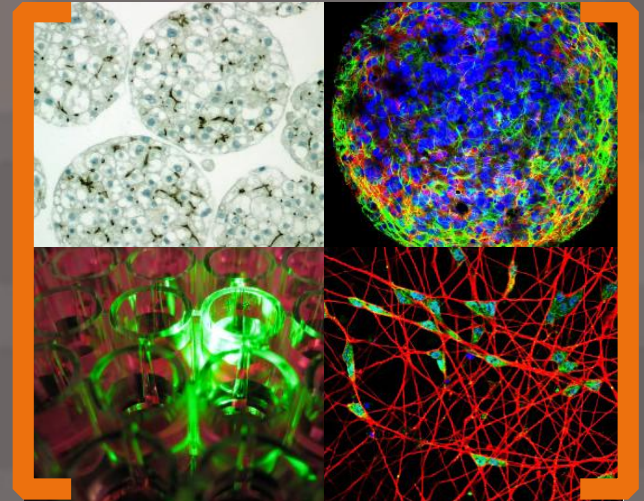


EU-ToxRisk Final Symposium

Talk title:
Application of an AOP approach
in a RAx safety assessment:
the case of mitochondrial complex I inhibitors

Presenter: M. Leist



Why do we need AOP?

Echa: Animal testing for complex endpoints 'unavoidable' without regulatory change

21 October 2021

System is based on adversity, which NAMs do not measure directly, says senior agency scientist

Europe

EDCs

REACH

Animal testing

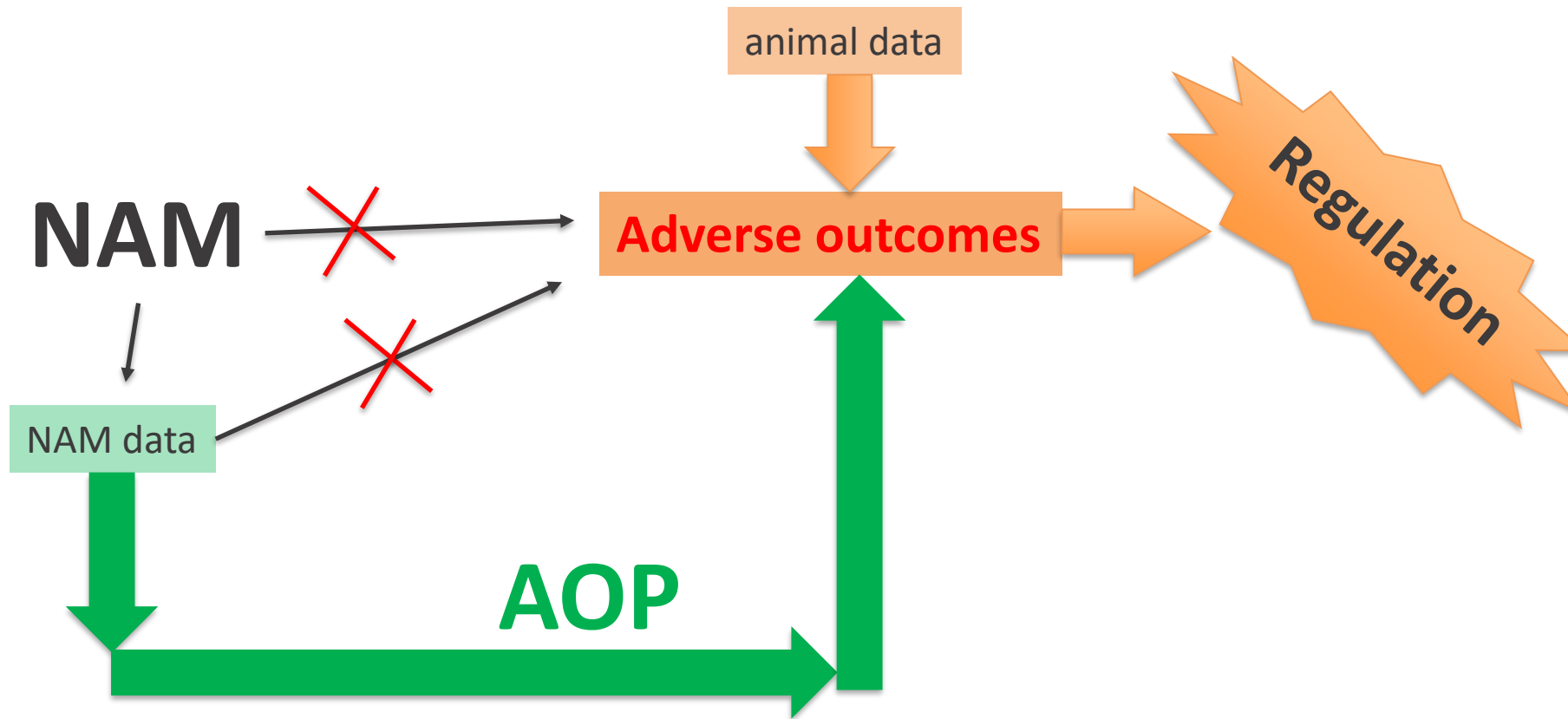


Animal testing for complex endpoints, such as endocrine disruption, cannot be avoided using currently available science without change to the regulatory framework, Echa has said.

In recent weeks, senior figures at the agency, including outgoing executive director Bjorn Hansen, have commented on the situation, following industry and animal welfare organisation accusations that it is not doing enough to ensure unnecessary animal testing is



Why do we need AOP?



 AOP link NAM data to classical adverse outcomes

Background: AOP#3 (used here)

Short name: Mitochondrial dysfunction and Neurotoxicity

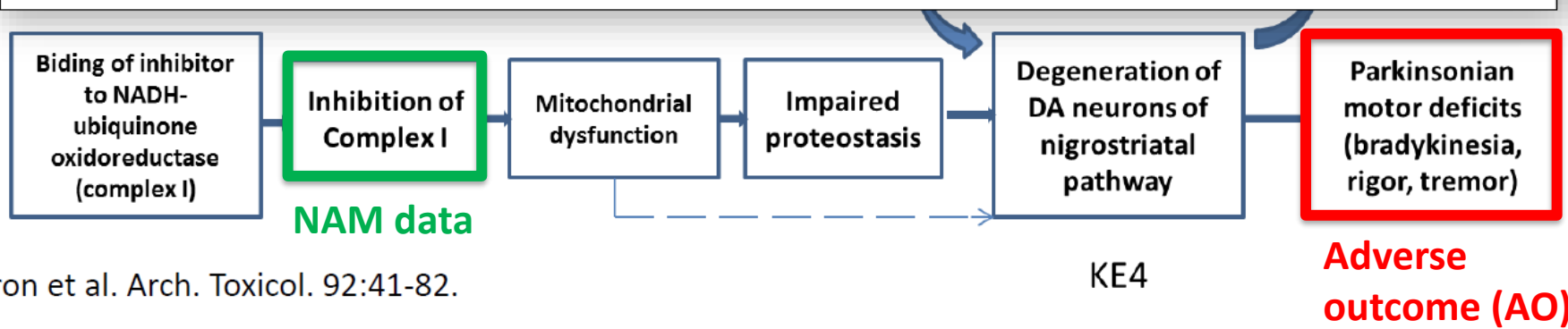
Archives of Toxicology (2018) 92:41–82
<https://doi.org/10.1007/s00204-017-2133-4>

REVIEW ARTICLE



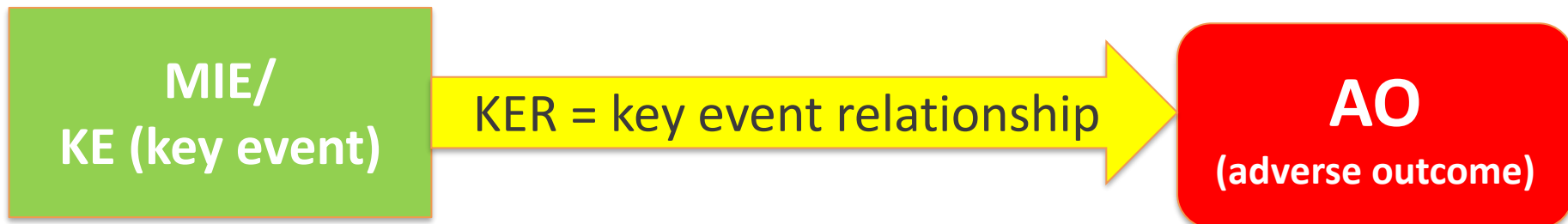
An adverse outcome pathway for parkinsonian motor deficits associated with mitochondrial complex I inhibition

Andrea Terron¹ · Anna Bal-Price² · Alicia Paini² · Florianne Monnet-Tschudi³ · Susanne Hougaard Bennekou⁴ · EFSA WG EPI1 Members¹ · Marcel Leist⁵ · Stefan Schildknecht⁵



Terron et al. Arch. Toxicol. 92:41-82.

Uses of AOP



1. Full quantitative knowledge of KER (mathematical model):

Construction of a qAOP (quantitative AOP)

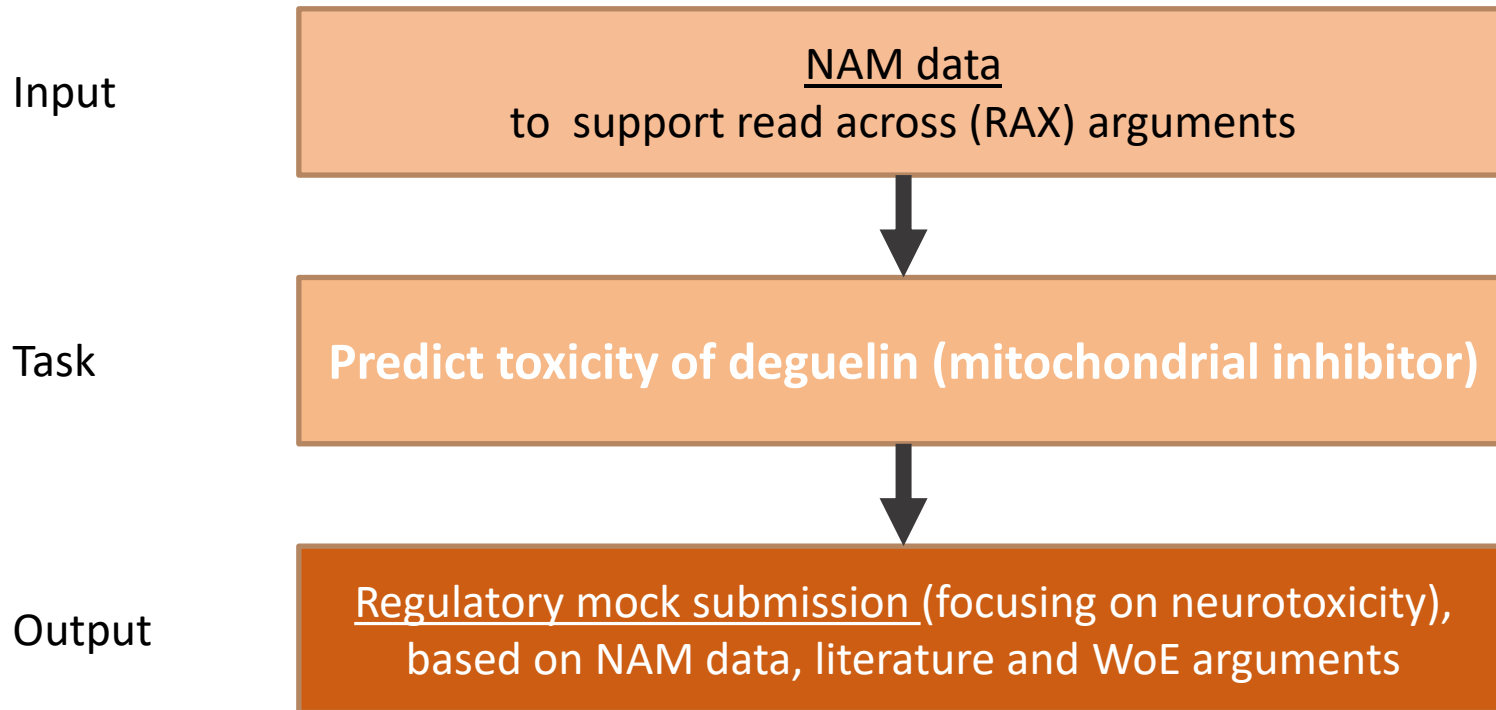
Use for full prediction on unknown compounds, based on KE data

2. Partial knowledge of KER (qualitative model):

Fill quantification gaps by anchoring to reference compounds

Readacross (Rax) procedure

Uses of AOP: option 2 (=RAX)



- **Study 1: rotenoids** – predict toxicity of **deguelin**, a rotenone analogue
- **Study 2: strobilurins** – arguments for non-neurotoxicity of **azoxystrobin**

Study example: rotenoids

Identification and characterization of parkinsonian hazard liability of deguelin

Purpose

1. Replace animal tests (e.g. OECD TG424 (neurotoxicity))
2. Use available AOP#3 to guide test strategy
3. Use NAM to reduce overall RAX uncertainty

Background

Rotenone has known neurotoxicity and liability to trigger PD motor deficits

Deguelin is structurally similar to rotenone

Production of NAM data on broad panel of mitotoxics


Archives of Toxicology

<https://doi.org/10.1007/s00204-020-02970-5>

IN VITRO SYSTEMS



Neurotoxicity and underlying cellular changes of 21 mitochondrial respiratory chain inhibitors

Johannes Delp^{1,2} · Andrea Cediell-Ulloa^{3,10} · Ilinca Suciuc^{1,4}  · Petra Kranaster^{1,4} · Barbara MA van Vugt-Lussenburg⁵ · Vesna Munic Kos^{3,11} · Wanda van der Stel⁶ · Giada Carta⁷ · Susanne Hougaard Bennekou⁸ · Paul Jennings⁷ · Bob van de Water⁶ · Anna Forsby^{3,9} · Marcel Leist¹

Received: 16 November 2020 / Accepted: 29 December 2020


Archives of Toxicology (2020) 94:2707–2729

<https://doi.org/10.1007/s00204-020-02792-5>

MOLECULAR TOXICOLOGY



Multiparametric assessment of mitochondrial respiratory inhibition in HepG2 and RPTEC/TERT1 cells using a panel of mitochondrial targeting agrochemicals

Wanda van der Stel¹ · Giada Carta² · Julie Eakins³ · Salihanur Darici¹ · Johannes Delp⁴ · Anna Forsby⁵ · Susanne Hougaard Bennekou⁶ · Iain Gardner⁷ · Marcel Leist⁴ · Erik H. J. Danen¹ · Paul Walker³ · Bob van de Water¹ · Paul Jennings² 

Conclusions on deguelin RAX

Hazard data and toxicokinetics predictions (*in vitro* and *in silico*) are similar for rotenone and deguelin

NAMs have been used to reduce uncertainties of RAX



Data from our study (*in vitro* and *in silico*) agree well with known potency difference of *in vivo* data (used for deguelin AFTER the study for confirmation)

our regulatory conclusion

Deguelin has the same hazard properties as rotenone, but a slightly lower potency (factor 3). Thus its acceptable exposure/intake should be max. 3 times higher than for rotenone.

Research Article

ALTEX 38(4), 815-835. doi:10.14573/altex.2103051

New Approach Methods (NAMs) Supporting Read-Across: Two Neurotoxicity AOP-based IATA Case Studies

Wanda van der Stel¹, Giada Carta², Julie Eakins³, Johannes Delp⁴, Ilinca Suci^{4,5}, Anna Forsby⁶, Andrea Cediel-Ulloa⁷, Kristina Attoff⁶, Florentina Troger⁸, Hennicke Kamp⁹, Iain Gardner¹⁰, Barbara Zdrzil⁸, Martijn J. Moné¹, Gerhard F. Ecker⁸, Manuel Pastor¹¹, Jose Carlos Gómez-Tamayo¹¹, Andrew White¹², Erik H. J. Danen¹, Marcel Leist⁴, Paul Walker³, Paul Jennings², Susanne Hougaard Bennekou¹³ and Bob van de Water¹

ENV/JM/MONO(2020)22



Organisation for Economic Co-operation and Development

Unclassified

English - Or. English

24 September 2020

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING
PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

CASE STUDY ON THE USE OF INTEGRATED APPROACHES TO TESTING AND ASSESSMENT FOR IDENTIFICATION AND CHARACTERISATION OF PARKINSONIAN HAZARD LIABILITY OF DEGUELIN BY AN AOP-BASED TESTING AND READ ACROSS APPROACH

Series on Testing and Assessment
No. 326

CASE STUDY ON THE USE OF INTEGRATED APPROACHES TO TESTING AND ASSESSMENT FOR MITOCHONDRIAL COMPLEX-III-MEDIATED NEUROTOXICITY OF AZOXYSTROBIN - READ-ACROSS TO OTHER STROBILURINS

Series on Testing and Assessment
No. 327

How to move on?

In vitro concentration response data for many compounds and many KE / MIE



Calibration of qAOP



Establish NAM data
for new compounds



Predict concentration-
response
for AO

EUROTOX 2021
VIRTUAL CONGRESS
27 SEPTEMBER – 1 OCTOBER 2021



Quantitative Bayesian network analyses of mitochondrial toxicity

F. Y. Bois, C. Tebby,
J. Delp, G. Carta, W. van der Stel,
M. Leist, P. Jennings, B. van de Water

Certara, INERIS, Leiden University, VU Amsterdam, Konstanz University



[:::] EUTOXRISK



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[:::] EUTOXRISK

Thank you

