Setting the basis for future health risk assessments: A case study on Parkinson's disease and paraquat

Dr Jose V. Tarazona
Head Pesticides Unit
European Food Safety Authority

Parkinson's disease: causes and cures
European Parliament 2018

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Brief history on use and assessment of pesticides

- **Use of pesticides for protecting crops from pests, diseases and weeds**
  - First reported uses (up to 4500 years ago)
    - Sumerians, sulphur compounds to control insects and mites
    - China, mercury and arsenic compounds
    - Ancient Greece and Rome, large variety of mineral and vegetal pesticides, such as pyrethrum, dried flowers of *Chrysanthemum cinerariaefolium*
  - Development of synthetic pesticides
    - Early 20th Century synthetic organic compounds such as nitrophenols, chlorophenols, creosote, naphthalene
    - 1940s, DDT and other organochlorinated pesticides
    - 1950s, Organophosphates and other insecticides, first herbicides such as 2,4-dichlorophenoxyacetic and fungicides such as captan
    - More recently, pheromones and microbial pesticides
- **EU Regulatory activities**
    - 1991, Directive 91/414; Regulation 1107/2011, EU assessment of pesticides
    - 2005, Regulation 396/2005 full harmonisation of Maximum Residue Levels
    - 2009, Directive 2009/128/EC sustainable

REG. 1107/2009
EU DUAL REGULATORY SYSTEM FOR PESTICIDES

EU assessment and approval decision of the active pesticide substance

Periodic Renewals

- Submission: • Active substance
- Risk Assessment: • Rapporteur MS • **EFSA Peer-Review**
- Decision: • EU approval

MS assessment and pre-marketing authorisation of each formulation

- Submission: • PPP dossier
- Risk Assessment: • Member State • Zonal process
- Decision: • MS PPP authorisation

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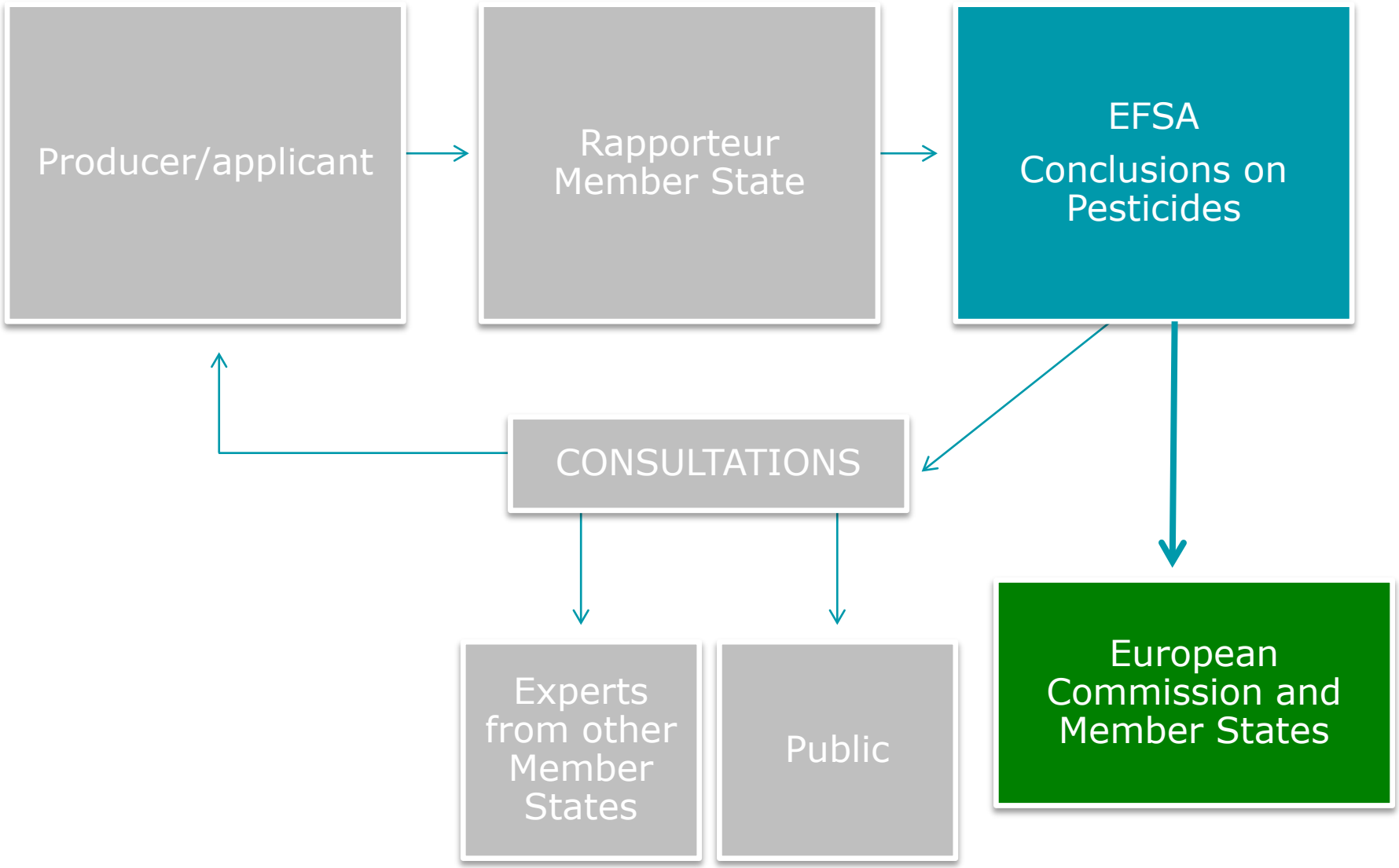
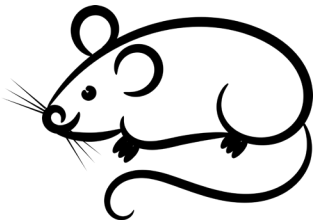
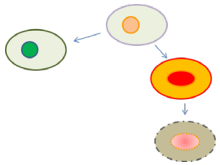
ASSESSMENT OF PESTICIDES: THE ACTORS



The animal model for setting toxicological reference values





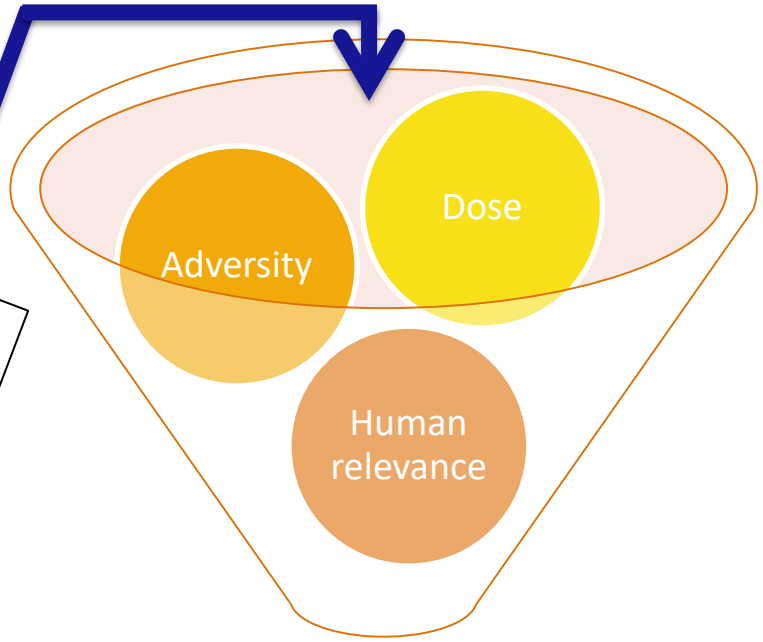
Mandatory animal studies

In vitro studies and scientific publicatio

Additional triggered studies

Full data package

Data extraction
100s-1000s endpoints



Dose not producing adverse relevant effects in animals

Factor of 100 or higher for extrapolating to humans

Toxicological reference value

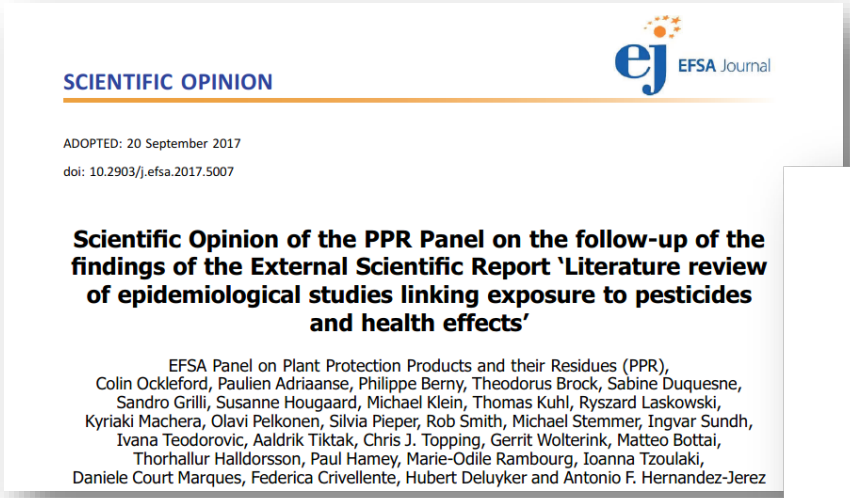
Exploring options for the future

- The challenge: human unique diseases like Parkinson's
- The question: is the animal model (including assessment factors) sufficiently conservative for covering these human specific endpoints?
- The opportunity: Linking mechanistic understanding with human epidemiological data
  - Pesticides are appropriate models due to the combination of availability of data, societal concern, and regulatory interest
- The way forward:
  - Assessing new scientific tools for connecting information on the mode of action and in vivo adverse effects

Epidemiological studies

- Epidemiological studies on pesticides are mostly conducted on farmers, but its use for assessing the risk of individual pesticides is very complex.
- E.g. some epidemiological studies suggest a possible association of Parkinson's disease and exposure to pesticides in general, and specifically to the herbicide paraquat.
- Farmers are exposed to a combination of pesticides, e.g. high correlation between pesticide use and paraquat use (r = 0.84), or insecticide use and fungicide use (r = 0.90) .
- EFSA PPR Scientific Panel has developed clear recommendations
- One is based on the development of Adverse Outcome Pathways for evaluating the biologic

EFSA PPR Panel recent outputs



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

SCIENTIFIC OPINION

EFSA Journal

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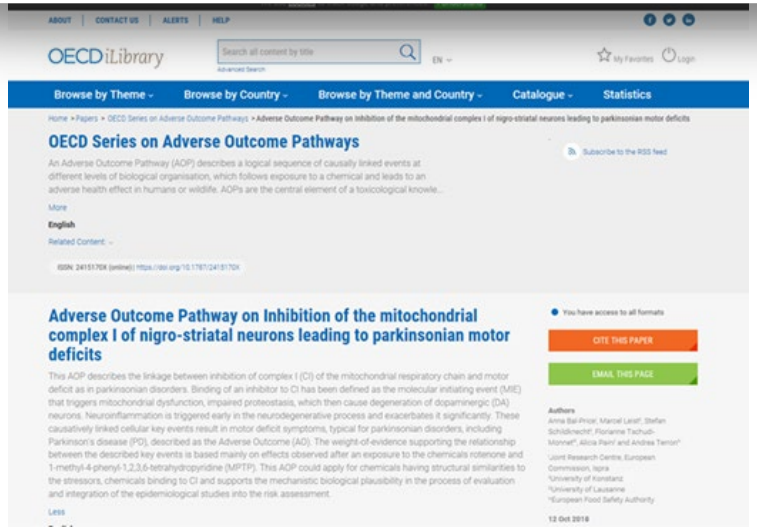
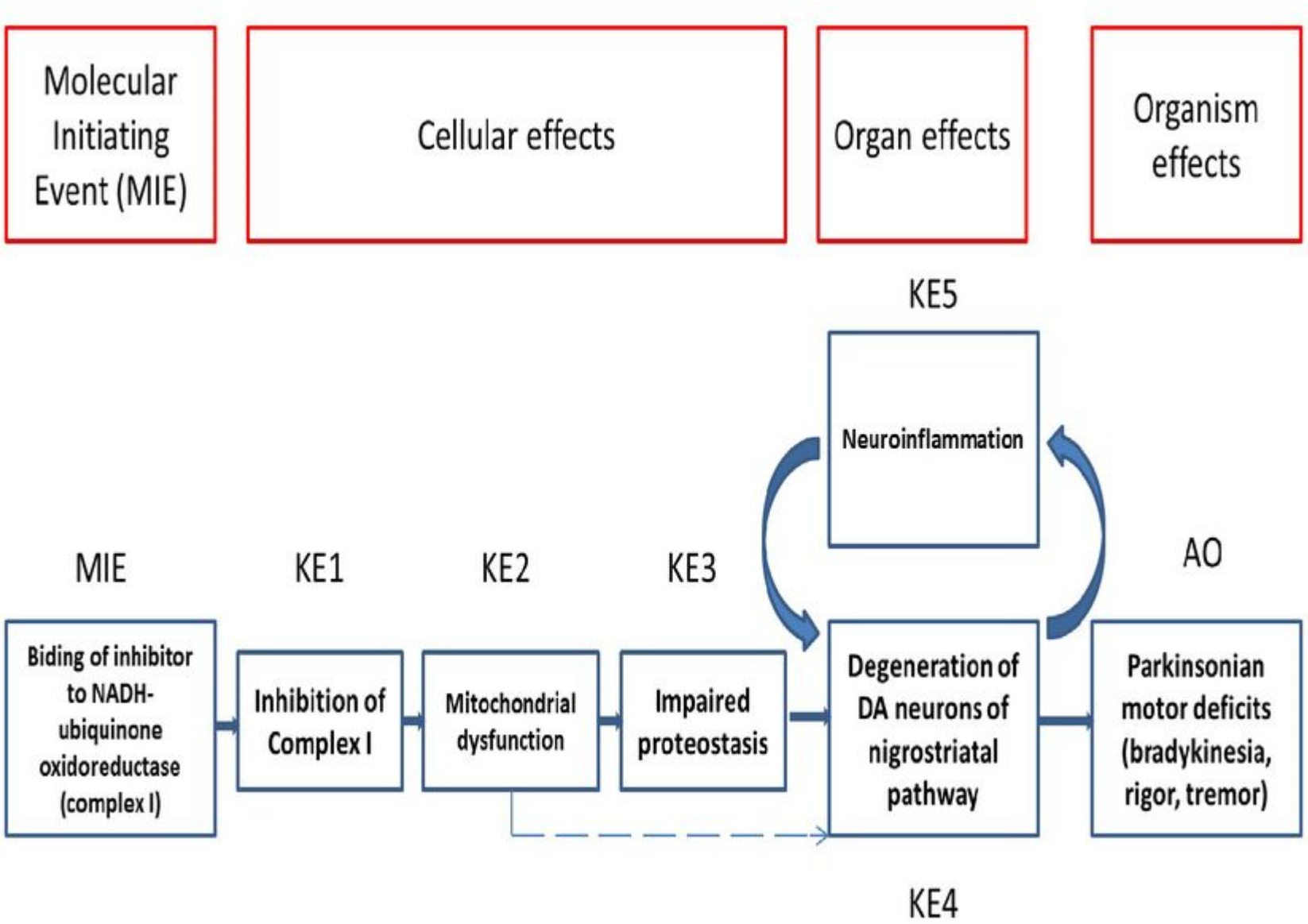
doi: 10.2903/j.efsa.2017.4691

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



Use of new science: Adverse Outcome Pathways



Paraquat and Parkinson's

Paraquat

- Herbicide, of the chemical class of bipyridyl quaternary ammonium.
- Currently not approved in the EU, but was used in the past.
- General toxicity of paraquat is well characterised, lungs are considered the main target organ, and the mechanism oxidative stress associated to the redox cycling.
- Neurotoxic effects have been explored recently (Baltazar et al., 2014). The proposed mechanism is assumed to be linked to its redox potential.

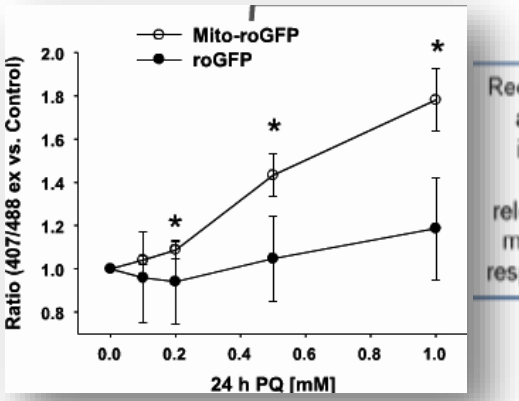
Parkinsonian disorders

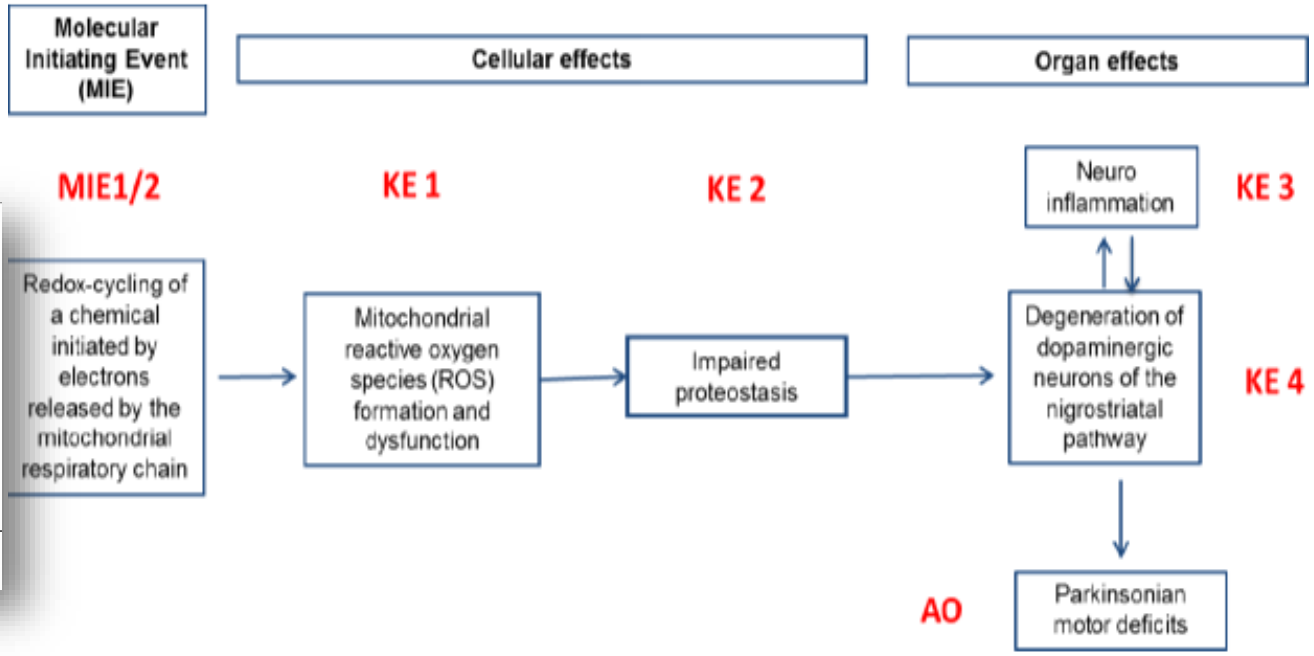
- Primary pathology is a selective degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which project mainly to the striatum
- Development of Lewy bodies, cytoplasmic inclusions rich in proteins including the aberrant oligomeric α-synuclein (a presynaptic neuronal protein)

Paraquat was selected as a model chemical to define an pathway between oxidative stress and mitochondrial dysfunction in dopaminergic neurons and Parkinsonian motor disorders

Linking oxidative stress in key neurons with Parkinson

- Target: Dopaminergic neurons of the Substantia Nigra pars compacta and striatum
- Model chemical: Herbicide paraquat
- Mechanism: Selective induction of oxidative stress in the mitochondria
  1. Disruption of redox cycling: increase in reactive oxygen
  2. Mitochondrial dysfunction due to the formation of reactive oxygen species (ROS)
  3. Disturbance of proteins homoeostasis accumulation of "toxic proteins" e.g. α-synuclein
  4. Degeneration of dopamine neurons, possible role for inflammation
  5. Parkinsonian motor deficits





Conclusions

- EU has implemented a sophisticated system for ensuring a high level of protection regarding the use of pesticides
  - Premarketing approval and regular renewals of all active substances at EU level
  - Premarketing authorisation and regular renewals of all Plant Protection Products at Member State level
  - Harmonised system of Maximum Residue Levels in food, including a default generic value of 0.01 mg/kg food in case of no assessment
  - Implementation of additional measures on sustainable use

- The assessment of effects on human health is currently based on animal models and extrapolation factors
- New scientific developments are opening new approaches and alternatives
- These are particularly relevant for assessing “human unique diseases” such as Parkinson’s
- The EFSA PPR Panel has proposed the use of Adverse Outcome Pathways
- This approach, once developed, will provide additional certainty in future assessments of pesticides

Thank you

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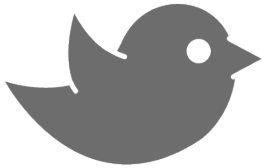

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