

Occupational exposure to pesticides

Challenges for research, evaluation
and prevention

**Literature review on epidemiological
studies linking exposure to
pesticides and health effect**



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Conference
28&29
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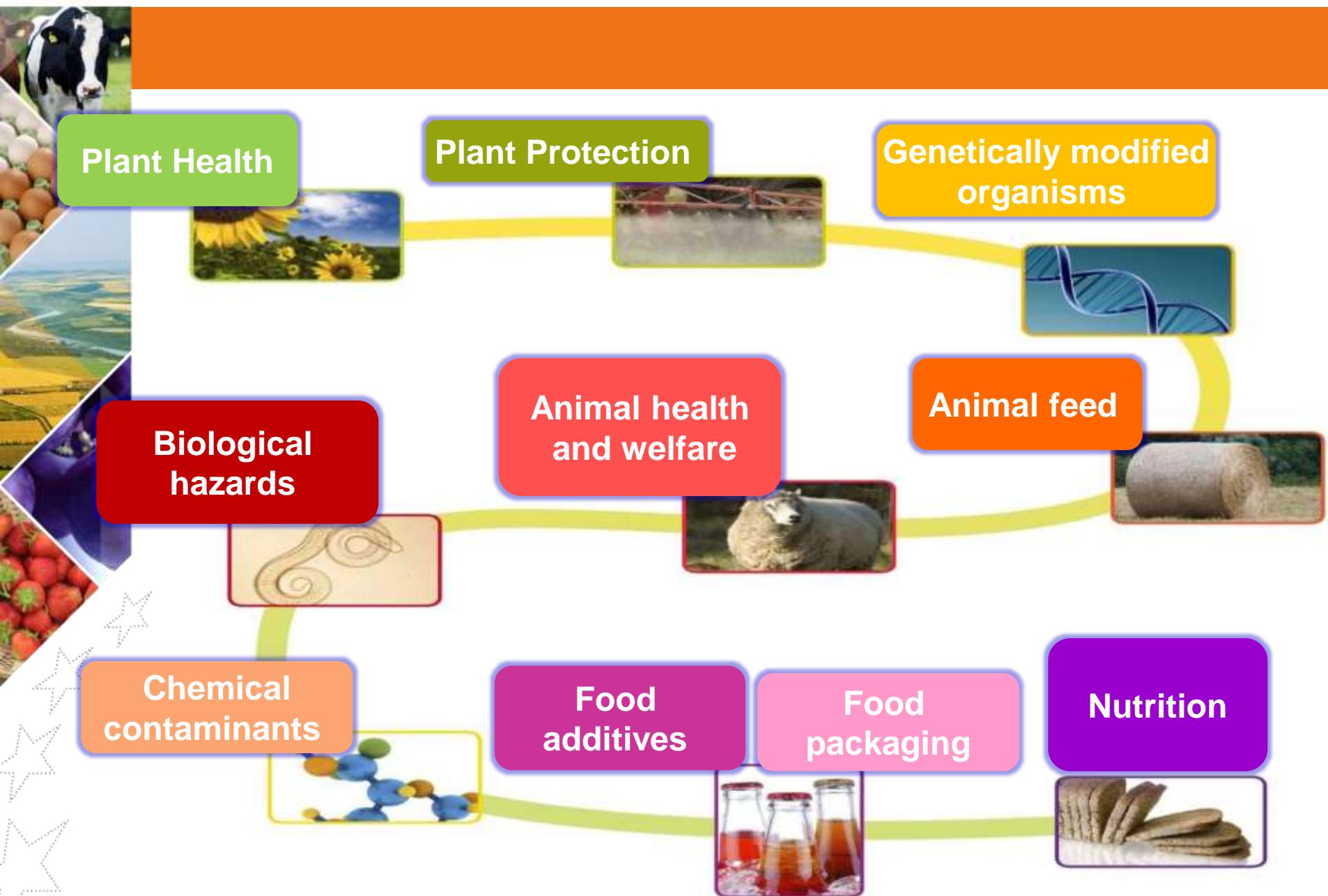
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What is EFSA?

- **E**uropean • The European reference body
- **F**ood • Covers the entire food chain
- **S**afety • Assess, advise, communicate
- **A**uthority • Independent, trusted, based on sound science



Pesticides Unit activities

Supports the Scientific Panel for pesticides PPR (Plant Protection Product and their Residues).

- Opinions
- Guidance documents
- Ad-hoc mandates

Coordinates the Peer Review of active substances

Provides **Conclusions** for single active substances to support the EU decision-makers

Maximum Residue Levels
MRLs

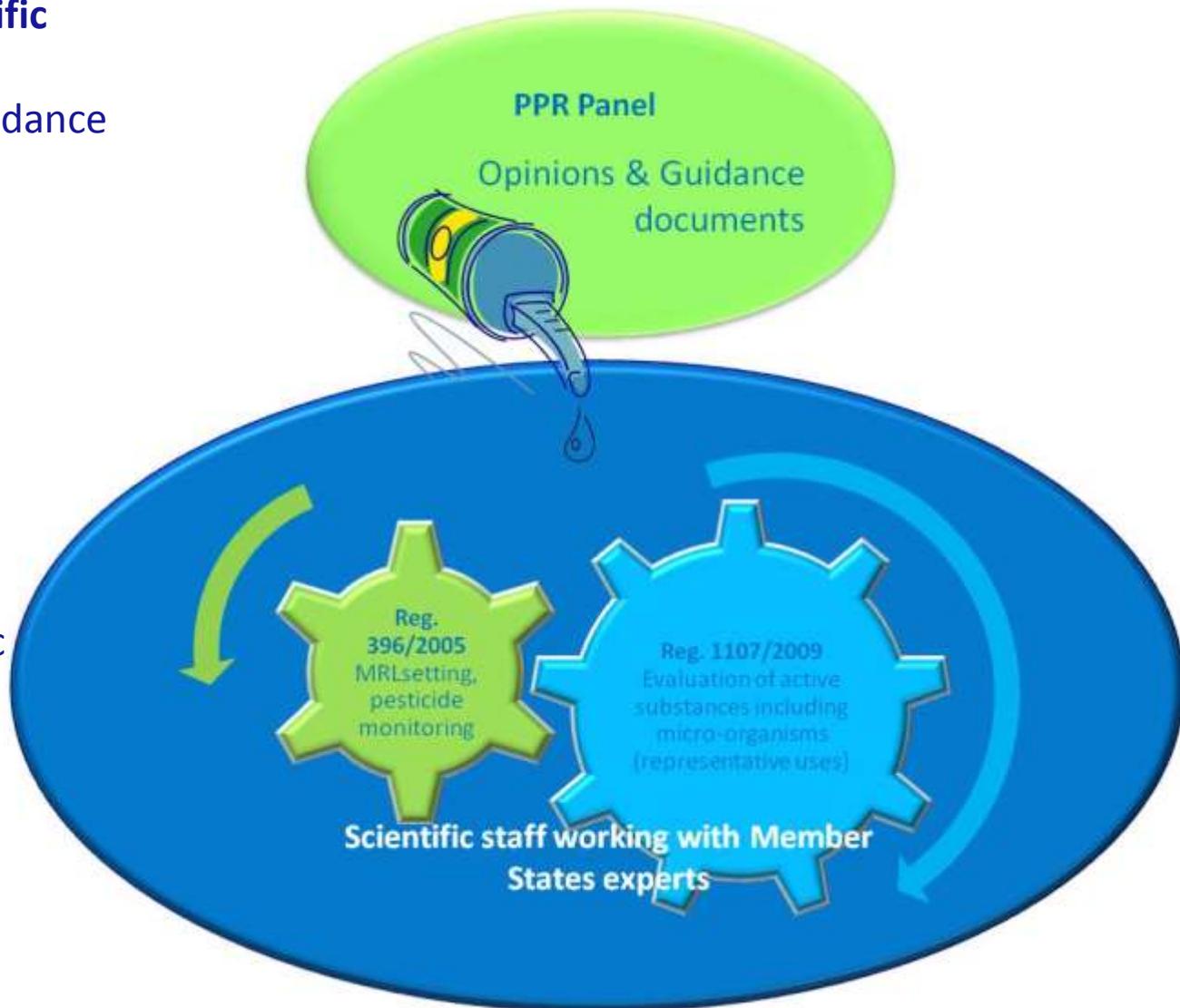
- Reasoned Opinions
- Annual report

Scientific consistency

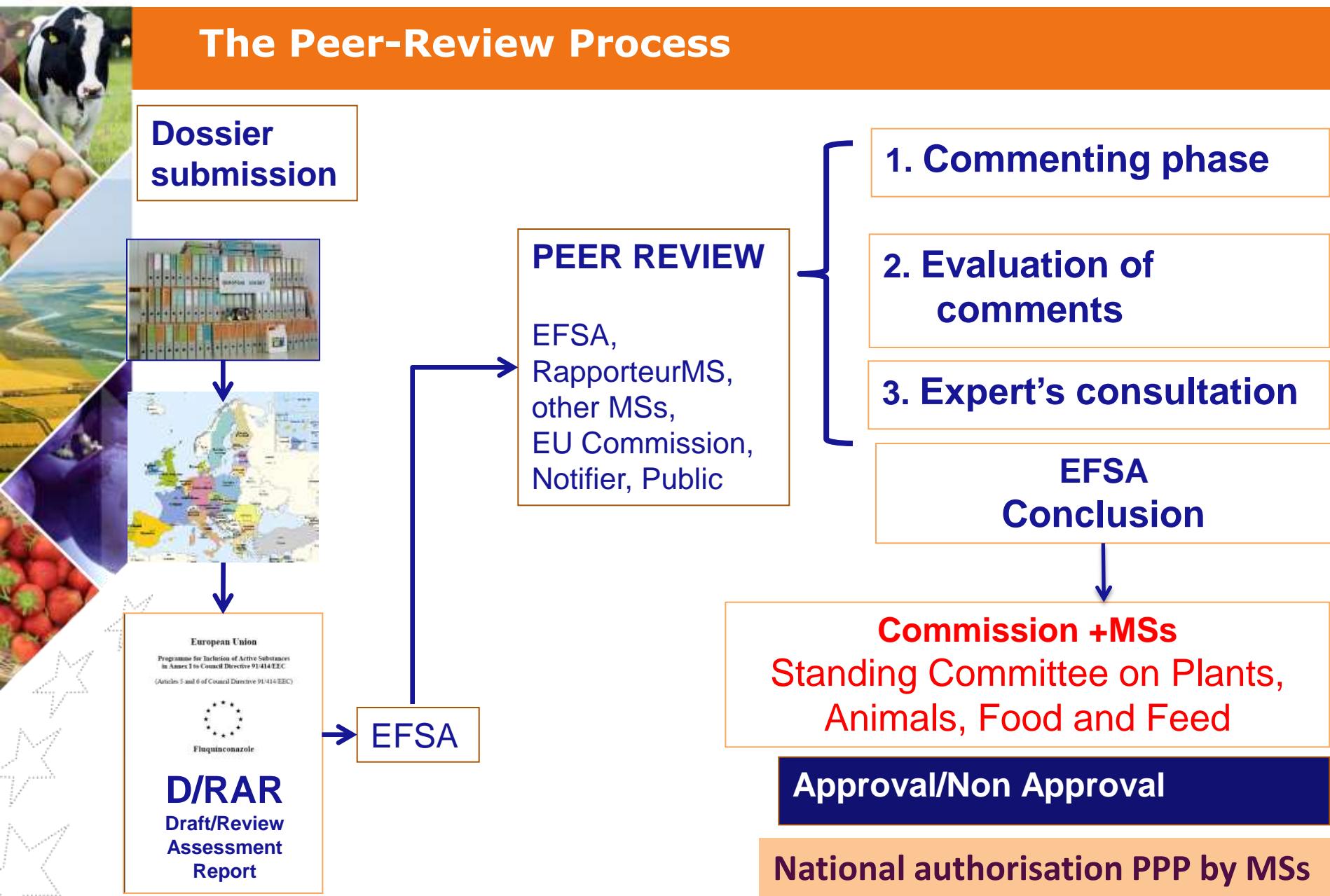
General Scientific assessment:
Opinions & Guidance

Dossier specific assessment:

Conclusions
MRL Reasoned opinions



The Peer-Review Process





EFSA CONCLUSIONS OVERVIEW

- Conclusions typically cover:
 - Identity and Phys/Chem properties
 - Mammalian Toxicology & Workers/Bystander/residents risks
 - Residues & Consumers risks
 - Environmental Fate and Behaviour
 - Ecotoxicology & Ecosystem risks
- New elements for 2014
 - First conclusions on new actives Reg. 1107/2009
 - First conclusions on AIR II



New data requirements: systematic literature review covering last 10 years and broader coverage of observed human health effects, including medical data and epidemiological studies when available



BACKGROUND

- Over the last years an abundance of epidemiological studies investigating possible associations of pesticide exposure with adverse health effects have become available
- However, contradictory or ambiguous studies exist for many adverse health effects that are attributed to pesticide exposure
- **2012** - EFSA launched an Open call on 'Literature review on epidemiological studies linking exposure to pesticides and health effects'
- Objectives
 - Collect scientific publications (published 2006-2012) in which possible links between pesticide exposure and human health effects have been investigated
 - Review and evaluate the studies in regard to its qualitative aspects
 - Provide a database for the scientific publications and a report of the results
- Contractor/beneficiary - University of Ioannina Medical School in Greece
- **2013** - External scientific report and database published on EFSA's website (<http://www.efsa.europa.eu/en/supporting/pub/497e.htm>)



RESULTS FROM THE EXTERNAL REPORT

- Statistical significant associations were observed in the meta-analysis between pesticide exposure and *liver-, breast- and stomach cancer, amyotrophic lateral sclerosis, asthma, type II diabetes, Parkinson's disease and childhood leukaemia*.
- Associations observed for Parkinson's disease and childhood leukaemia were supported by previous meta-analysis published in the scientific literature.

However...

- The literature review was not restricted to Europe only
- Many of the pesticides in the epidemiological studies are not approved in the EU
- Firm conclusions could not be made for the majority of the results because of the acknowledged limitations of the studies and the large heterogeneity of data including
 - Broad and non-consistent pesticide definitions
 - Differences in study design, statistical analyses, adjustment for confounders and population groups



EXTERNAL SCIENTIFIC REPORT - RESULTS

Health outcome	Pesticides examined	Country	Results OR [95% CI]
Leukaemia	Insecticides, Pesticides Chlorophenol, Fungicides	Thailand, China, France, Germany, Italy	1.26 [0.93; 1.71]
Childhood cancer; Exposure during pregnancy	Insecticides	America, France, Australia	1.55 [1.14; 2.11]
Breast cancer	DDE, Pesticides, Lindane Organochlorines	America, Japan, Spain, China	1.24 [1.08; 1.43]
Stomach cancer	Pesticides, DBCP Pentachlorophenol, Methyl bromide, Organochlorines	Spain, America, Canada, China, Sweden	1.79 [1.30; 2.47]
Liver cancer	Pesticides, DDT, Atrazine, Chlorophenol	China, America, Canada	2.50 [1.57; 3.98]
Risk of abortion	Pesticides, DDT	Italy, Europe, Australia, Armenia, Netherlands	1.52 [1.09; 2.13]
Parkinson's disease	Paraquat	America	1.32 [1.10; 1.60]
Amyotrophic lateral sclerosis	Pesticides	Australia, America, India, Italy	1.58 [1.31; 1.90]
Asthma	DDT	Spain, America	1.29 [1.14; 1.45]
Type II diabetes	DDT and DDE	Slovakia, America, Sweden	1.89 [1.25; 2.86]



TRIGGERING POINTS

The results from the External scientific report raises the question if;

- The available experimental data and information on mechanisms of pesticide toxicity can support the observed associations for Parkinson's disease and childhood leukaemia?
- The regulatory risk assessments, that are regularly carried out for authorising the placing of PPPs on the market, cover the hazard assessment of pesticides with regard to Parkinson's disease and childhood leukaemia?
- The findings observed in the individual epidemiological studies can be of use when assessing risks to pesticides and how these studies can be integrated into the process of regulatory pesticide risk assessments?



FOLLOW UP

- **2014** - 2 scientific mandates on the follow-up of the findings from the External scientific report 'Literature review on epidemiological studies linking exposure to pesticides and health effect' was approved by EFSA
- **Mandate [1]**
The PPR Panel of EFSA is requested to prepare a Scientific Opinion investigating experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia based on the findings in the External scientific report (2013)
- **Mandate [2]**
The PPR Panel is requested to prepare a Scientific Opinion on the follow-up of the findings of the External scientific report (2013)



MANDATE [1]

- **Scientific opinion**
 - **2014 – 2016:** The working group is expected to:
 - Develop a prototype for assessing risk factors for Parkinson's disease/ childhood leukaemia using the principles established for adverse outcome pathways (OECD, 2013)
 - Evaluate if, how and to what extent the experimental toxicity studies on mechanisms of toxicity cover effects and modes of action that are relevant for Parkinson's disease and childhood leukaemia
 - Address eventual data gaps and potential weaknesses in the current regulatory dossiers in supporting the hazard assessment
- **Call for tender** (OC/EFSA/PRAS/2014/01)
 - **2014** Systematic literature review on Parkinson's disease and childhood leukaemia and mode of actions for pesticides
- **Public consultation**
 - **2016** - Public consultation on the scientific opinion will be available on EFSA's website



MANDATE [2]

- **Scientific opinion**

- **2014 – 2017:** The working group is expected to:
 - Discuss how the findings from the External scientific report could be interpreted and integrated into regulatory pesticide risk assessments
 - Review sources of gaps and limitations identified and defined in the External scientific report
 - Propose potential refinements for future epidemiological studies to increase the quality, relevance and reliability of the findings
 - Provide recommendations to improve and optimize the application of epidemiological studies in regulatory pesticide risk assessments
 - **Considerations:** Commission Regulation (EU) No 283/2013

- **Public consultation**

- **2016** - Public consultation on the scientific opinion will be available on EFSA's website

LITERATURE SEARCH

Renewal (AIR II) / New active substances [(Reg. 1107/2009)]

- Most of the DARs reported that there were no epidemiological studies available in the open literature often because the substances have not yet been commercialised
- 2,4-D and Glyphosate provided a number of epidemiological studies:

Substance	Notifier/Applicant	EFSA conclusion
2,4-D	Association questionable due to lack of statistical precision, small sample sizes and exposure misclassification	No conclusive evidence that 2,4-D exhibits toxicological properties other than those concluded from toxicity studies
Glyphosate	Studies unreliable, lack of information on exposure duration and frequency, use of application, concomitant exposure, selection of cases and controls, biological plausibility, deficiencies in methodological reporting, questionable dosage regimen and endpoints, no control for confounders,...	Undergoing peer review



MANDATE 2

The approved mandate [2] of EFSA aims to address;

1] these methodological limitations of the epidemiological studies with focus on:

- The quality of the study designs
- Exposure assessment (including population, sampling methods and laboratory analysis of pesticides, pesticide nomenclature, acute/chronic exposure, time-trend analysis)
- Data quality
- Diagnostic classification of the health outcomes
- Biostatistical analyses (including control group, time-trend analysis, confounders, multiple hypothesis testing, sensitivity analysis)

2] how to integrate epidemiological studies into pesticide risk assessment



STAKEHOLDER CONFERENCE

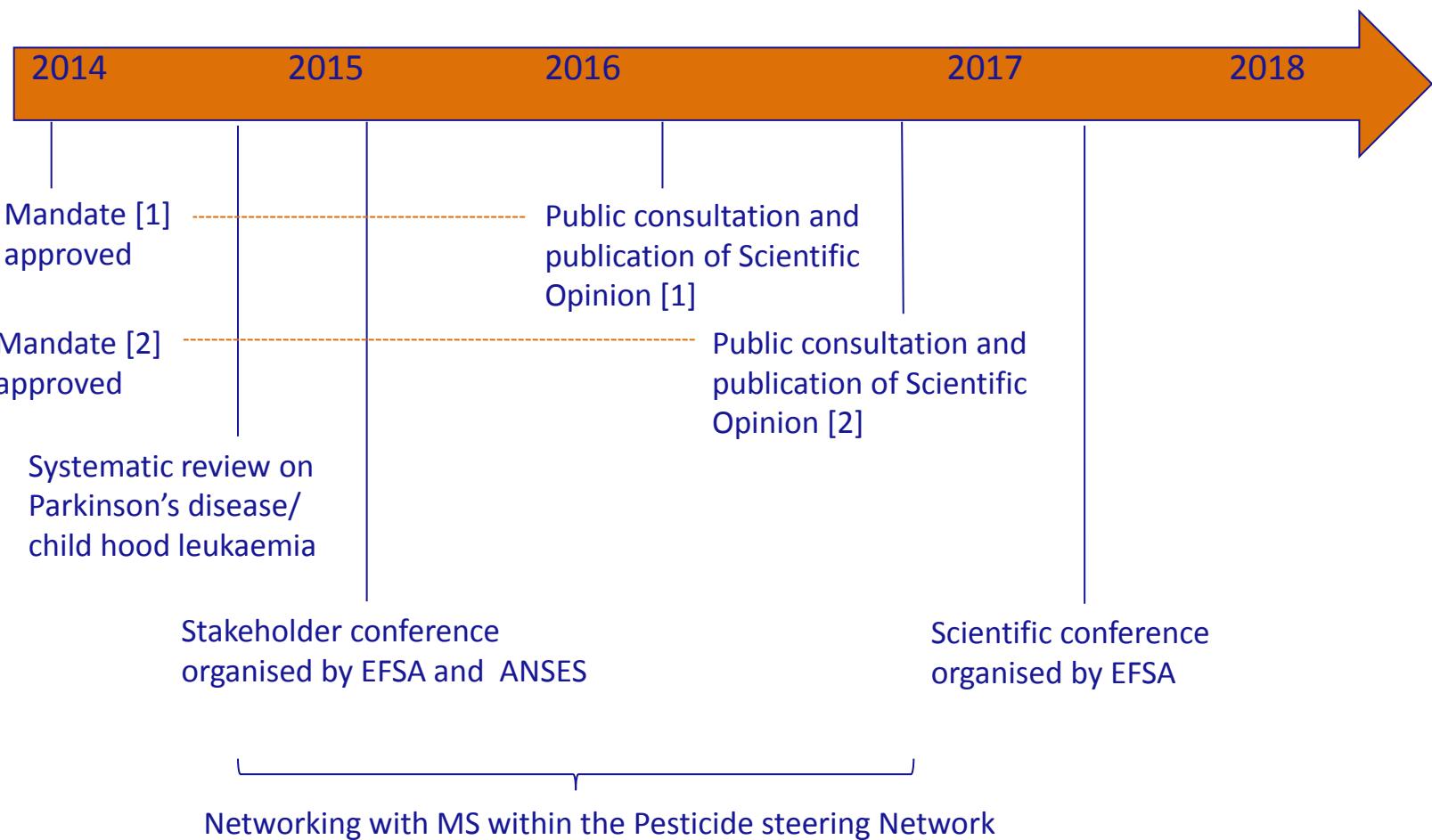
- **Stakeholder conference**
 - **2015**: organised by EFSA in collaboration with ANSES
- **Objectives**
 - To introduce EFSA's activities in the area of pesticide epidemiology
 - To allow for an open scientific discussion
 - To invite stakeholders and international partners to share views and knowledge
 - To create networking opportunities
- **Report**
 - **2015** – A report on the outcome of the conference will be published on EFSA's website



SCIENTIFIC CONFERENCE

- **Scientific conference**
 - **2017**: organised by EFSA
- **Objectives**
 - To communicate with stakeholders on the achievements and outcome of the 2 scientific opinions
 - To provide recommendations on further actions, especially in the area of scientific cooperation and networking
- **Report**
 - **2017** – A report on the outcome of the conference will be published on EFSA's website

TIMELINE OVERVIEW





VALUE OF EPIDEMIOLOGICAL STUDIES

How to interpret and integrate epidemiological studies into regulatory risk assessment of pesticides?

Generic impact, contribution to multi-stress approaches

- **Epidemiological studies on general pesticides**

- Identify potential links with adverse health effects not detected in the toxicity studies, including specific diseases

Direct impact, contribution to cumulative assessments

- **Epidemiological studies on specific classes of active substances**

- Identify adverse health effects that are biologically plausible for the pesticide group, e.g. based on mode of action
- Characterising exposure and population sensitivity

Immediate impact, support to the approval process

- **Epidemiological studies on specific active substances**

- Identify adverse health effects that are biologically plausible
- Quantifying exposure and population sensitivity
- Supporting evidence for deriving reference values

Thank you

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