A vision for regulatory application of NAMs – personal reflections

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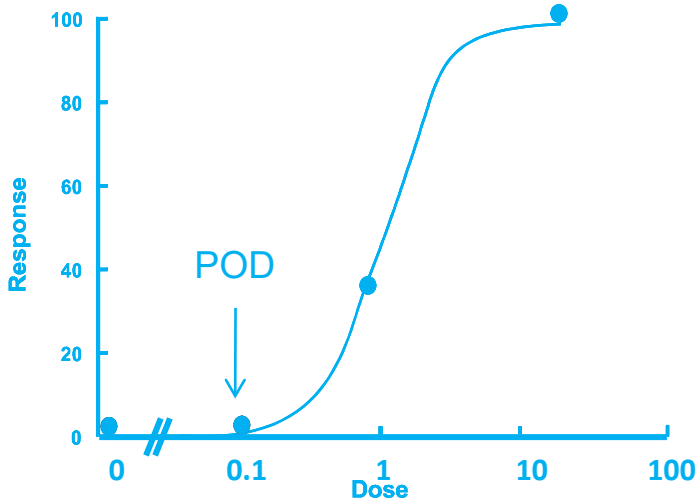
Disclosure statement

- Member of several science advisory boards (public and private sector): ILSI, ILSI Europe, Cosmetics Europe LRSS, MSU Center for Research on Ingredient Safety, A*STAR Food and Chemical Safety Programme Singapore, Owlstone Medical, PCPC Expert Group on Carcinogenicity
- Member/chair of several national and international scientific advisory committees: UK COT, UK COMEAP, JMPR, JECFA, WHO TobReg, ISO TC126 WG10 Intense Smoking Regime
- I have no financial interests in the subject matter of the session

Risk assessment

Hazard assessment



Exposure assessment

Uncertainty factor

Health-Based Guidance Value (e.g. ADI)
HBGV = POD/UF

Risk characterisation (Exposure cf HBGV)

Use of laboratory species

- Structure of macromolecules the same as in humans (lipids, carbohydrates, nucleic acids, proteins)
- Qualitative and semi-quantitative similarities in:
  - Biochemical processes
  - Cell biology and cell signalling
  - Physiological processes
  - Basic anatomy
  - Reproduction
  - Neurotransmission
  - …….

NAMs are of proven value in studies of biokinetics and mechanisms of toxicity

BJCP British Journal of Clinical Pharmacology

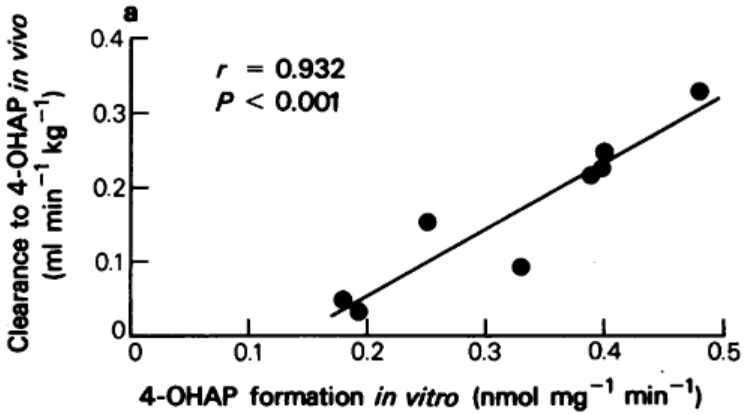
Volume 12, Issue 6
December 1981
Pages 771-777

Free Access

Comparison of the in vivo and in vitro rates of formation of the three main oxidative metabolites of antipyrine in man.

AR Boobis, MJ Brodie, GC Kahn, EL Toverud, IA Blair, S Murray, DS Davies

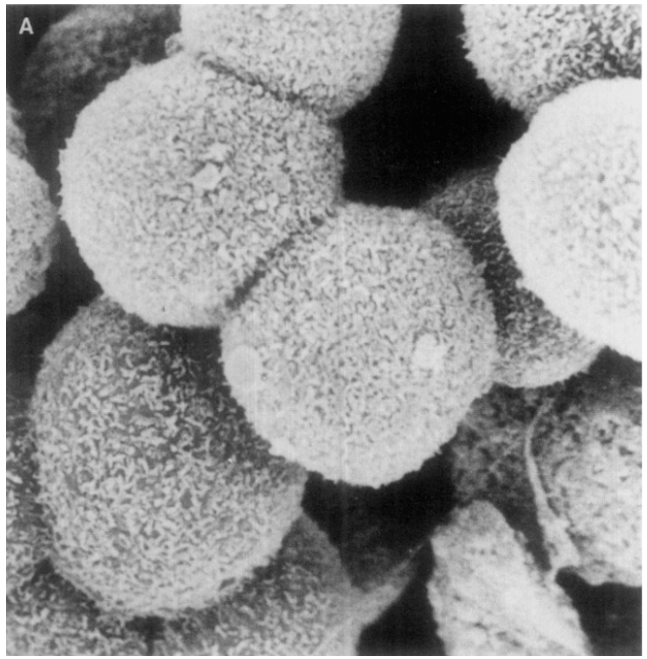
First published: December 1981 | https://doi.org/10.1111/j.1365-2125.1981.tb01305.x | Citations: 53

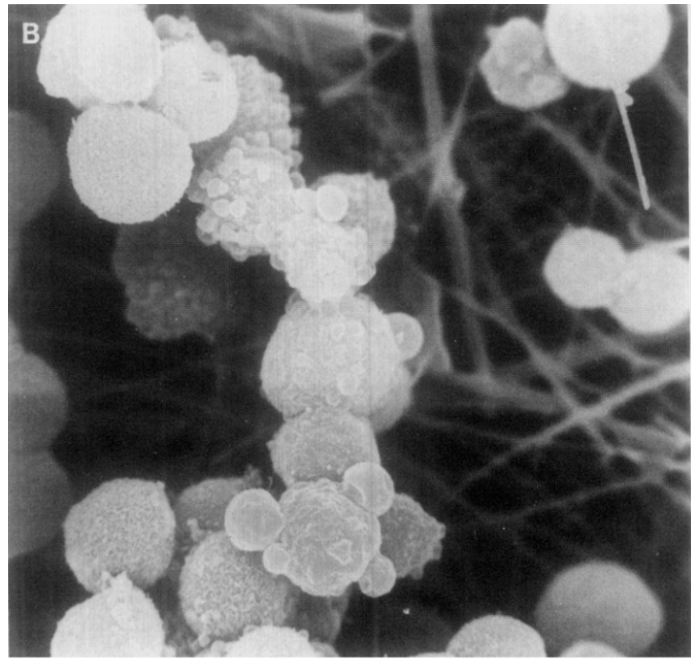


TOXICOLOGY AND APPLIED PHARMACOLOGY 83, 294–314 (1986)

Reversal of Acetaminophen Toxicity in Isolated Hamster Hepatocytes by Dithiothreitol

LISA B. G. TEE, ALAN R. BOOBIS,[1] ANTHONY C. HUGGETT,[2] AND DONALD S. DAVIES





N-Hydroxy-MeIQx is the major microsomal oxidation product of the dietary carcinogen MeIQx with human liver

Get access >

Kim J. Rich, Bernard P. Murray, Ivor Lewis, Nigel B. Rendell, Donald S. Davies, Nigel J. Gooderham, Alan R. Boobis

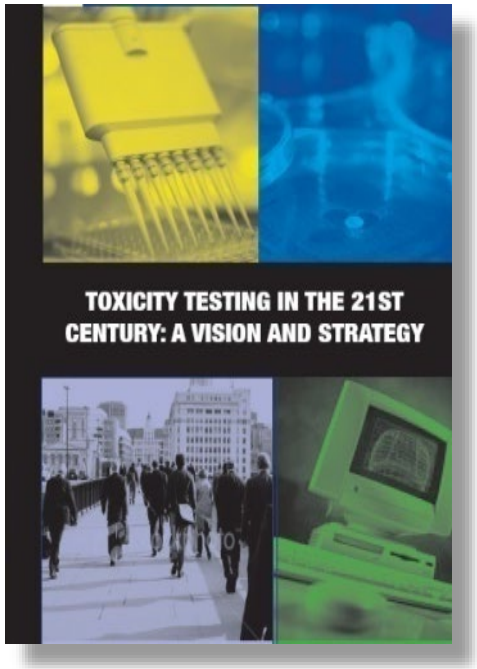
Carcinogenesis, Volume 13, Issue 12, December 1992, Pages 2221–2226,

Why do we need NAMs more generally

- There are large numbers of chemicals with limited or no toxicity information; metabolites and degradation products; process intermediates
- Novel materials and processes, e.g. nanomaterials, biocomposites
- The need to assess risk from combined exposures to multiple chemicals
- Accuracy and reliability of risk assessments, based on laboratory species, are being questioned and it is not possible to assess some effects in test animals
- Societal and other demands for the move to non-animal assessment methods
- Rapid advances in scientific knowledge, e.g.
  - Genomics and epigenetics
- Profound technological advances
  - Analytical chemistry, high-throughput technologies, high content analysis, computational toxicology, systems biology, bioinformatics
    - The era of ‘big data’

Need for more accurate, efficient and resource-effective solutions that meet societal needs

Toxicity Testing in the 21st Century (2007)



- A new toxicity-testing system that evaluates biologically significant perturbations in key toxicity pathways
- Implementation of the vision will require suites of in vitro tests that are sufficiently comprehensive to assess the broad array of possible toxic responses
- Validation of tests and test strategies. Validation will be especially challenging for the mechanistically based tests.
- Evidence that the results of tests are adequately predictive for use in decision-making
- A substantial and focused research effort will be needed, which will need to be long-term, large-scale and concerted.
- An appropriate institutional structure that fosters multidisciplinary intramural and extramural research is needed. There would be far less chance of success within a reasonable time if the research were dispersed.
- Development of the strategy will require substantial funding - hundreds of millions of dollars.
- Given the political will and the availability of funds to adapt the current regulatory system to take advantage of the best possible scientific approaches to toxicity testing, the committee foresees no insurmountable obstacles to implementing the vision.
- Noticeable changes in toxicity-testing practices should be introduced within 10 years. Within 20 years, testing approaches will more closely reflect the proposed vision than current approaches. This assumes adequate and sustained funding.

Regulatory impact

- Validation/verification that a NAM is fit for its intended purpose
- Adequacy of a NAMs-based approach in assessing the toxicity of a chemical, i.e. coverage of toxicological space
- Acceptance and utilisation of NAMs as a basis for regulatory decision making

- Related but separate issues, each needing their own solutions

Method validation

- Progress in EU on NAMs to date (human health effects)
  - Genotoxicity (as part of tiered approach)
  - Eye corrosion
  - Eye irritation
  - Skin corrosion
  - Skin irritation (depending on regulatory framework)
  - Phototoxicity
  - Skin permeability
  - Dermal sensitisation (OECD IATA)
- These methods took 15-20 years from “invention” to regulatory acceptance
- All (except genotoxicity) reflect local effects

[ECVAM was established over 30 years ago (1991)]

Innovation is outpacing validation

Toxicol Sci. 2018 Jun; 163(2): 655–665
Published online 2018 Mar 24. doi: 10.1093/toxsci/kfy058
PMCID: PMC5974779
PMID: 29590495

Prediction of Drug-Induced Hepatotoxicity Using Long-Term Stable Primary Hepatic 3D Spheroid Cultures in Chemically Defined Conditions

Sabine U Vorrink, Yitian Zhou, Magnus Ingelman-Sundberg, and Volker M Lauschke

Toxicology and Applied Pharmacology 354 (2018) 24–39
Contents lists available at ScienceDirect
Toxicology and Applied Pharmacology
journal homepage: www.elsevier.com/locate/taap

Testing for developmental neurotoxicity using a battery of *in vitro* assays for key cellular events in neurodevelopment☆

Joshua A. Harrill[a,*], Theresa Freudenrich[b], Kathleen Wallace[b], Kenneth Ball[b,c], Timothy J. Shafer[b], William R. Mundy[b]

SCIENTIFIC REPORTS
nature research
Sci Rep. 2020; 10: 8879.
Published online 2020 Jun 1. doi: 10.1038/s41598-020-65817-0
PMCID: PMC7264205
PMID: 32483208

Repeated dose multi-drug testing using a microfluidic chip-based coculture of human liver and kidney proximal tubules equivalents

Ni Lin,[#1,2,6] Xiaobing Zhou,[#1,6] Xingchao Geng,[1] Christopher Drewell,[3] Juliane Hübner,[3] Zuogang Li,[1] Yingli Zhang,[1] Ming Xue,[✉2] Uwe Marx,[✉4] and Bo Li[✉5]

Chemical Research in Toxicology
Perspective
Cite This: Chem. Res. Toxicol. 2019, 32, 536–547
pubs.acs.org/crt

Advancing Computational Toxicology in the Big Data Era by Artificial Intelligence: Data-Driven and Mechanism-Driven Modeling for Chemical Toxicity

Heather L. Ciallella[†] and Hao Zhu*[,†,‡]

The Journal of Toxicological Sciences (J. Toxicol. Sci.)
Vol.45, No.2, 95-108, 2020
95

Original Article

Integration of read-across and artificial neural network-based QSAR models for predicting systemic toxicity: A case study for valproic acid

Tomoka Hisaki[1,2], Maki Aiba née Kaneko[1], Morihiko Hirota[1], Masato Matsuoka[2] and Hirokazu Kouzuki[1]

npj | Systems Biology and Applications
volume 7, Article number: 7 (2021)
www.nature.com/npjsba

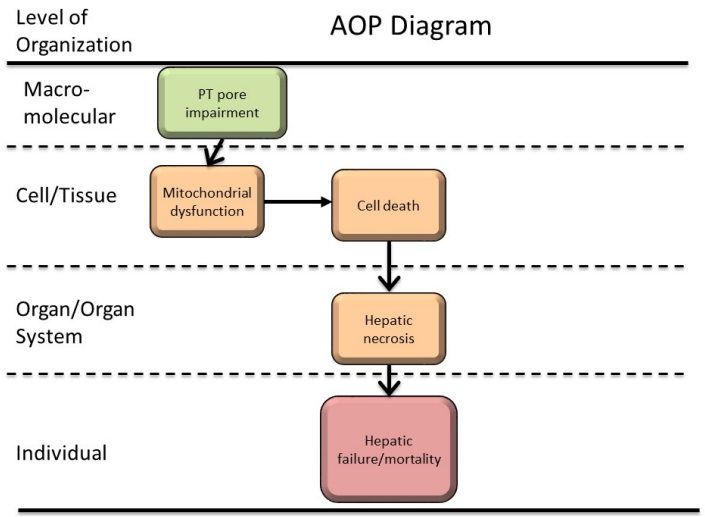
ARTICLE OPEN

High-throughput toxicogenomic screening of chemicals in the environment using metabolically competent hepatic cell cultures

Jill A. Franzosa[1], Jessica A. Bonzo[2], John Jack[1], Nancy C. Baker[3], Parth Kothiya[1], Rafal P. Witek[2], Patrick Hurban[4], Stephen Siferd[4], Susan Hester[1], Imran Shah[1], Stephen S. Ferguson[5], Keith A. Houck[1] and John F. Wambaugh[1✉]

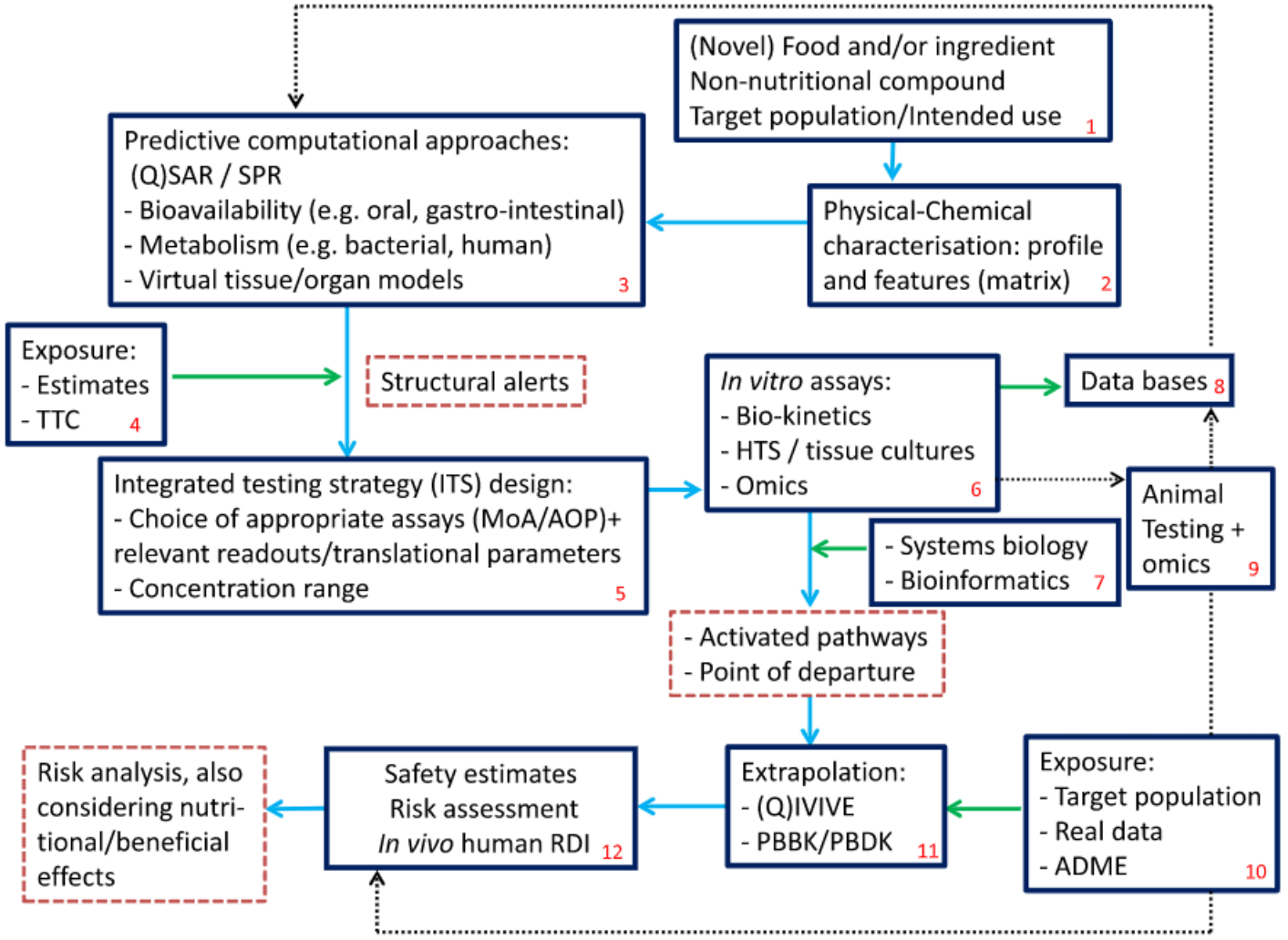
Establish biological relevance and fitness for purpose

- Method performance characterization
  - e.g. In vitro assay for mitochondrial PT pore impairment (KE)
- Value of information re potential adverse outcome
  - e.g. Prediction of proximal tubular damage (AOP)
- Utility for decision making
  - e.g. Identification of POD for establishing HBGV



Consider context of use: Prioritisation, Hazard screening, risk assessment

New methodologies in safety assessment



Blaauboer et al (2016)

Assessing coverage of toxicological space

Ontology for developmental toxicity

Molecular targets

Molecular Mechanisms associated with MIEs

- Receptor interactions (e.g. with oestrogen receptor (ER), androgen receptor (AR), peroxisome proliferator-activated receptor (PPAR), other nuclear hormone receptors, cytokine receptor and signal transducer and activator of transcription (STAT), Toll/interleukin-1 receptor, nitric oxide receptor, G protein-coupled receptor (GPCR), etc.
- Developmental signaling pathways (e.g., Wnt, Notch-Delta, TGF-β, FGF, hedgehog, RTK,etc.
- Cell stress pathways (e.g. nuclear factor NF-κB).

Receptors
Signalling pathways
Cell stress pathways

Cellular mechanisms

Cellular Mechanisms / Alterations

- Cell proliferation
- Motility
- Morphogenetic movements broken down into component parts
- Cell recruitment
- Extracellular matrix
- Pattern formation
- Altered differentiation
- Intracellular pH
- Apoptosis
- Oxidative stress
- Biological clocks (e.g. somite clock)
- Folate antagonism
- Tight junctions
- Cytoskeleton
- Angiogenesis/vasculogenesis
- Gap junctions
- Ligand-gated cation channels

Maternal / Placental Mechanisms

- Nutritional deficiencies
- Chelation
- Altered blood flow
- Uterine pressure
- Acid/base disturbances
- Altered gas exchange
- Placental insufficiency

Maternal mechanisms

Adverse Developmental Outcomes

- Malformation
- Intrauterine death
- Intrauterine growth restriction

Outcomes

AOP coverage

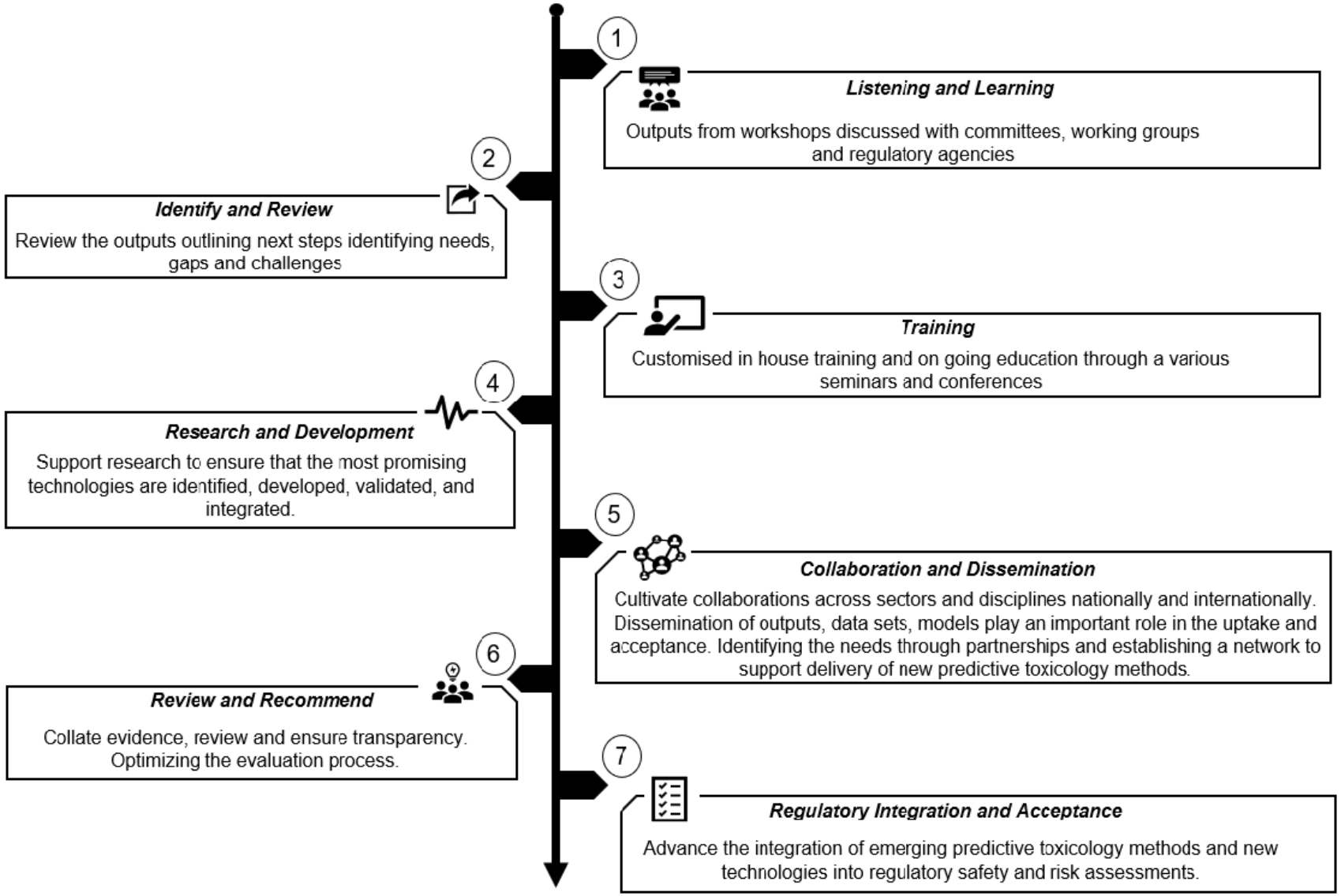
KE coverage (verified methods)

Baker et al, 2018

Regulatory acceptance

- Familiarisation and experience
- Case studies
  - Ideally prospective, but retrospective if necessary
    - Comparison with outcome using current approches
  - e.g. Joint FAO/WHO Meeting on Pesticide Residues
    - List of Substances Scheduled for Evaluation and Request for Data
    - Data from new molecular, cell and computer-based approaches
    - JMPR offers to evaluate without prejudice, in parallel, any data generated using emerging methods that in the view of sponsors could substitute for information obtained using conventional testing methods

FSA/COT roadmap to implementation of NAMs



The future of chemical risk assessment

- Four futures, all likely to be quite different from each other
  - The future we would like (“The Vision”)
  - The future we are investing resources in (e.g. HorizonEU)
  - The future we convince ourselves has been achieved
  - The future we actually find ourselves in
- We need to recognise which future it is that we are most likely to achieve, based on resources committed and state of knowledge (be objective)
  - If unacceptable for needs, commit more resources on research and/or development as necessary
- The timescale for scientific advances to impact meaningfully on risk assessment is almost always under-estimated
  - This needs to be taken into account