systems, there appears to be no systematic central collection of relevant information published worldwide.

ix. Most attention appears to be on the 'active' substance, with little attention being paid to co-formulants, or to mixtures. Yet there has been evidence of harm occurring unexpectedly as a result of co-formulants in medications (for example, the odds ratio was 8 for the development of peanut allergy when peanut (arachis) oil was included in commonly used creams and lotions for skin rashes (Lack, Fox, Northstone, & Golding, 2003); a link with childhood cancer probably associated with inclusion of phenol (a known carcinogen) in Vitamin K injections given to new-borns (Golding, Greenwood, Birmingham, & Mott, 1992).

x. The problems with the current methods of collecting evidence include a concentration on high exposures to the relatively fit (e.g. occupational exposures). However, many subgroups of the population are likely to be substantially more at risk from much lower and/or continuous exposures than those occupationally exposed.

xi. There appears to be little recognition, as yet, in either the experimental or epidemiological fields in examining intergenerational and/or transgenerational effects of a product.

xii. In assessing the risk of exposure to the population it is important to include the more minor as well as the major adverse (and beneficial) consequences, with particular emphasis on chronic disorders such as intellectual and behavioural disorders (e.g. autism and ADHD), depression and anxiety, diabetes and obesity, or reproductive health (including fertility and semen quality).

3. IDENTIFICATION OF EXPOSURES

It will be the responsibility of a new Institute to document and assess the reliability of all methods for estimating exposures.

Currently the ways in which human exposures are calculated use mainly mapping, occupational exposures, questioning study participants, or analysing biological samples. Future strategies for identifying human exposures are likely to include DNA methylation signatures (see below), but many more ways of identifying exposures to pesticides are likely to become available.

3.1. Methods currently used to identify exposures

3.1a. Mapping of exposures using data concerning the spraying of pesticides on local fields. This has the major problem of uncertainty concerning the "dose" received by the individual without detailed data on wind direction, whether the individual was at home at the time, whether windows were open, and other details

of the individual that might be important in assessing any associations between exposure and outcome (e.g. smoking habit).

3.1b. Occupational exposures can be more accurate depending on the records that are kept, but can have a variety of disadvantages in that they are usually only concerned with adult exposures, and mostly of men who are fit enough to work, and of relatively short-term outcomes. Unless specific studies are mounted, there may be very little information on other exposures or genetic variants that may have important synergistic or protective roles to play.

3.1c. Questioning: A traditional method of obtaining data on exposures is to ask individuals as part of a detailed study. This can be very accurate depending on the question asked (e.g. current occupation, or current medication taken). However, questioning about pesticides is more problematic. For example, the Avon Longitudinal Study of Parents and Children (ALSPAC) attempted to ask pregnant women and their partners how frequently they had used (i) pesticides; and (ii) "weed killers" during the pregnancy. A validation study was carried out on a subsample of the 13,433 women who answered the questionnaire. This showed that, on detailed interview of those who stated in the questionnaire that they did not use pesticides, 90% were found to have done so (Nieuwenhuijsen, Grey, & Golding, 2005). The authors thought that a detailed list of the pesticides that could have been used would have produced more accurate responses. However, the authors showed that over 85 different pesticide products were found to be stored in the targeted homes, with 76 different types of pesticide active ingredients. This complexity suggests that even though exposures are common and often at fairly high intensity, a detailed questionnaire on all possible products in the home is probably impractical in general health surveys (Grey et al., 2006).

3.1d. Choice of biological samples for assessment of exposure: Assays of biological samples are probably more accurate for current exposure than the three methods described above. Among the samples most frequently used are urine and blood (including plasma, serum, or whole blood). However, the data obtained in this way are most likely to refer to recent, rather than historic, exposures. This may be useful for pregnancy exposures using prenatal samples, but is less likely to be useful for adult exposures, unless one uses samples repeated over time, or samples that have included exposures over time (e.g. hair and toenails). One such ingenious technique used by the CHAMACOS study (Center for the Health Assessment of Mothers and Children of Salinas) used the milk teeth shed by children in their cohort and analysed the manganese content in the dentine laid down in the prenatal and infancy stages, as a marker for pesticides containing manganese (Gunier et al., 2013;

Mora et al., 2015). This technique, however, probably has limited use for pesticides that do not include trace metals. Nevertheless, toenails and hair may be useful for other chemicals.

The Institute would keep a library of human biological samples for use in detecting exposures, with details of the substances for which they would be able to provide valid information.

3.2. Methods for identification of exposures in the future

DNA Methylation signature. Epigenetics is a field that is increasing in importance as a potential marker of environmental exposure. Epigenetic variation is considerably influenced by environmental exposures, and can be specific to types of exposure. For example, there are methylation signatures to cigarette smoking (comprising an algorithm of methylation levels at various CpG specific sites in the genome) which are evident over many years even when the individual has stopped smoking (Ambatipudi et al., 2016). More intriguingly, there is a specific signature that indicates an exposure to cigarette smoking during fetal life (Richmond et al., 2015), a signature that is still apparent even when the offspring has reached adulthood (Richmond, Suderman, Langdon, Relton, & Davey Smith, 2017).

It is possible that smoking is an extreme example of DNA methylation markers since cigarette smoke contains an estimated 5000 different chemicals (Talhout, Schulz, Florek, Van Benthem, Wester, & Opperhuizen, 2011). Each component of pesticides and herbicides may have a more unique and specific epigenetic marker, or set of markers. Research in this field is in its infancy, although there have been some promising studies recently (e.g. van den Dungen, Murk, Kampman, Steegenga, & Kok, 2017).

The Institute would be expected to keep abreast of all developments in the field, and ensure that those markers that have been identified as related to PPP products (including co-formulants) are appropriately validated for use in PPP assessments.

4. CHOICE OF OUTCOMES

4.1 General considerations

The general concentration in toxicological studies on the identification of human carcinogens could be questioned for two reasons: (a) the long time-delay from exposure to development of a cancer makes it difficult to identify the nature of the exposure; (b) there are many other outcomes that may be more appropriate to study

in order to calculate the possible risks inherent in exposures of a human population as discussed below.

4.2 Timing of exposures

Humans are at their most vulnerable to environmental exposures when a fetus or during early infancy, particularly in regard to influences on the early development of organs such as the brain, effects of which may not be recognised until adolescence or even later (Silbergeld & Patrick 2005; Courchesne et al., 2000). These effects may have substantial economic and health consequences – in Europe, for example, the gain of an IQ point was estimated to increase a nation's GDP by 10,000 Euros per child in 2010 (Bierkens, Buekers, Van Holderbeke, & Torfs, 2012).

Other times at which exposures may be important for the individual include: (a) pre-pregnancy (including exposure history of the mother and/or the father prior to conception); (b) early childhood (< 5 years); (c) later childhood (pre-puberty); (d) adolescence; (e) various stages of adult life, especially the older ages.

Exposures at different ages may have different consequences for the individual both in the short and long-term – such associations with exposure-time intervals are largely uncharted and likely to vary by substance and outcome.

The Institute will keep a library concerning the types of outcome that may be influenced by exposures to toxins at different times during the life course.

4.3 Choice of outcome measures

4.3a. General points

Various outcome measures can be useful markers indicating that an environmental exposure has influenced exposed individuals, even though the outcome may seem relatively trivial.

Examples from the ALSPAC study concern an unexpected finding of increased birthweight among infants born to mothers who had consumed paracetamol (acetaminophen) in pregnancy; this was not followed up at the time but later it has been shown that women with this exposure (even at low doses) have children with an increased risk of asthma (Shaheen, Newson, Smith, & Henderson, 2010) as well as of behavioural difficulties (Stergiakouli, Thapar, & Davey Smith, 2016). Thus, the recognition of a change in birthweight when the mother had used paracetamol, even though it may have been interpreted as a beneficial effect, should have been used

as a pointer to the need for further consideration of possible adverse effects.

As well as birthweight (particularly birthweight-for-gestational age) in response to prenatal exposures, a variety of other outcomes including neurocognitive and psychiatric (see below) can be the result of exposures at various ages (including during fetal life). In addition, changes in telomere length and the divergence of epigenomic age (the biological age of a cell type or tissue as determined from the level of DNA methylation at specified sites) from calendar age may be a response to exposures at any time of life. Although these are non-specific, they provide useful indicators that a biological effect (whether positive or negative) has occurred (see descriptions below).

4.3b. Neurocognitive outcomes

In childhood, the most commonly studied neurocognitive outcomes are measures of behaviour and aspects of cognitive ability. Both can be measured using continuous scales, making them ideal for assessing associations with environmental exposures.

Measures of attention and identification of a diagnosis of ADHD were among the behavioural outcomes identified in children participating in the CHAMACOS study as being associated with prenatal organophosphorous pesticide (OPP) levels in urine (Marks et al., 2010). Childhood IQ also showed an association with OPPs (Stein et al., 2016), a finding that was particularly pronounced in the presence of social adversity. Maternal serum measures of DDT/DDE metabolites were also associated with childhood IQ and were more pronounced in girls than boys (Gaspar et al., 2015).

As the human adult ages, there is often a general loss of cognitive function, sometimes with the onset of dementia. There is now considerable evidence linking the gradual loss of cognitive function to the use of pesticides (Zaganas et al., 2013). Other neurological disorders reported as associated with pesticides include Parkinson's disease (Kamel et al., 2007).

4.3c. Mental health

In adolescence and adulthood, poor mental health becomes more prevalent, and has been little studied to date in regard to pesticide exposure (apart from a number of studies of suicides using pesticides such as paraquat). Key to future studies of mental health is the question as to when any pesticide exposure has occurred. Occupational studies have demonstrated that farmers exposed to organophosphorous pesticides suffered from increased rates of severe depression

and anxiety, as well as poorer attention and memory skills compared with non-exposed controls (Malekirad et al., 2012). One study of female spouses of pesticide applicators also showed a link with depression (Beseler et al., 2006). In spite of these studies, a literature review in 2013 concluded that there was insufficient evidence to draw robust conclusions (Freire & Koifman, 2013), thus pointing to the need for more studies worldwide.

4.3d. Environmentally-induced epigenetic transgenerational effects

Environmental exposures of rodents have repeatedly shown effects down the generations after an initial exposure either in utero or during infancy (Miska & Ferguson-Smith 2016; Xin, Susiarjo, & Bartolomei, 2015). They have also repeatedly demonstrated effects of pesticides that have had intergenerational and transgenerational consequences (e.g. Manikkam, Tracey, Guerrero-Bosagna, & Skinner, 2012; Manikkam, Haque, Guerrero-Bosagna, Nilsson, & Skinner, 2014), even though the impact on the first generation of offspring was minimal. For example, the heavily used herbicide Atrazine has no direct exposure effects in a rodent model, but three generations later down the male line there is significant transgenerational pathology in over 70% of the population (McBirney et al., 2017).

That such responses can occur in humans was postulated by Pembrey in 1996, but has only started obtaining credence in the last decade. First, by the Őverkalix studies, which have demonstrated: (i) that the grandson's health is influenced by paternal grandfather's exposure pre-puberty, and (ii) that the granddaughter's health is influenced by prenatal or infancy exposure to the paternal grandmother's exposure (Bygren et al., 2014; Pembrey et al., 2014b). Studies to test these hypotheses were undertaken in the framework of the Avon Longitudinal Study of Parents and Children. They have demonstrated the sensitivity of both male and female lines in the prenatal and prepubertal (defined as ages 6-11) periods to exposures such as cigarette smoking and traumatic events, resulting in sex-specific outcomes to children and grandchildren as varied as birthweight, adolescent obesity, asthma and autistic traits (Miller et al., 2014a,b; Northstone et al., 2014; Pembrey et al., 2014a; Golding et al., 2017). Subsequent studies have mostly confirmed the importance of these sensitive periods, though it should be noted that not all such trans- and intergenerational associations result in adverse outcomes. For example, a transgenerational study of exposure in mid-childhood to the German 1916-18 famine showed that exposure of the grandfather was associated with better mental health scores in his grandsons (van den Berg, Pinger, & Schoch, 2016).

Thus, a chemical may appear to have a low risk for direct exposure with all the

standard toxicology considerations today, but through epigenetic effects on the germline (sperm and eggs) this exposure may promote transgenerational inheritance of disease susceptibility in generations far removed from the exposure.

4.4 Epigenetic markers

Epigenetics is a field that is increasing in importance as a potential marker of environmental exposure as well as of influence on outcomes. Currently there are two possible epigenetic measures that are used as outcomes in epidemiological studies, but many more are likely to become available in the future.

The Institute would be expected to keep abreast of all developments in the field, and ensure that those markers that have been identified are appropriately validated for use in PPP assessments.

4.4a. Telomere length

The average telomere length (TL) decreases with age. However, independent of age, short TLs are a marker of increased risk of both cancer (Ma et al., 2011) and cardiovascular disease including stroke, myocardial infarction, and type 2 diabetes (D'Mello, et al. 2015). Although research concerning effects of environmental exposures on TLs is in its infancy, there is some evidence that prenatal and childhood exposures to stress are associated with shorter telomere lengths in adulthood (Entringer et al., 2011; Kananen et al., 2010); and that in adulthood duration of smoking is associated with shorter, and fruit and vegetables in the diet with longer TLs (Mirabello et al., 2009). Zhang and colleagues (2013) reviewed the literature on environmental and occupational exposures to chemicals and reported reduced TL with some pesticides, but increased TL with arsenic and persistent organic pesticides. They concluded that "the study of TL in easily obtainable surrogate tissues may well identify novel and easy-to-measure biomarkers of past exposure as well as predictors of future disease, thus contributing to the development of preventive strategies and policies for environmental and occupational diseases". Others have endorsed this view – e.g. after showing that exposure to complex mixtures of pesticides was associated with reduced TLs, Kahl et al., (2016) stated that "TLs may be a good biomarker of (outcome in) occupational exposure". A recent population study of men born in Helsinki between 1934-44, and followed up in both 2001-2004 and 2011-2014, showed relationships between blood levels of certain pesticides at the first visit and shorter TLs at the second (Guzzardi et al., 2016).

4.4b. DNA Methylation age

This measure uses a set of specific DNA methylation sites identified because their level of methylation changes with age, using an algorithm to calculate the DNA's methylation age (MA). This is closely correlated with the actual age of the individual, but discrepancies between the two are closely associated with disease risk. There are two algorithms in current use: those of Horvath (2013) and Hannum et al., (2013). Exposures identified with accelerating methylation age include ammonium and sulphate (Nwanaji-Enwerem et al., 2017), and cigarette smoking (Gao, Zhang, Breitling, & Brenner, 2016). Outcomes shown with accelerated aging include Parkinson's disease (Horvath & Ritz, 2015), psychiatric disorder (Fries et al., 2017), cancer (Murabito et al., 2017; Zheng et al., 2016) and all-cause mortality (Perna et al., 2016).

Comment on the above

It is notable that TL and MA appear, at this point in time, to be independent predictors of mortality (Marioni et al., 2016), and so are unlikely to be measuring exactly the same biological mechanism. In support of this, a German aging cohort study showed that although MA was correlated with frailty, TL was not (Breitling et al., 2016).

5. DEVELOPING A RESOURCE OF WORLD-WIDE COHORT STUDIES

Although individuals working in occupations resulting in exposure to pesticides are important, they are a relatively small proportion of the general population. Of more importance to public health is the safety of exposures to the general population, especially those most susceptible (the very young and the elderly). There are a large number of cohort studies in Europe and a growing number in the Americas, Asia, and Australasia. Many have been designed to assess environmental factors that influence health and well-being. Apart from the CHAMACOS cohort (Eskenazi et al., 2003; 2014; 2017), none were specifically designed to look at pesticides, but many have biological samples available (often with repeat samples) that can be used to assess pesticide exposure to a population.

The Institute should enrol a group of existing cohort studies (including, but not confined to, birth cohorts) with stored biological samples (ideally collected at multiple time points), and a variety of outcome measures. Diagnostic outcomes would be optional since they have the disadvantage of often varying with country

and/or clinician, but quantitative continuous measures would be valuable.

The advantages of enrolling existing cohort studies include the following:

- The data will have been prospectively collected, and therefore lacking in problems of retrospective reporting bias.
- The biological samples could be measured using the same techniques in each cohort.
- All results will be published electronically, thus obviating any bias involved in selective publication.
- By using several cohort studies there will be sufficient power to ensure repeatability across studies.
- Numbers will be sufficiently large (tens of thousands) so that results between cohorts can be compared, meta-analyses can be undertaken, and differences in outcomes between the sexes can be ascertained.
- Large numbers will allow analysis of gene-environment interactions, as well as environment-environment interactions, both of which may be important for explaining any differences in results between cohorts.
- DNA will be available for the development of algorithms for DNA methylation profiles (pattern of differentially methylated sites) for the different pesticides, thus providing quantifiable evidence for past exposures.
- The feasibility of ensuring that data can be shared across cohort studies is evidenced by the I4C group of studies, which concentrates on childhood cancer (Brown et al., 2007) and has included ~300,000 pregnancies. Such cohort studies, or groups of cohort studies, whether starting prior to birth or later, could be of key importance in the identification of adverse effects of pesticides.
- Examples of quantitative outcomes that could be tested within cohort populations, and which could be compared with biomarkers of exposure include, for early exposures: fetal growth, childhood growth, BMI or level of fat mass, bone mineralisation, cognitive function (e.g. IQ), various behaviour characteristics (e.g. hyperactivity), depressive symptoms, age at onset of puberty, sperm count, time to pregnancy, age at menopause, blood pressure, and level of blood glucose as well as epigenetic markers such as telomere length and DNA methylation age. For exposures at late middle age, similar markers could be used, particularly concentrating on changes over time.

Additional points to consider when enrolling existing cohort studies:

- Although finances would be involved in setting up and running such a facility, considerable savings would be made from the fact that it will be building on data already collected at great expense by the funders of the different cohorts.
- The strategy will work only if the cohorts are happy to be involved. However,

there is considerable pressure from major funders (in the UK at least), and from participants in the cohort studies, for data to be used for the public good. A study of pesticides would likely be seen as an important investment by them as long as the analyses are seen to be independent of pesticide manufacturers.

- Although the strategy would be valid for calibrating associations with a variety of different outcomes, the chance of having sufficient data over the time scale to look at rare outcomes such as childhood cancer or major malformations will be low. However, for middle-aged adult exposures, cohorts such as UK Biobank (with 500,000 individuals) would provide sufficient data to look at particular cancers.
- There is the possibility that existing studies will not be looking at the most relevant exposures. However, new cohort studies are frequently being initiated, and being able to influence their data collection prospectively would be valuable.

The Institute will take advantage of cohorts with biological samples that are already extant to measure exposures to components of pesticides and herbicides, and use quantitative continuous outcome measures such as telomere length, DNA methylation age, growth, and changes in cognitive function as markers of possible adverse effects. Ideally, academics based at the Institute will undertake analyses and compare results across cohorts.

6. METHODOLOGICAL ISSUES

6.1. Registration of proposed studies

There is potential bias from failure to publish completed studies that provide unwelcome or inconclusive results. This can be prevented if all anticipated studies involving PPPs are registered in advance of the investigation. **Advance registration of studies could be organised by the Institute** in ways similar to those the Cochrane Registry has advised: http://www.cochrane.org/uk/about-us/our-governance-and-policies/cochrane-policies/prospective-rct-registration-policy.

6.2. Statistical techniques

The Institute will be a resource for the development and teaching of appropriate statistical concepts and techniques for the assessment of the safety (or otherwise) of PPPs. These will include the following:

6.2a. Use of genetic markers for assessing causal inferences

Confounding is one of the major challenges in observational epidemiology. To address this problem, Mendelian randomisation studies assess the association of

disease with genes that modify the metabolism of chemicals of interest (Lawlor, Harbord, Sterne, Timpson, & Davey Smith, 2008). For a given exposure, such genes may modify the internal dose of a chemical, and therefore the risk that it will cause (or reduce) adverse effects. Thus, an association between an outcome and a gene that increases internal levels of a chemical may be a strong indication that the chemical influences the outcome.

6.2b. Use of Exposome techniques

One method of identifying relevant exposures contributing to an outcome is the hypothesis-free Exposome technique (Wild, 2012), also known as an Environment-Wide Association Study (Patel, Bhattacharya, & Butte, 2010), whereby all available biological measures of the environment are tested against a given outcome. An example is the exposome study of type 2 diabetes undertaken with NHANES data – which identified strong associations with the pesticide derivative heptachlor epoxide, and with PCBs such as PCB170. At the same time, they identified a possible protective effect of beta-carotene (Patel et al., 2010). Exposome analyses do not necessarily involve the results of biological assays, and are not necessarily cross-sectional in nature. For example, an exposome using the non-biological environmental data collected from conception onwards, and involving parents and grandparents in ALSPAC has identified independent predictive environmental time-specific exposures for motor coordination (e.g. Golding et al., 2014).

Jones (2016) has summarised the exposome concept as "both refreshingly simple and dauntingly complex". He concludes with the statement: "investment and cooperation to sequence the human exposome will advance scientific knowledge and provide an important foundation to control adverse environmental exposures to … improve prediction and management of disease".

7. CREATION OF AN INSTITUTE AS A CENTRAL SCIENTIFIC CENTRE OF EXPERTISE IN REGARD TO PESTICIDES AND HERBICIDES

This could be developed rather as the International Agency for Research on Cancer (IARC) has been (https://www.iarc.fr/en/about/index.php). IARC is the specialised cancer agency of the World Health Organization. Its objective is to promote international collaboration in cancer research. The Agency is interdisciplinary, bringing together skills in epidemiology, laboratory sciences and biostatistics to identify the causes of cancer so that preventive measures may be adopted, and the burden of disease and associated suffering reduced. A significant feature of

IARC is its expertise in coordinating research across countries and organisations; its independent role as an international organisation facilitates this activity.

IARC is recognised as a major resource worldwide, and is acknowledged as being independent and scientifically sound. It provides scientific resources and training. However, although it has the responsibility of investigating a variety of different chemicals for carcinogenicity, it does not investigate other health or developmental effects.

The Institute proposed in this document would be a **Centre of Scientific Excellence with a variety of responsibilities, including those outlined below. In general, it would be expected to be both reactive and proactive.**

7.1. Experimental resources and initiatives

Among a variety of experimental resources, the centre could be responsible for the following:

7.1.a. Developing techniques for measuring the exposure of an individual to an active substance, or co-formulant, using biological samples. Of particular use in epidemiology would be the development of assays using small samples such as blood spots.

7.1.b. Developing a resource to measure epigenetic biomarkers of short and long-term effects of exposures to PPPs and their metabolites, and to co-formulants.

7.1.c. Developing in-vitro tests of the results of exposures using animal and human biological samples, and thus reducing the need for animal experimentation. This has already been shown to be feasible (e.g. Zhang et al., 2012).

7.1.d. Ensuring that tests of trans- and inter-generational effects were considered experimentally.

7.1.e. Keeping an easily accessible library of all experimental results, including genetic and epigenetic interactions.

7.1.f. Carrying out the relevant testing (in vivo and in vitro) to assess and advise on the safety of pesticide products (new and old).

7.2. Developing epidemiological resources

There are two major types of epidemiological study: the case-control and the cohort

study. Case-control studies tend to be more focused on a particular outcome or exposure, whereas the cohort study has the potential to measure a wide variety of exposures and outcomes within a community. Both types of study can be important in identifying adverse effects of health and development to human populations. However, in epidemiology, no one study will be considered able to provide sufficient valid information to enable decisions to be made. In consequence it is normal to compare and contrast a number of studies using techniques such as meta-analysis, but also information to evaluate the Bradford-Hill and more recent criteria (Lucas & McMichael, 2005; Gage, Munafò, & Davey Smith, 2016), and those particularly relevant to birth cohort studies (Richmond, Al-Amin, Smith, & Relton, 2014). This requires access to various sources of information.

I suggest therefore that the proposed Institute provides the following:

7.2a. A library of details of all case-control and cohort studies with PPP or equivalent measures, as a publicly available resource. This could include details of the methodology and a commentary on the advantages and disadvantages of each study, which could be open to electronic discussion.

7.2b. A database concerning the likely developmental time points at which an exposure may influence the health and development of the individual. This would be a resource for deciding on the choice of outcomes for a particular exposure.

7.2c. A system whereby all proposed epidemiological studies worldwide are required to register, in advance, their intention to carry out any study involving PPPs.

7.2d. A training centre and resource to advise on ethical issues, choice of outcomes, strategies for enrolling participants, collection and storage of biological samples, and statistical analyses.

7.2e. A continuously updated comprehensive review of the literature on differing outcomes, methods of measurement, and identification of sudden unexplained increases in health and/or developmental problems.

7.2f. A maintained resource of worldwide cohort studies with available biological, exposure, and outcome information, so that results can be pooled where appropriate.

8. POINTERS TO FUTURE DEVELOPMENTS THAT COULD BE FOSTERED BY THE INSTITUTE

Several authors have recently summarised the developing literature and made the following suggestions:

(a) "Future studies should consider … the role of underlying genetic variants." (Ruiz-Hernandez et al., 2015).

(b) "Available evidence supports the concept that epigenetics holds substantial potential for furthering our understanding of the molecular mechanisms of pesticides' health effects, as well as for predicting health-related risks due to conditions of environmental exposure and individual susceptibility." (Collotta, Bertazzi, & Bollati, 2013).

(c) "Rapidly growing evidence has linked environmental pollutants with epigenetic variations, including changes in DNA methylation, histone modification and microRNAs." (Hou, Zhang, Wang, & Baccarelli, 2012).

(d) "Large prospective studies will be needed to understand whether changes in risk factors are associated with changes in DNA methylation patterns, and if changes in DNA methylation patterns are associated with changes in disease endpoints." (Terry et al, 2011).

(e) The implications of epigenetics for environmental law should be developed. Vandenbergh and associates (2017), for example, have begun to discuss the possibility of developing worldwide regulations on chemical exposures, especially focussing on the fact that epigenetic effects can be transmitted down the generations.

9. POSTSCRIPT

This document has been produced after attending the SAPEA expert workshop in October 2017. Although the participants in the workshops have seen the drafts of this document, it has not been endorsed by them, and therefore stands as a personal view.

Jean Golding
Emeritus Professor of Paediatric and Perinatal Epidemiology, Centre for Child and Adolescent Health, University of Bristol, Bristol, UK
jean.golding@bristol.ac.uk   19 November 2017

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LIST OF ABBREVIATIONS USED IN ANNEX 4:

ADHD: Attention Deficit Hyperactivity Disorder
ALSPAC: Avon Longitudinal Study of Parents and Children
CHAMACOS: Center for the Health Assessment of Mothers and Children of Salinas
DDE: Dichlorodiphenyldichloroethylene
DDT: Dichlorodiphenyltrichloroethane
GDP: Gross Domestic Product

HELIX Project: Human Early-Life Exposome

IARC: International Agency for Research on Cancer

I4C: International Childhood Cancer Cohort Consortium

MA: Methylation Age

NHANES: National Health and Nutrition Examination Survey

OPP: Organophosphorous Pesticides

PCBs: Polychlorinated bisphenols

PPP: Plant Protection Products

TL: Telomere length

WHO: World Health Organization

Annex 5. Background to the Report

The request to the Scientific Advice Mechanism (SAM) to investigate the topic 'Authorisation Processes of Plant Protection Products in Europe' came from the Commissioner for Health and Food Safety, Vytenis Andriukaitis, via the Commissioner for Research, Science and Innovation, Carlos Moedas, and was taken up by the Group of Chief Scientific Advisors.

Based on the scoping paper (SAM-HLG, 2017)[w] , the key question asked was: 'Could the current EU dual system for approval and authorisation of plant protection products be rendered more effective, efficient, and transparent, and if so, how could this be achieved?'

Within the Group of Chief Scientific Advisors, Professor Sir Paul Nurse led on this topic, in cooperation with the Group of Chief Scientific Advisors members Professor Rolf-Dieter Heuer and Professor Janusz Bujnicki.

The SAPEA Consortium was asked to conduct a rapid evidence review and to produce an Evidence Review Report (ERR) on the topic.

Staff members from SAPEA and the SAM Unit met from April 2017 to discuss project scope and working processes. The SAPEA Working Group met from June 2017

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[w] SAM-HLG (2017). Scoping paper: Authorisation processes of plant protection products in Europe from a scientific point of view. Revision 7, 23 April 2017. Available for download at https://ec.europa.eu/research/sam/index.cfm?pg=pesticides

to develop scientific content based on the scoping paper. A Coordination Group meeting in August 2017, chaired by Professor Nurse, further refined project scope. The Coordination Group was composed of the involved Members of the Group of Chief Scientific Advisors and the SAPEA Working Group Chair and Deputy-Chair. From September 2017, Professor Ole Petersen joined the Coordination Group as a representative of the SAPEA Board.

SAPEA set up an international and interdisciplinary Working Group, based on a process of formal nomination by academies and the academy networks participating in the SAPEA. Nominee assessment by the SAPEA Board followed established guidelines, whilst adhering to the primary criterion of scientific excellence in the field. All members of the Working Group (Annex 1) were required to declare any conflict of interest. The Working Group was chaired by Professor Evangelia Ntzani, University of Ioannina (Greece), with Professor David Coggon, University of Southampton (United Kingdom) as her deputy.

The Working Group held two face-to-face meetings and five meetings via telephone conference between June 2017 and January 2018. Appointed staff members from SAPEA and the SAM Unit attended these meetings. The Working Group reviewed and revised the original sub-questions, wrote the ERR, and provided scientific input in supporting literature searches conducted by the Joint Research Centre. The SAM Unit provided further references, mostly covering grey literature.

A first draft of the ERR was scrutinised at an expert workshop with invited external experts on 26 October 2017, hosted at the European Commission and set up to act as a bridge between the SAPEA ERR and the Scientific Opinion, written by the SAM Unit and the Group of Chief Scientific Advisors. The attending experts (Annex 2) provided written and verbal input on the first draft during and after the workshop, resulting in a revised ERR.

Some Working Group members also attended two additional workshops on PPP-related topics that could not be covered in this ERR due to time limitations (see Annex 6). The first was a 'Sounding Board' workshop examining the potential environmental impacts of the Options proposed in this ERR, organised by the SAM Unit and held in Berlin (Germany) on 19 December 2017. The second was a workshop entitled 'Risk Perception and the Acceptability of Human Exposure to Pesticides', organised by SAPEA in collaboration with the Institute for Advanced Sustainability Studies (IASS) and held in Berlin on 20 December 2017 (Annex 6). Both workshops resulted in separate reports that additionally inform the Scientific Opinion of the Group of Chief Scientific Advisors.

The revised report was peer reviewed in December 2017 and revised to address all reviewers' comments.

The final version of the report was approved by the SAPEA Board, on behalf of the Networks' member academies.

Both the Evidence Review Report and the Scientific Opinion were published at the same time, in June 2018. Together they inform the REFIT Evaluation of the EU legislation on plant protection products and pesticides residues[x] and thus contribute to the implementation of a more effective, efficient, and transparent authorisation system of plant protection products that incorporates the latest scientific developments and discoveries. In addition, both reports aim to make important contributions to the planning of the EU's future political priorities and resource allocation.

[x] The Evaluation and Fitness Check Roadmap for the REFIT Evaluation of Regulations (EC) No 1107/2009 and No 396/2005) is available for download here: http://ec.europa.eu/smart-regulation/roadmaps/docs/2016_sante_197_ealuation_plant_protection_products_en.pdf.

Annex 6. Additional events informing ERR and Scientific Opinion

Due to time limitations, the SAPEA Working Group was requested to focus on human-health considerations in this evidence review report (ERR). However, pesticides have numerous strong environmental impacts and public concerns about the risks from pesticides are manifold. To ensure that the Group of Chief Scientific Advisors' Scientific Opinion is broadly informed, the following events provided additional information for both the SAPEA ERR and the Group of Chief Scientific Advisors' Scientific Opinion. Both events were attended by members of the Group of Chief Scientific Advisors, members of the SAPEA Working Group, experts in the respective fields, and staff members of SAPEA and the Scientific Advice Mechanism (SAM Unit).

1. ENVIRONMENTAL IMPACTS OF PLANT PROTECTION PRODUCTS - SOUNDING BOARD

This workshop was organised by the SAM Unit and held on 19 December 2017 at the Berlin-Brandenburg Academy of Sciences and Humanities, Berlin (Germany). The goals of this workshop were (1) to examine the draft SAPEA evidence review report, ensuring that the proposed Options for improvement intended to be beneficial for human health would not be detrimental for the environment, or for the efficiency and transparency of the assessment of risks to the environment; and (2) to identify any other observations which might enhance the protection of the environment (and human health). These latter observations would signal to the European Commission Group of Chief Scientific Advisors important terms relating to the environment that would need to be considered further in a possible future assessment. The workshop concluded that none of the proposed Options were identified as potentially reducing levels of environmental protection, but it was highlighted that most PPPs are designed to reduce weeds and invertebrate pest species so that products safe to humans may be harmful to non-target organisms in the environment. The attending experts made several suggestions for possible improvements to the authorisation process that might enhance the protection of the environment.

A Summary Report of this workshop is available for download at: https://ec.europa.eu/research/sam/pdf/topics/pesticides_meeting_122017_summary.pdf#view=fit&pagemode=none

2. WORKSHOP 'RISK PERCEPTION AND THE ACCEPTABILITY OF HUMAN EXPOSURE TO PESTICIDES'

This workshop was organised jointly by SAPEA and the Institute for Advanced Sustainability Studies (IASS) and held on 20 December 2017 at the Berlin-Brandenburg Academy of Sciences and Humanities, Berlin (Germany). The objectives were (1) to facilitate an exchange of experiences and research results among regulators and natural and social scientists in the field of pesticide regulation, and specifically to reach a better understanding of the underlying mechanisms and triggers for public concern about human exposure to pesticides; (2) to provide and discuss empirical evidence about risk perception and its implication for individual and political behaviour; and (3) to delineate risk management and communication strategies that address public concerns and their psychological and social causes. The workshop concluded that toxicological risks from pesticides in food are assessed and perceived very differently by scientific researchers, stakeholders, and the public. Stakeholders and members of the public are often unable to react appropriately to scientific risk assessments and tend to over- or underestimate risks. The level of trust in the risk-assessing authority is one of the crucial variables that determine whether a person is willing to accept a certain risk to obtain the corresponding benefit, or whether that person weights the risk higher than the benefit. Successful risk communication has to acknowledge that risk perception is an essential part of handling risk in society and has a strong influence on how a society copes with uncertainty and ambiguity. Risk communication can only be effective if risk communicators put risks in context, and has to show the boundaries between what is possible, likely, certain or definitely wrong, or absurd. Scientific assessments are able to place risk in a proper perspective, characterise remaining uncertainties, and provide reliable anchors for prudent judgements of how to manage and regulate risks.

A report of this workshop is available for download at:
www.sapea.info/workshopriskperceptionacceptability

Annex 7. Glossary of key definitions and terms

Glossary compiled from various sources, including consultations with experts.

Active substance	A component of a plant protection product, the biological activity of which is responsible for the product's intended beneficial effect(s).
Apical effects	An effect (or endpoint) that is an observable outcome in a whole organism, such as a clinical sign or pathologic abnormality, that is indicative of a disease state, which can result from exposure to a toxicant. When it is the most sensitive, relevant effect observed, it often serves as the basis for establishing a reference value, and it is then known as the critical effect.
Benchmark Dose	An estimate of the dose that causes a low but measurable effect (e.g. a 5% reduction in body or organ weight or a 10% increase in the incidence of kidney toxicity), referred to as the Benchmark Response (BMR).
Biomarker	An objectively measurable characteristic that can be used as an indicator of a person's or animal's exposure to an external agent or its biological effects.
Biopesticides	Active substances in plant protection products or biocides that are microbial organisms, pheromones or attractants, or natural extracts (e.g. from plants).
Carcinogenicity	Cancer-causing property of a chemical, physical or biological agent, or process.
Chemometrics	The science relating measurements made on a chemical system or process to the state of the system through application of mathematical or statistical methods.
Codex Alimentarius	The Codex Alimentarius, or «Food Code» is a collection of standards, guidelines and codes of practice adopted by the Codex Alimentarius Commission. The Commission, also known as CAC, is the central part of the Joint FAO/WHO Food Standards Programme and was established by FAO and WHO to protect consumer health and promote fair practices in food trade. It held its first meeting in 1963.
Co-formulant	Any component not classed as an active substance that is intentionally included in a formulation ("plant protection product").
Cohort study	An epidemiological study in which characteristics and/or exposures that might influence or predict future health outcomes are assessed in a sample of people (cohort), selected according to specified criteria, and related to the subsequent occurrence of those outcomes.

Confounding	A potential source of error in epidemiological research, which occurs when an exposure of interest is statistically associated with a second exposure or attribute, which independently determines the risk of a health outcome. As a consequence of confounding, the causal effect of the exposure of interest on the health outcome may be under- or over-estimated.
de novo evaluation	Evaluation for the first time.
Degradate / degradation product	A chemical that is formed when a substance breaks down or decomposes.
Developmental (neuro) toxicity	i) The occurrence of adverse effects on the (neurological) development of humans or animals through the action of a chemical or physical agent. ii) The ability of a chemical or physical agent to cause adverse effects on the (neurological) development of humans or animals through its biochemical activity.
Epidemiology	The branch of science that investigates the distribution of health and disease in populations and its determinants.
Epigenetics	The study of heritable changes that are not the result of changes in the DNA sequence. Information that is heritable during cell division other than the DNA sequence itself. Changes in gene expression that are not regulated by the DNA nucleotide sequence.
Hazard	A potential adverse effect of an agent or circumstance.
Immunotoxicity	i) The occurrence of adverse effects on the immune system or function of animals or humans through the action of a chemical or physical agent. ii) The ability of a chemical or physical agent to cause adverse effects on the immune system or function of animals or humans through its biochemical activity.
in silico approach	Integration of modern computing and information technology to model, simulate, or predict any aspect of the toxicokinetics or toxicodynamics of chemicals.
in vitro	"In glass", a term applied to research that involves tests on cell constituents, cells, or tissues extracted from living organisms.
in vivo	A term applied to research that involves tests on individual live animals or populations of live animals.
Mendelian randomisation study	A type of epidemiological study that investigates possible effects of a chemical on a health outcome by assessing the association of the outcome with genes that modify metabolism of the chemical.
Microphysiological systems	Devices capable of emulating human (or any other animal species') biology in vitro at the smallest biologically acceptable scale, defined by purpose.

Mode(s) of action	A sequence of events, identified by research, which explain an observed outcome.
Moiety	A segment, portion, or part of a molecule that may include a substructure of the functional group. For example, benzyl acetate has an acetyl moiety and benzyl alcohol moiety.
Molecular docking	The study of how two or more molecular structures (e.g. drug and enzyme or protein) fit together. In a simple definition, docking is a molecular modelling (in silico) technique that is used to predict how a protein (enzyme) interacts with small molecules (ligands). The ability of a protein (enzyme) and nucleic acid to interact with small molecules to form a supramolecular complex plays a major role in the dynamics of the protein, which may enhance or inhibit its biological function. The behaviour of small molecules in the binding pockets of target proteins can be described by molecular docking.
Molecular initiating events	The initial interaction between a chemical and a biomolecule or biosystem that can be causally linked to an outcome via a pathway.
Nanoparticle	A microscopic particle, at least one dimension of which ranges from 1 to 100 nanometers.
Nanopesticides	A pesticide which contains miniscule particles or droplets, typically measuring between 1 and 100 nanometers in diameter.
No Observed Adverse Effect Level	The highest dose level in an in-vivo toxicity study at which, based on statistical comparison with unexposed contemporary controls, together with any other relevant considerations (e.g. findings at higher doses), there is judged to be no clear evidence of any treatment-related adverse effect.
Points of departure	Doses of an active substance, at which relevant studies indicate no or only minimal toxicity, according to specified criteria.
Read-across	A technique for predicting endpoint information for one substance (target substance), by using data on the same endpoint from (an)other substance(s).
Risk	The probability of an adverse effect occurring in an organism, system, or (sub-)population in specified circumstances of exposure to a hazardous agent.
Sensitising effects	Effects in which the immune system becomes sensitised to a chemical so that future exposures generate an enhanced immunological response, which in some cases may cause illness.
Structure-activity analysis / structure activity relationships	A set of methods by which the effects of different compounds are related to their molecular structures. It allows the likely adverse or beneficial effects of a particular chemical to be predicted by comparing it with others which have similar structures. An in silico approach.

Surveillance	Systematic, continuous or repeated collection, analysis, and interpretation of data.
Suspension concentrate	A stable suspension of active substance(s) that is intended for dilution with water before use.
Synergic effects / synergistic effect	An interaction that results in an outcome greater than that predicted through dose or response addition. The outcome in question may be beneficial or adverse.
Tank mix	A mixture of two or more PPPs that is prepared by an operator in a spray tank before they are applied.
Toxicity pathway / adverse outcome pathway	A causal chain of events that is responsible for a harmful outcome for an organism or the environment.
Toxicodynamics	The process of interaction of chemical substances with target sites of action within the body and the subsequent reactions leading to adverse effects and responses.
Toxicokinetics	The processes by which potentially toxic substances are taken up and handled in the body. This involves the processes of absorption, distribution, metabolism and excretion of such substances.
Toxicological reference value	A level of exposure to an active substance, below which there is high confidence that adverse effects will not occur, even in individuals who are relatively sensitive (e.g. because of genetic predisposition or their age).
Toxicology	Scientific discipline involving the study of the actual or potential danger presented by the harmful effects of substances on living organisms and ecosystems, of the relationship of such harmful effects to exposure, and of the mechanisms of action, diagnosis, prevention, and treatment of intoxications.
Xenobiotic (disposition, toxicities)	A chemical compound that is foreign to a biological or an ecological system. A substance, typically a synthetic chemical, that is foreign to the body. Examples include many synthetic pesticides and their derivatives, food additives, or persistent toxic substances such as dioxins and polychlorinated biphenyls (PCBs).

Annex 8. List of abbreviations

AChE: Acetylcholinesterase

ADHD: Attention Deficit Hyperactivity Disorder

ADME: Absorption, Distribution, Metabolism, and Excretion

ALSPAC: Avon Longitudinal Study of Parents and Children

AOP: Adverse Outcome Pathways

BMD: Benchmark Dose

BMDL: Benchmark Dose Lower Bound

BMI: Body Mass Index

CAC : Codex Alimentarius Commission

DBCP : 1,2-dibromo-3-chloropropane

DNA: Desoxiribonucleic Acid

EC: European Commission

ECHA: European Chemicals Agency

EFSA: European Food Safety Authority

EPA: Environmental Protection Agency, USA

EU: European Union

EURL

-ECVAM: The European Union Reference Laboratory for Alternatives to Animal Testing

EWAS: Environment-wide association studies

FAO: Food and Agriculture Organization

GAP: Good Agricultural Practice

GWAS: Genome-wide association studies

ICVAM: Interagency Coordinating Committee on the Validation of Alternative Methods (US)

IPCS: International Programme on Chemical Safety

MIE: Molecular Initiating Event

MOA: Mode of Action

MRL: Maximum Residue Level

NAMs: New Approach Methods

NHANES: National Health and Nutrition Examination Survey

NOAEL: No Observed Adverse Effect Level

NRC: National Research Council

OECD: Organisation for Economic Co-operation and Development

PAHES: Pesticides Adverse Health Effects Surveillance Scheme

PPP: Plant Protection Product

PPR: Plant Protection Products and Residues

QSAR: Quantitative Structure Activity Relationship

REACH: Regulation EC 1907/2006 on Registration, Evaluation, Authorisation and Restriction of Chemicals

RNA: Ribonucleic Acid

SAPEA: Scientific Advice for Policy by European Academies

TG: Test Guidelines

WHO: World Health Organization

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Spanning the disciplines of engineering, humanities, medicine, natural sciences and social sciences, SAPEA brings together the outstanding knowledge and expertise from over 100 academies, young academies and learned societies in over 40 countries across Europe.

SAPEA is part of the European Scientific Advice Mechanism (SAM), which provides independent, interdisciplinary and evidence-based scientific advice on policy issues to the European Commission. SAPEA works closely with the European Commission Group of Chief Scientific Advisors.

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