



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

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Parkinson's disease: causes and cures
European Parliament 2018

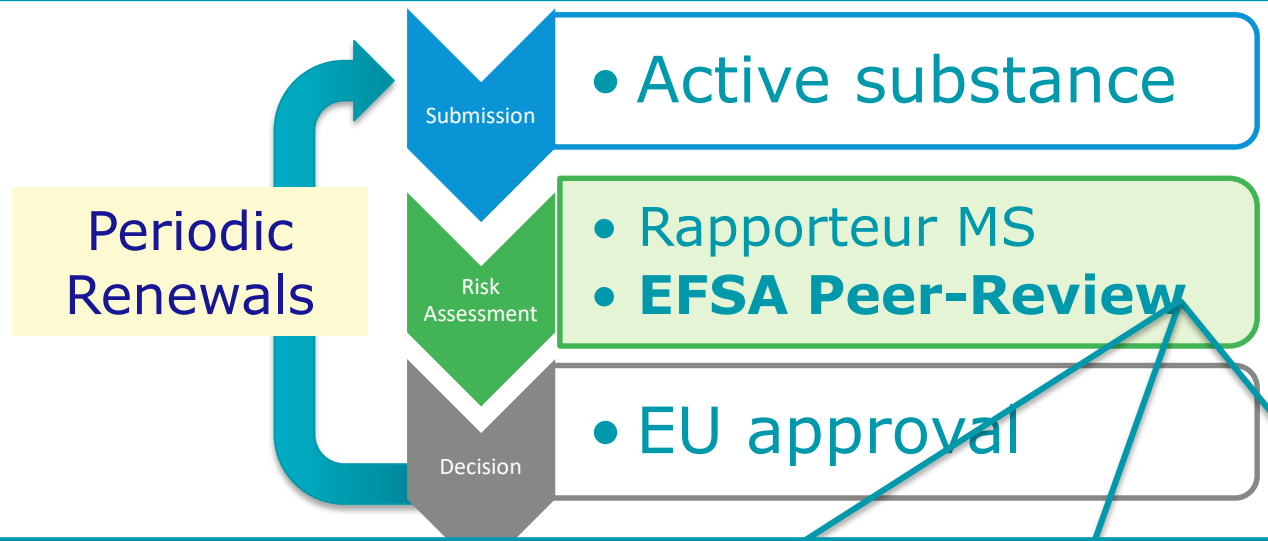
Brief history on use and assessment of pesticides

- **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

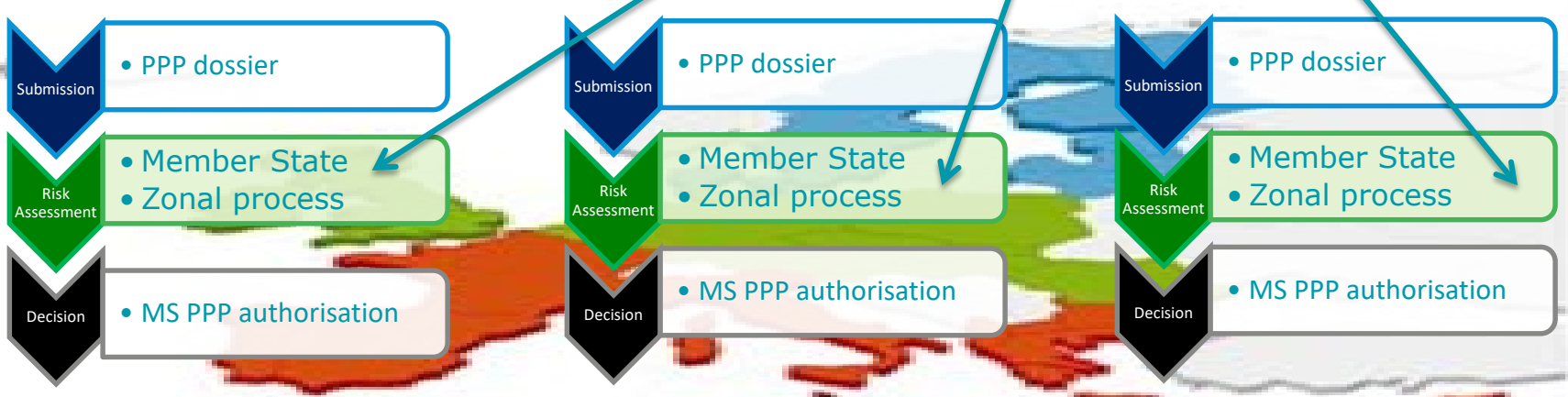


REG. 1107/2009 EU DUAL REGULATORY SYSTEM FOR PESTICIDES

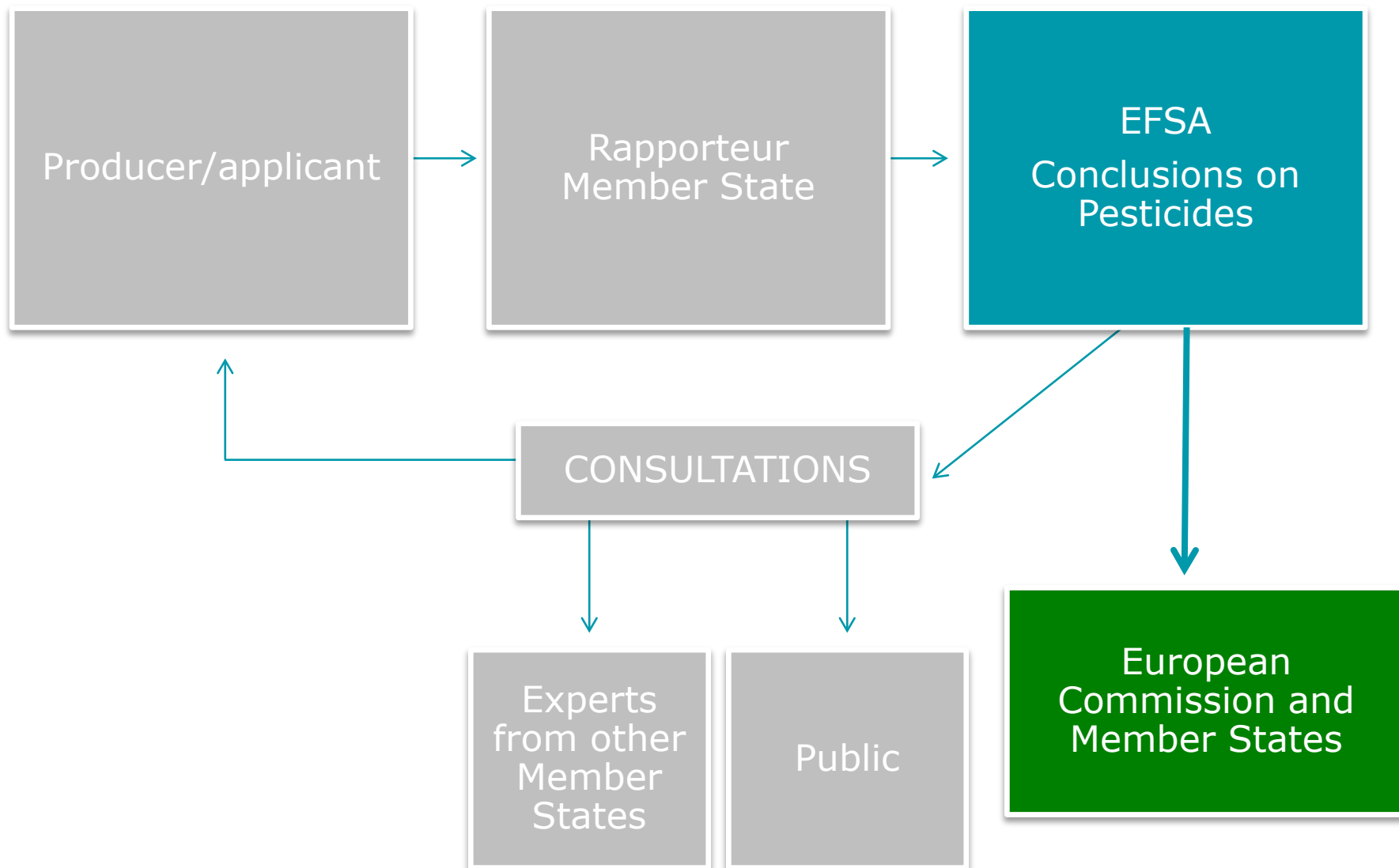
EU assessment and approval decision of the active pesticide substance



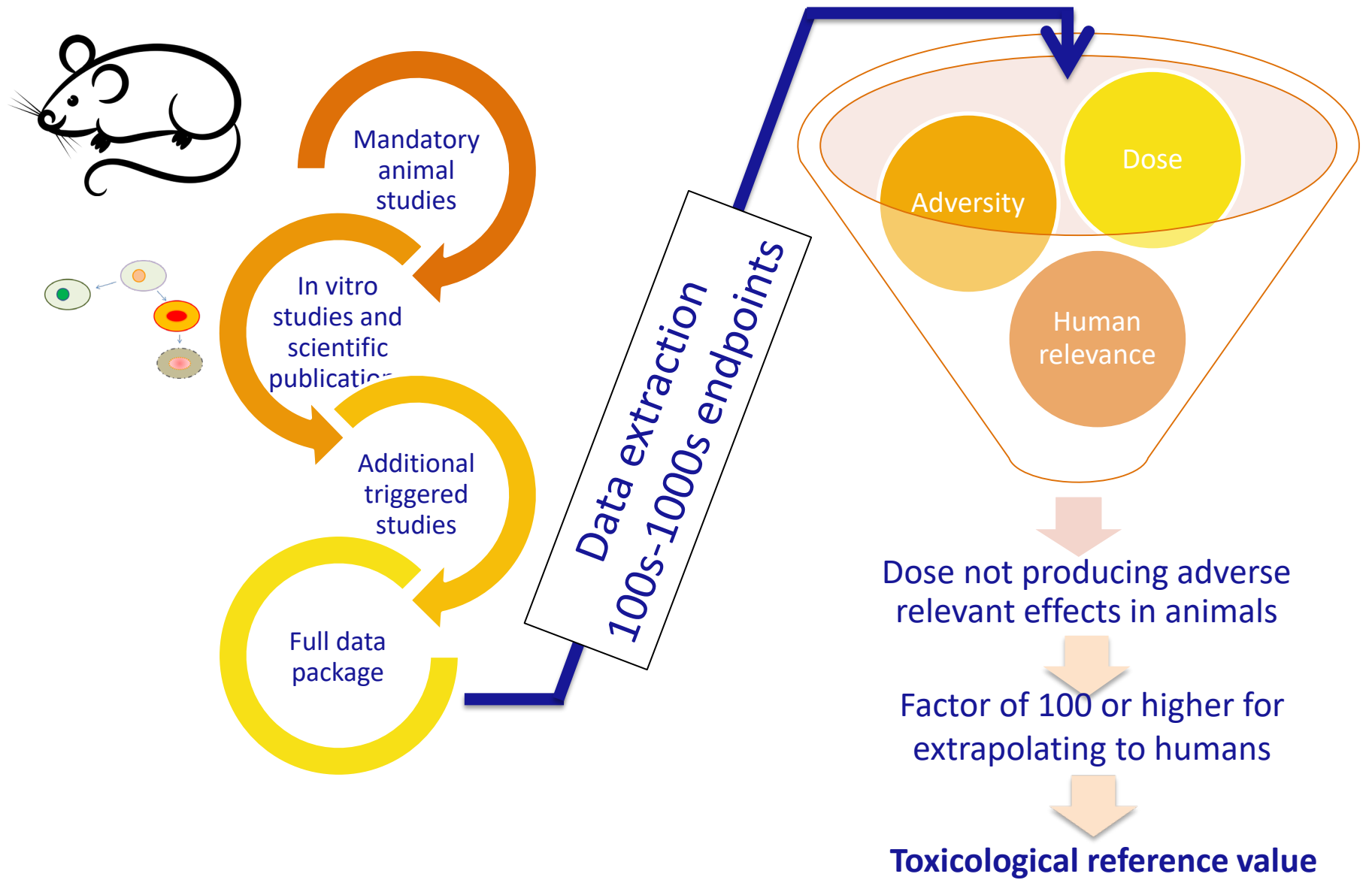
MS assessment and pre-marketing authorisation of each formulation



ASSESSMENT OF PESTICIDES: THE ACTORS



The animal model for setting toxicological reference values



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

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Pesticides: how can risk assessors make better use of epidemiological data?

EFSA's pesticide experts have developed an approach that could help risk assessors to make better use of epidemiological data in the assessment of active chemical substances used in pesticides.

Subject area

- Pesticides
- PPR
 - Panel on Plant Protection Products and their Residues

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EFSA PPR Panel recent outputs

SCIENTIFIC OPINION



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 Macherera, Olavi Pelkonen, Silvia Pieper, Rob Smith, Michael Stemmer, Ingvar Sundh,
 Ivana Teodorovic, Aaldrik Tiktak, Chris J. Topping, Gerrit Wolterink, Matteo Bottai,
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 Daniele Court Marques, Federica Crivellente, Hubert Deluyker and Antonio F. Hernandez-Jerez

SCIENTIFIC OPINION



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 leukaemia¹

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 Macherera, Olavi Pelkonen, Silvia Pieper, Rob Smith,
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 Arianna Chiusolo, Federica Ruffo, Andrea Terron and Susanne Hougaard Bennekou

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OECD Series on Adverse Outcome Pathways

An Adverse Outcome Pathway (AOP) describes a logical sequence of causally linked events at different levels of biological organisation, which follows exposure to a chemical and leads to an adverse health effect in humans or wildlife. AOPs are the central element of a toxicological knowledge...

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Adverse Outcome Pathway on Inhibition of the mitochondrial complex I of nigro-striatal neurons leading to parkinsonian motor deficits

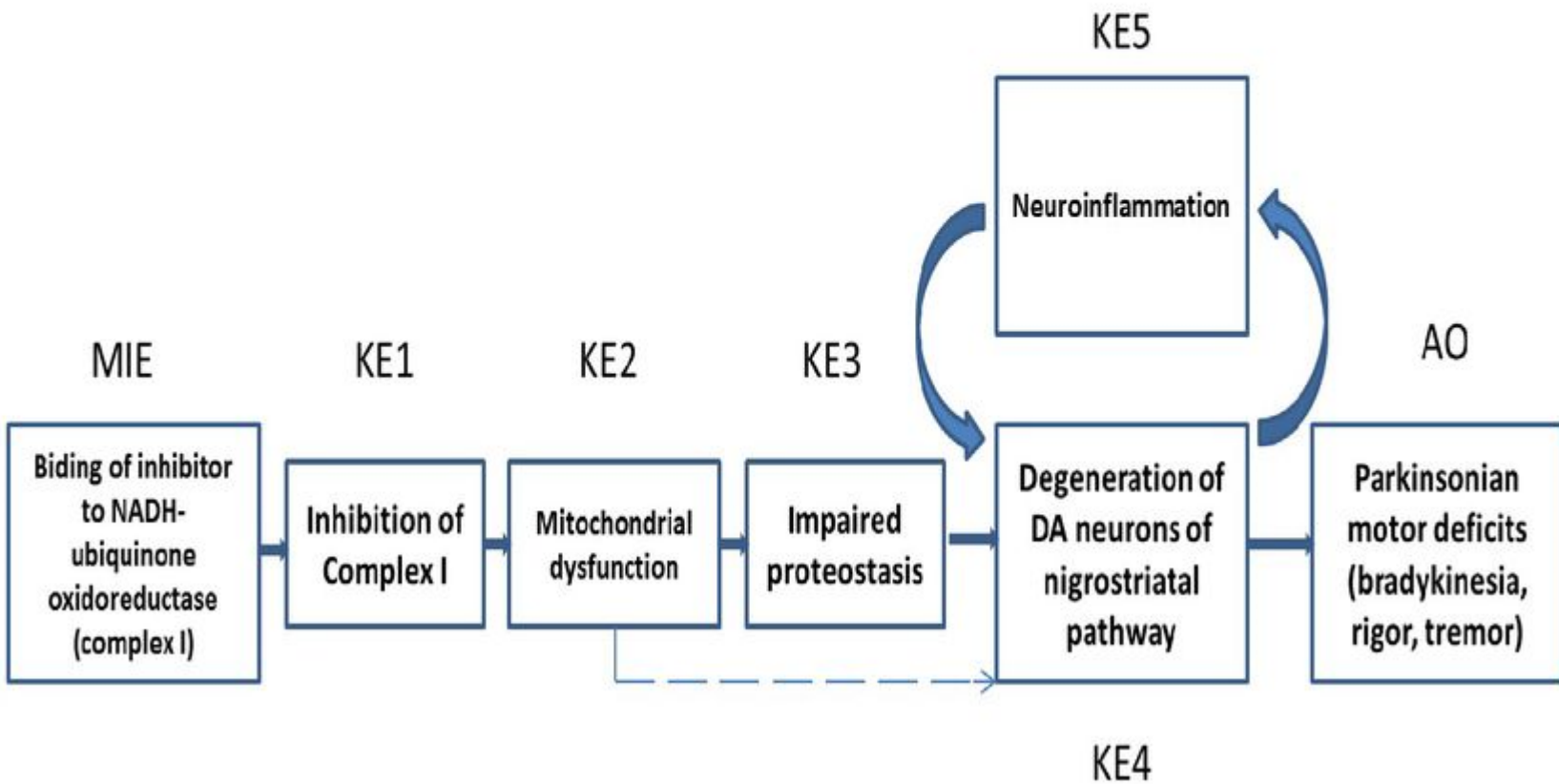
This AOP describes the linkage between inhibition of complex I (CI) of the mitochondrial respiratory chain and motor deficit as in parkinsonian disorders. Binding of an inhibitor to CI has been defined as the molecular initiating event (MIE) that triggers mitochondrial dysfunction, impaired proteostasis, which then cause degeneration of dopaminergic (DA) neurons. Neuroinflammation is triggered early in the neurodegenerative process and exacerbates it significantly. These causatively linked cellular key events result in motor deficit symptoms, typical for parkinsonian disorders, including Parkinson's disease (PD), described as the Adverse Outcome (AO). The weight-of-evidence supporting the relationship between the described key events is based mainly on effects observed after an exposure to the chemicals rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). This AOP could apply for chemicals having structural similarities to the mentioned chemicals binding to CI and supports the mechanistic biological plausibility in the process of evaluation and integration of the epidemiological studies into the risk assessment.

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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.

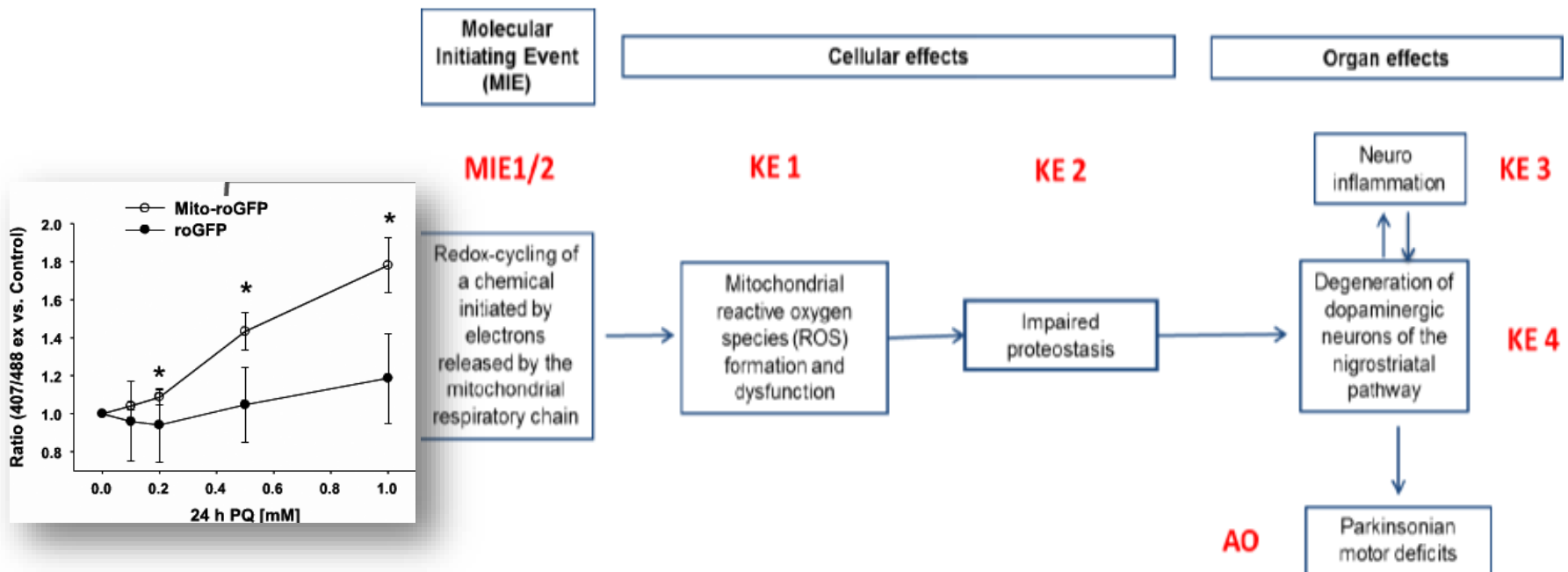
Parkinsonian disorders

- 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 a 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



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