Introduction to the «EFSA epidemiology project»

Federica Crivellente,
Pesticides Unit - EFSA

Scientific Conference on the "Use of Epidemiological findings in regulatory Pesticide Risk Assessment", EFSA, Parma
21 November 2017

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European Food Safety Authority

EPIDEMIOLOGICAL STUDIES ON PESTICIDES - REGULATION

In Europe, plant protection products are regulated by:

- **Regulation 1107/2009** concerning the placing of plant protection products on the market
- **Regulation 283/2013** setting out the data requirements for active substances:

«Relevant epidemiological studies shall be submitted, where available»

- No obligation for the petitioners to conduct epidemiological studies for the AS undergoing the approval or renewal process
- systematic literature review is required for the a.s. and its relevant metabolites and published within the last ten years before the date of the submission of the dossier
- in Europe usually available after the first approval of an a. s. and therefore not included in the DAR (unless prior approval in another jurisdiction)

BACKGROUND- EFSA ESTERNAL SCIENTIFIC REPORT

EXTERNAL SCIENTIFIC REPORT

Literature review on epidemiological studies linking exposure to pesticides and health effects[1]

Evangelia E Ntzani, Chondrogiorgi M, Ntritsos G, Evangelou E, Tzoulaki I

Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, Greece

http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2013.EN-497/abstract

- Systematic literature review of epidemiological studies published between 2006 and 2012 (summarises the association between pesticide exposure and any health outcome)
- A statistically significant association was observed through fixed and random effect meta-analysis between pesticide exposure and:
  - Liver, breast and stomach cancer
  - Amyotrophic lateral sclerosis
  - Asthma
  - Type II diabetes
  - Childhood leukaemia
  - Parkinson's disease

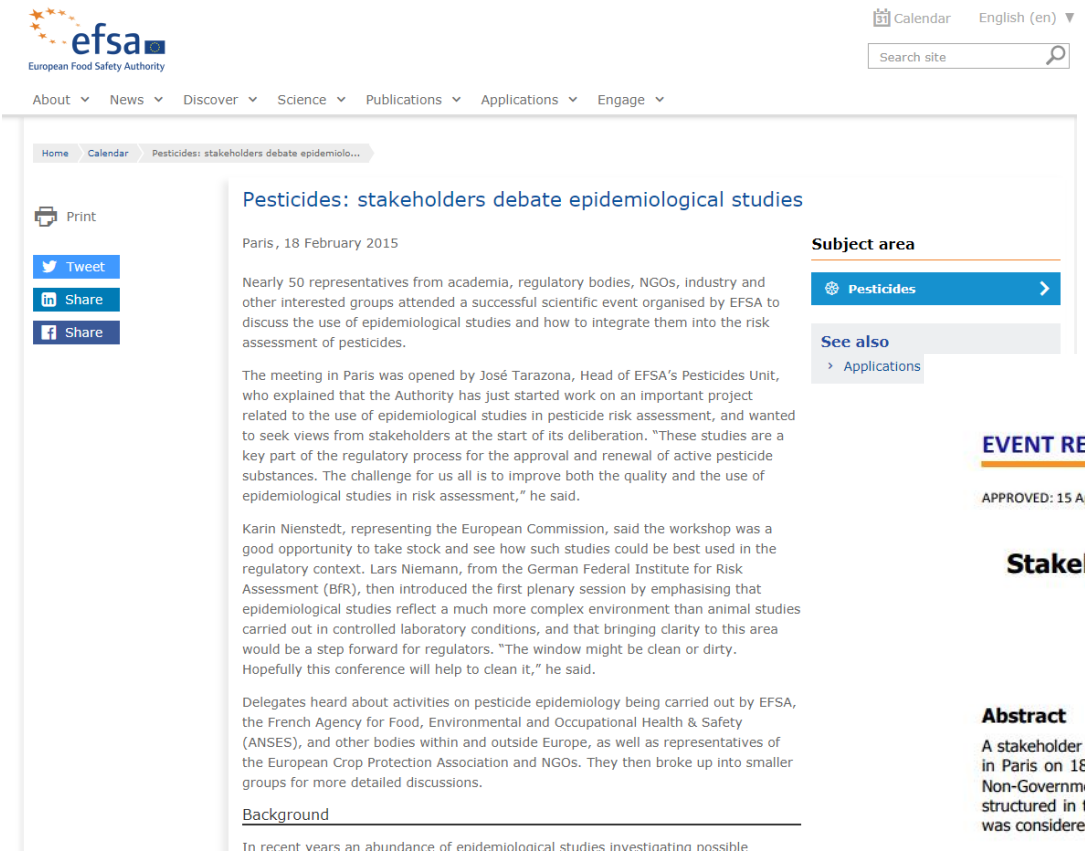
BACKGROUND – CONT'D

- The authors of the report could not draw firm conclusions for the majority of the health outcomes
  - Epidemiological studies suffer from a number of limitations and large heterogeneity of data
  - Broad pesticides definitions
  - The scope of the report did not allow the in-depth associations between pesticide exposure and specific health outcomes

- Mandate for 2 Scientific Opinions:
  1. Investigation into experimental toxicological properties of PPP having a potential link to Parkinson's disease and childhood leukaemia
  2. Epidemiological studies in Pesticide Risk Assessment

SUMMARY OF EFSA ACTIVITIES

STAKEHOLDER WORKSHOP-PARIS 2015



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Pesticides: stakeholders debate epidemiological studies

Paris, 18 February 2015

Nearly 50 representatives from academia, regulatory bodies, NGOs, industry and other interested groups attended a successful scientific event organised by EFSA to discuss the use of epidemiological studies and how to integrate them into the risk assessment of pesticides.

The meeting in Paris was opened by José Tarazona, Head of EFSA's Pesticides Unit, who explained that the Authority has just started work on an important project related to the use of epidemiological studies in pesticide risk assessment, and wanted to seek views from stakeholders at the start of its deliberation. "These studies are a key part of the regulatory process for the approval and renewal of active pesticide substances. The challenge for us all is to improve both the quality and the use of epidemiological studies in risk assessment," he said.

Karin Nienstedt, representing the European Commission, said the workshop was a good opportunity to take stock and see how such studies could be best used in the regulatory context. Lars Niemann, from the German Federal Institute for Risk Assessment (BfR), then introduced the first plenary session by emphasising that epidemiological studies reflect a much more complex environment than animal studies carried out in controlled laboratory conditions, and that bringing clarity to this area would be a step forward for regulators. "The window might be clean or dirty. Hopefully this conference will help to clean it," he said.

Delegates heard about activities on pesticide epidemiology being carried out by EFSA, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), and other bodies within and outside Europe, as well as representatives of the European Crop Protection Association and NGOs. They then broke up into smaller groups for more detailed discussions.

Background

In recent years an abundance of epidemiological studies investigating possible

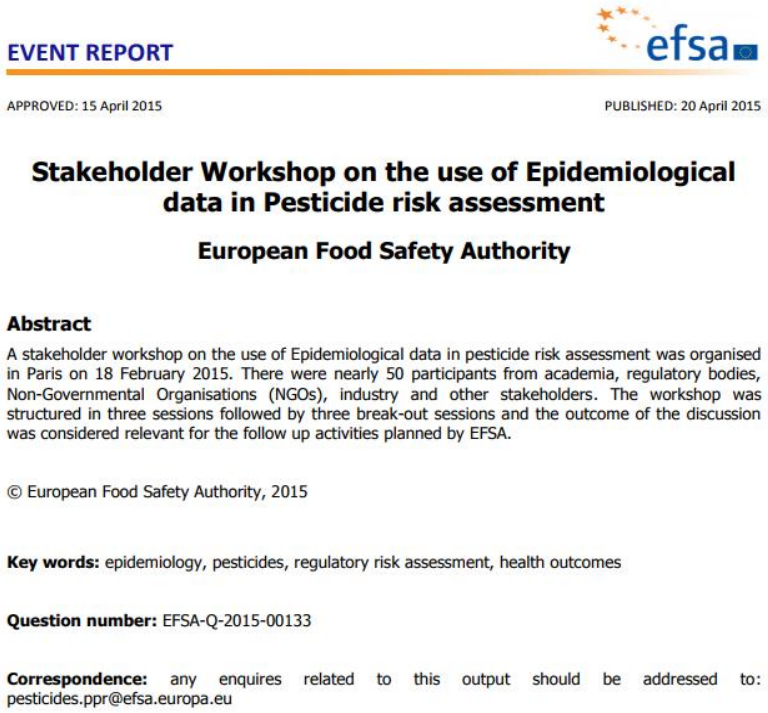
Subject area

Pesticides

See also

› Applications

- 50 participants from academia, regulatory bodies, NGOs, industry and other stakeholders



EVENT REPORT

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APPROVED: 15 April 2015

PUBLISHED: 20 April 2015

Stakeholder Workshop on the use of Epidemiological data in Pesticide risk assessment

European Food Safety Authority

Abstract

A stakeholder workshop on the use of Epidemiological data in pesticide risk assessment was organised in Paris on 18 February 2015. There were nearly 50 participants from academia, regulatory bodies, Non-Governmental Organisations (NGOs), industry and other stakeholders. The workshop was structured in three sessions followed by three break-out sessions and the outcome of the discussion was considered relevant for the follow up activities planned by EFSA.

Key words: epidemiology, pesticides, regulatory risk assessment, health outcomes

Question number: EFSA-Q-2015-00133

Correspondence: any enquires related to this output should be addressed to: pesticides.ppr@efsa.europa.eu

http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2015.EN-798/abstract

AIM AND OUTCOME OF THE STAKEHOLDER WORKSHOP

- Organised to discuss the use of epidemiological studies in the risk assessment of pesticides
- Structured in three sessions followed by three break out sessions
- The use of epi studies and their integration in regulatory RA was still limited
- Intrinsic difficulties to evaluate epidemiological observational studies (definition of causality, lack of reliable characterisation of exposure and biological plausibility). Need to improve exposure assessment was considered a priority

1ST SCIENTIFIC OPINION

https://www.efsa.europa.eu/it/efsajournal/pub/4691

- Analysis of the involvement of pesticides exposure as a risk factor in the pathogenesis of PD and CHL (intrinsic weaknesses of epi studies that do not allow firm conclusions on causal relationships)
- The AOP framework was used to assess biological plausibility of epidemiological association between pesticide exposures and human health outcomes

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 14 December 2016

doi: 10.2903/j.efsa.2017.4691

Investigation into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia[1]

EFSA Panel on Plant Protection Products and their residues (PPR), Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne, Sandro Grilli, Antonio F Hernandez-Jerez, Susanne Hougaard Bennekou, Michael Klein, Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Rob Smith, Michael Stemmer, Ingvar Sundh, Ivana Teodorovic, Aaldrik Tiktak, Chris J Topping, Gerrit Wolterink, Karine Angeli, Ellen Fritsche, Antonio F Hernandez-Jerez, Marcel Leist, Alberto Mantovani, Pablo Menendez, Olavi Pelkonen, Anna Price, Barbara Viviani, Arianna Chiusolo, Federica Ruffo, Andrea Terron and Susanne Hougaard Bennekou

Abstract

In 2013, EFSA published a literature review on epidemiological studies linking exposure to pesticides and human health outcome. As a follow up, the EFSA Panel on Plant Protection Products and their residues (PPR Panel) was requested to investigate the plausible involvement of pesticide exposure as a risk factor for Parkinson's disease (PD) and childhood leukaemia (CHL). A systematic literature review on PD and CHL and mode of actions for pesticides was published by EFSA in 2016 and used as background documentation. The Panel used the Adverse Outcome Pathway (AOP) conceptual framework to define the biological plausibility in relation to epidemiological studies by means of identification of specific symptoms of the diseases as AO. The AOP combines multiple information and provides knowledge of biological pathways, highlights species differences and similarities, identifies research needs and supports regulatory decisions. In this context, the AOP approach could help in organising the available experimental knowledge to assess biological plausibility by describing the link between a molecular initiating event (MIE) and the AO through a series of biologically plausible and essential key events (KEs). As the AOP is chemically agnostic, tool chemical compounds were selected to empirically support the response and temporal concordance of the key event relationships (KERs). Three qualitative and one putative AOP were developed by the Panel using the results obtained. The Panel supports the use of the AOP framework to scientifically and transparently explore the biological plausibility of the association between pesticide exposure and human health outcomes, identify data gaps, define a tailored testing strategy and suggests an AOP's informed Integrated Approach for Testing and Assessment (IATA).

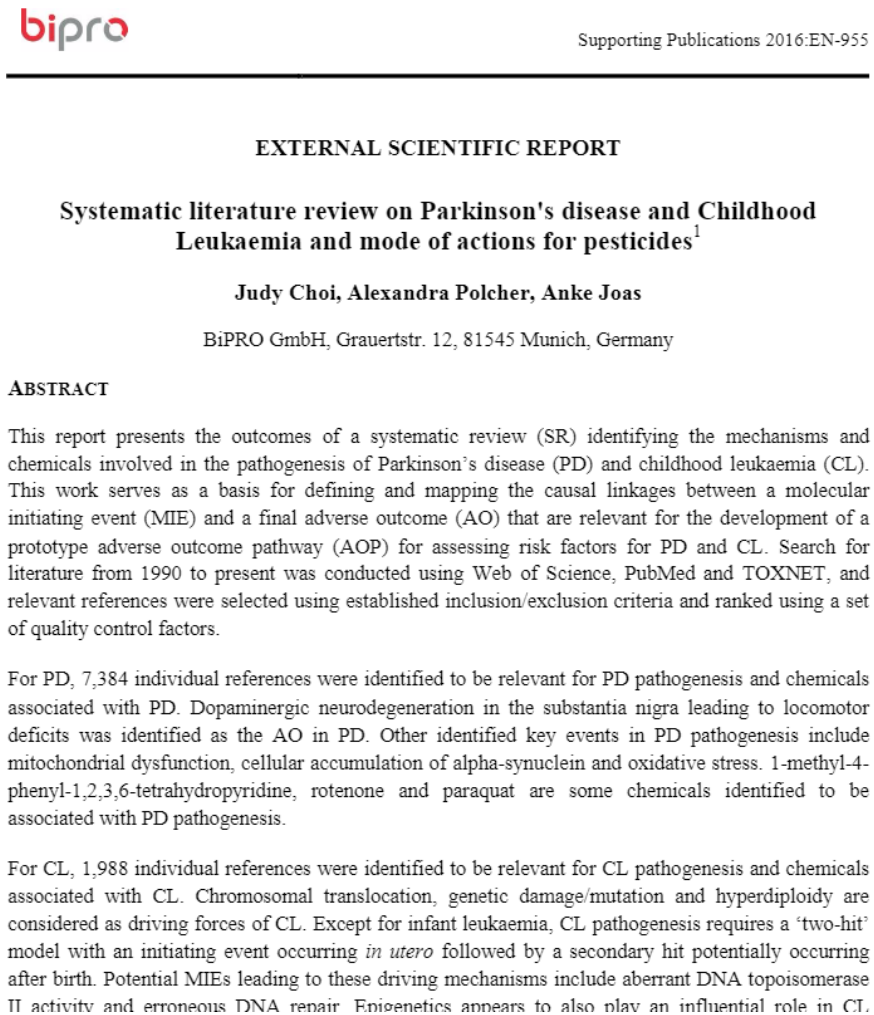
Keywords: AOP, Parkinson's disease, childhood leukaemia, infant leukaemia, pesticides, epidemiology

Requestor: European Food Safety Authority

Question number: EFSA-Q-2014-00490

SYSTEMATIC LITERATURE REVIEW ON PD AND CL

- http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2016.EN-955/epdf
- Systematic literature review of relevant publications related to the mechanisms involved in the pathogenesis of PD and CL
- to define and map the causal linkages between a molecular initiating event and a final adverse outcome at the biological level of the disease and to identify the key steps in the pathogenesis of these two diseases that might involve chemical agents (including pesticides)
- The outcomes of the SR provided basis for the development of a prototype Adverse Outcome Pathway (AOP) for assessing risk factors for PD and CL



bipro

Supporting Publications 2016:EN-955

EXTERNAL SCIENTIFIC REPORT

Systematic literature review on Parkinson's disease and Childhood Leukaemia and mode of actions for pesticides[1]

Judy Choi, Alexandra Polcher, Anke Joas

BiPRO GmbH, Grauertstr. 12, 81545 Munich, Germany

ABSTRACT

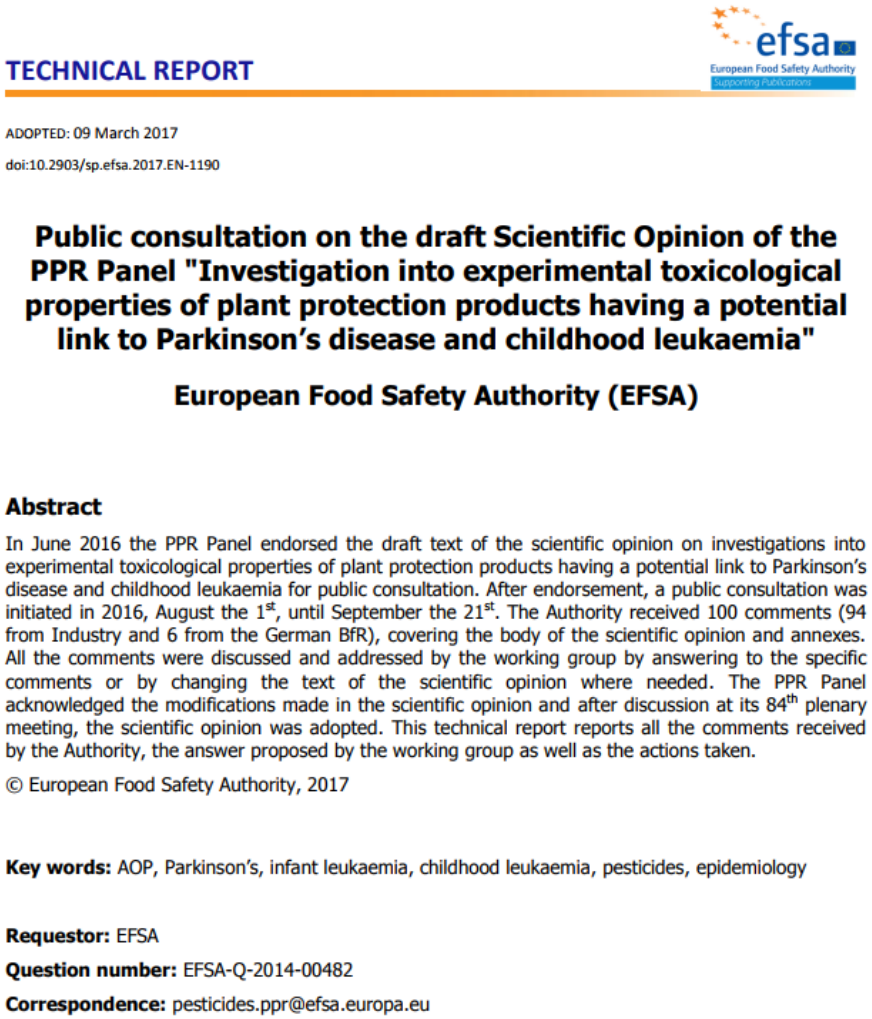
This report presents the outcomes of a systematic review (SR) identifying the mechanisms and chemicals involved in the pathogenesis of Parkinson's disease (PD) and childhood leukaemia (CL). This work serves as a basis for defining and mapping the causal linkages between a molecular initiating event (MIE) and a final adverse outcome (AO) that are relevant for the development of a prototype adverse outcome pathway (AOP) for assessing risk factors for PD and CL. Search for literature from 1990 to present was conducted using Web of Science, PubMed and TOXNET, and relevant references were selected using established inclusion/exclusion criteria and ranked using a set of quality control factors.

For PD, 7,384 individual references were identified to be relevant for PD pathogenesis and chemicals associated with PD. Dopaminergic neurodegeneration in the substantia nigra leading to locomotor deficits was identified as the AO in PD. Other identified key events in PD pathogenesis include mitochondrial dysfunction, cellular accumulation of alpha-synuclein and oxidative stress. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, rotenone and paraquat are some chemicals identified to be associated with PD pathogenesis.

For CL, 1,988 individual references were identified to be relevant for CL pathogenesis and chemicals associated with CL. Chromosomal translocation, genetic damage/mutation and hyperdiploidy are considered as driving forces of CL. Except for infant leukaemia, CL pathogenesis requires a 'two-hit' model with an initiating event occurring *in utero* followed by a secondary hit potentially occurring after birth. Potential MIEs leading to these driving mechanisms include aberrant DNA topoisomerase II activity and erroneous DNA repair. Epigenetics appears to also play an influential role in CL

PUBLIC CONSULTATION OF THE 1ST OPINION

- 100 comments received
- Public Consultation Report (http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2017.EN-1190/pdf)



TECHNICAL REPORT

ADOPTED: 09 March 2017

doi:10.2903/sp.efsa.2017.EN-1190

Public consultation on the draft Scientific Opinion of the PPR Panel "Investigation into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia"

European Food Safety Authority (EFSA)

Abstract

In June 2016 the PPR Panel endorsed the draft text of the scientific opinion on investigations into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia for public consultation. After endorsement, a public consultation was initiated in 2016, August the 1st, until September the 21st. The Authority received 100 comments (94 from Industry and 6 from the German BfR), covering the body of the scientific opinion and annexes. All the comments were discussed and addressed by the working group by answering to the specific comments or by changing the text of the scientific opinion where needed. The PPR Panel acknowledged the modifications made in the scientific opinion and after discussion at its 84th plenary meeting, the scientific opinion was adopted. This technical report reports all the comments received by the Authority, the answer proposed by the working group as well as the actions taken.

Key words: AOP, Parkinson's, infant leukaemia, childhood leukaemia, pesticides, epidemiology

Requestor: EFSA

Question number: EFSA-Q-2014-00482

Correspondence: pesticides.ppr@efsa.europa.eu

2ND SCIENTIFIC OPINION

http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.5007/full

- To assess the methodological limitations of pesticide epidemiological studies
- To provide recommedations to improve the quality and reliability of pesticide epidemiological studies to overcome the limitations and to facilitate an appropriate use for RA
- To propose a methodological approach to integrate and weight multiple lines of evidence, including epidemiological data for pesticide RA

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 20 September 2017

doi: 10.2903/j.efsa.2017.5007

Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'

EFSA Panel on Plant Protection Products and their Residues (PPR), Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne, Sandro Grilli, Susanne Hougaard, Michael Klein, Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Rob Smith, Michael Stemmer, Ingvar Sundh, Ivana Teodorovic, Aaldrik Tiktak, Chris J. Topping, Gerrit Wolterink, Matteo Bottai, Thorhallur Halldorsson, Paul Hamey, Marie-Odile Rambourg, Ioanna Tzoulaki, Daniele Court Marques, Federica Crivellente, Hubert Deluyker and Antonio F. Hernandez-Jerez

Abstract

In 2013, EFSA published a comprehensive systematic review of epidemiological studies published from 2006 to 2012 investigating the association between pesticide exposure and many health outcomes. Despite the considerable amount of epidemiological information available, the quality of much of this evidence was rather low and many limitations likely affect the results so firm conclusions cannot be drawn. Studies that do not meet the 'recognised standards' mentioned in the Regulation (EU) No 1107/2009 are thus not suited for risk assessment. In this Scientific Opinion, the EFSA Panel on Plant Protection Products and their residues (PPR Panel) was requested to assess the methodological limitations of pesticide epidemiology studies and found that poor exposure characterisation primarily defined the major limitation. Frequent use of case–control studies as opposed to prospective studies was considered another limitation. Inadequate definition or deficiencies in health outcomes need to be avoided and reporting of findings could be improved in some cases. The PPR Panel proposed recommendations on how to improve the quality and reliability of pesticide epidemiology studies to overcome these limitations and to facilitate an appropriate use for risk assessment. The Panel recommended the conduct of systematic reviews and meta-analysis, where appropriate, of pesticide observational studies as useful methodology to understand the potential hazards of pesticides, exposure scenarios and methods for assessing exposure, exposure–response characterisation and risk characterisation. Finally, the PPR Panel proposed a methodological approach to integrate and weight multiple lines of evidence, including epidemiological data, for pesticide risk assessment. Biological plausibility can contribute to establishing causation.

Keywords: epidemiology, pesticides, risk assessment, quality assessment, evidence synthesis, lines

HUMAN BIOMONITORING DATA COLLECTION FROM OCCUPATIONAL EXPOSURE TO PESTICIDES

file:///D:/Downloads/Bevan_et_al-2017-EFSA_Supporting_Publications%20(2).pdf

- Systematic literature review of available information on HBM of pesticides in occupational setting

EXTERNAL SCIENTIFIC REPORT

APPROVED: 20/02/2017

Human biomonitoring data collection from occupational exposure to pesticides

Risk & Policy Analysts Limited (RPA)

IEH Consulting Limited (IEH)

Health & Safety Laboratory (HSL)

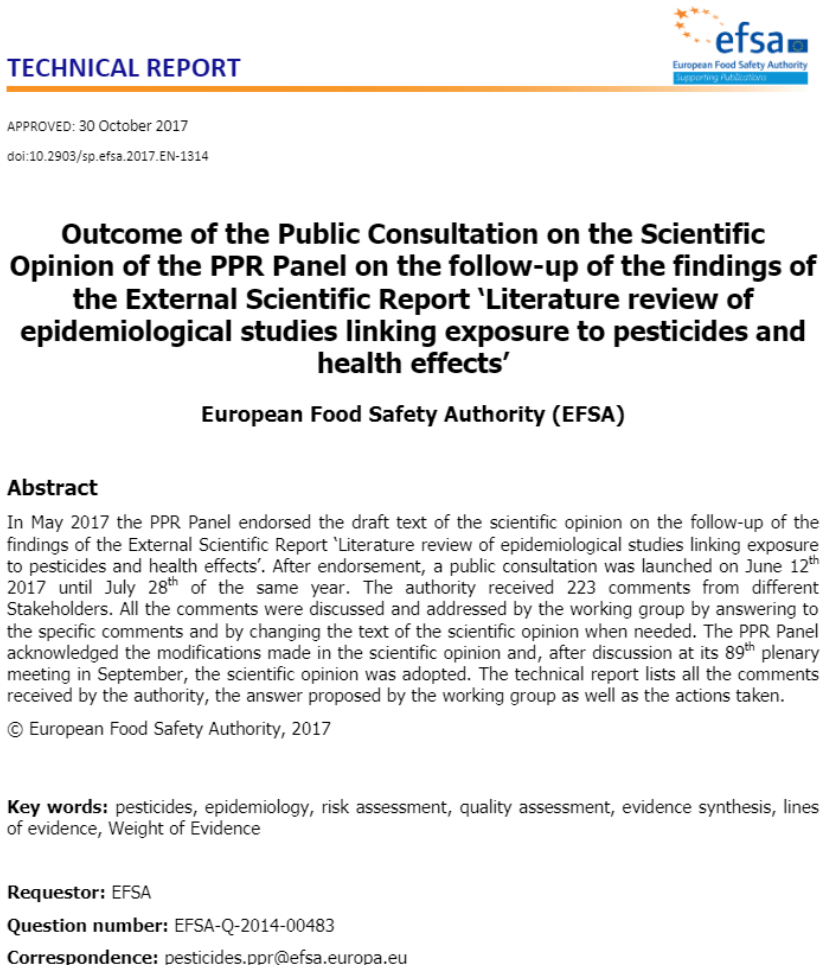
Main authors: Ruth Bevan (IEH), Terry Brown (IEH), Franziska Matthies (IEH), Craig Sams (HSL), Kate Jones (HSL), James Hanlon (RPA), Max La Vedrine (RPA)

Abstract

Human biomonitoring (HBM) as a tool for occupational exposure assessment has been reviewed, with a specific focus on pesticides. A systematic literature review (SLR) of available information on HBM of pesticides (or their metabolites) in occupational settings and from HBM studies/surveillance programmes has been carried out and the studies identified assessed for relevance and quality. HBM essentially involves the quantification of either a substance, one of its metabolites, or a surrogate marker of its effects in a biological sample obtained from a person who may have undergone an exposure. Thus, HBM is generally considered to be an estimate of exposure, rather than a measure of health. Over the past 10 to 20 years there has been an expansion in the use of HBM, especially into the field of environmental and consumer exposure analysis, and it is currently well-developed and widely used in both the occupational and environmental settings worldwide. As with any tool, HBM has its strengths and weaknesses and appreciation of these promotes the development of approaches to minimise their effects. Although HBM has been extensively used for monitoring worker exposure to a variety of pesticides, epidemiological studies of occupational pesticide use were seen to be limited by inadequate or retrospective exposure information. Very limited data was identified examining seasonal exposures and the impact of PPE, and many of the studies used HBM to assess only one or two specific compounds. A wide variety of exposure models are currently employed for health risk assessments and biomarkers are often used to evaluate exposure estimates predicted by a model. From the 178 publications identified to be of relevance, 41 individual studies included herbicides, 79 individual studies included insecticides, and 20 individual studies included fungicides. Remaining studies related to mixtures or non-specific biomarkers for groups of pesticides. Although a number of current limitations were identified, there is evidence within the literature for a potential role of HBM in occupational health and safety strategies, as both a tool for refined exposure assessment in epidemiology studies and to contribute to the evaluation of potential health risks from occupational exposure to pesticides. Some key issues were considered that would need to be overcome to enable implementation of HBM as part of the occupational health surveillance for pesticides in Europe. These included issues around priorities for the development of new specific and sensitive biomarkers, the

PUBLIC CONSULTATION OF THE 2ND OPINION

- 223 comments received
- Public Consultation Report (http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2017.EN-1314/epdf)



TECHNICAL REPORT

APPROVED: 30 October 2017

doi:10.2903/sp.efsa.2017.EN-1314

Outcome of the Public Consultation on the Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'

European Food Safety Authority (EFSA)

Abstract

In May 2017 the PPR Panel endorsed the draft text of the scientific opinion on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'. After endorsement, a public consultation was launched on June 12th 2017 until July 28th of the same year. The authority received 223 comments from different Stakeholders. All the comments were discussed and addressed by the working group by answering to the specific comments and by changing the text of the scientific opinion when needed. The PPR Panel acknowledged the modifications made in the scientific opinion and, after discussion at its 89th plenary meeting in September, the scientific opinion was adopted. The technical report lists all the comments received by the authority, the answer proposed by the working group as well as the actions taken.

Key words: pesticides, epidemiology, risk assessment, quality assessment, evidence synthesis, lines of evidence, Weight of Evidence

Requestor: EFSA

Question number: EFSA-Q-2014-00483

Correspondence: pesticides.ppr@efsa.europa.eu

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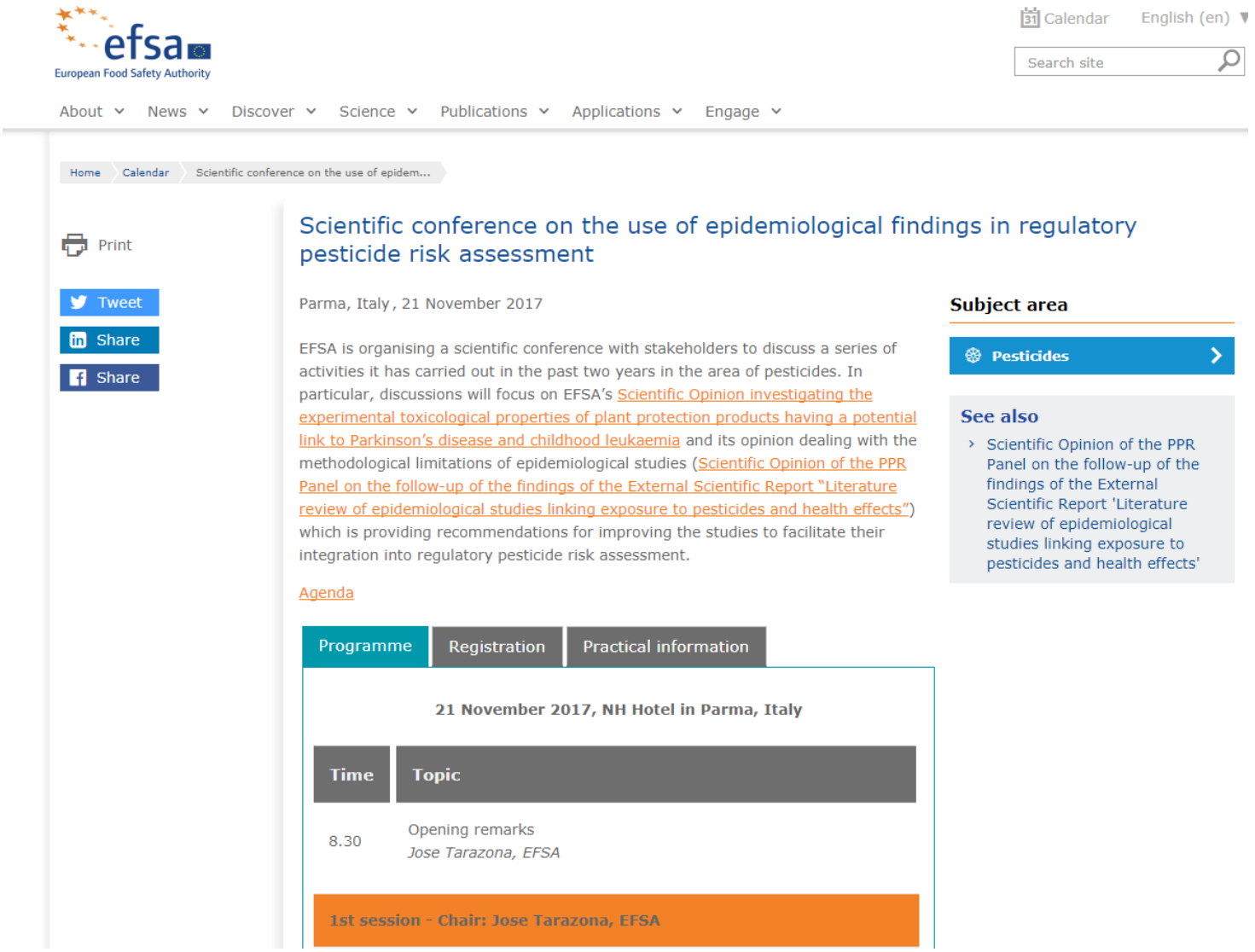

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Scientific conference on the use of epidemiological findings in regulatory pesticide risk assessment

Parma, Italy, 21 November 2017

EFSA is organising a scientific conference with stakeholders to discuss a series of activities it has carried out in the past two years in the area of pesticides. In particular, discussions will focus on EFSA's Scientific Opinion investigating the experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia and its opinion dealing with the methodological limitations of epidemiological studies (Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report "Literature review of epidemiological studies linking exposure to pesticides and health effects") which is providing recommendations for improving the studies to facilitate their integration into regulatory pesticide risk assessment.

Agenda

Subject area

Pesticides

See also

- Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'

Programme Registration Practical information

21 November 2017, NH Hotel in Parma, Italy

Time	Topic
8.30	Opening remarks *Jose Tarazona, EFSA*
1st session - Chair: Jose Tarazona, EFSA	

NEXT STEPS

- The Scientific Committee → overarching Guidance on the use of the epidemiological evidence in RA
- Other follow up activities?