National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Chemical carcinogenicity assessment – NAMs and beyond

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Carcinogenicity assessment

- Carcinogenicity: GTX vs NGTX
- REACH: GTX yes, carc "no"
  - NGTXCs largely undetected
  - CLP: mutagenicity, not carc
- Revision REACH -> opportunities and challenges
- Cancer hazard assessment (e.g. agrochemicals) typically involves a two-year carcinogenicity study in mice and rats
- The lifetime carcinogenicity study (TG 451/453) has been proven to detect genotoxic and non-genotoxic carcinogens, but also to suffer from serious limitations
- Agrochemicals: Forthcoming results are used for both hazard identification (potential) and hazard characterization (potency) to enable point-of-departure derivation
- Solution: To develop a **mechanism-based approach for predicting carcinogenic potential** of agrochemicals based on NAMs

› What mechanisms?

Identification of mechanisms – an example

- Data search conducted for >400 unique agrochemicals, using list of chemicals evaluated for carcinogenicity by US EPA and EU agencies
- Reports from regulatory bodies, e.g. EFSA, ECHA, US EPA, JMPR

- Identification and categorization of tumours, using standardized pathological nomenclature

→ **340 cases of tumour formation**

→ **170 non-genotoxic carcinogens**

Details described in Heusinkveld et al, Crit Rev Toxicol, 2020

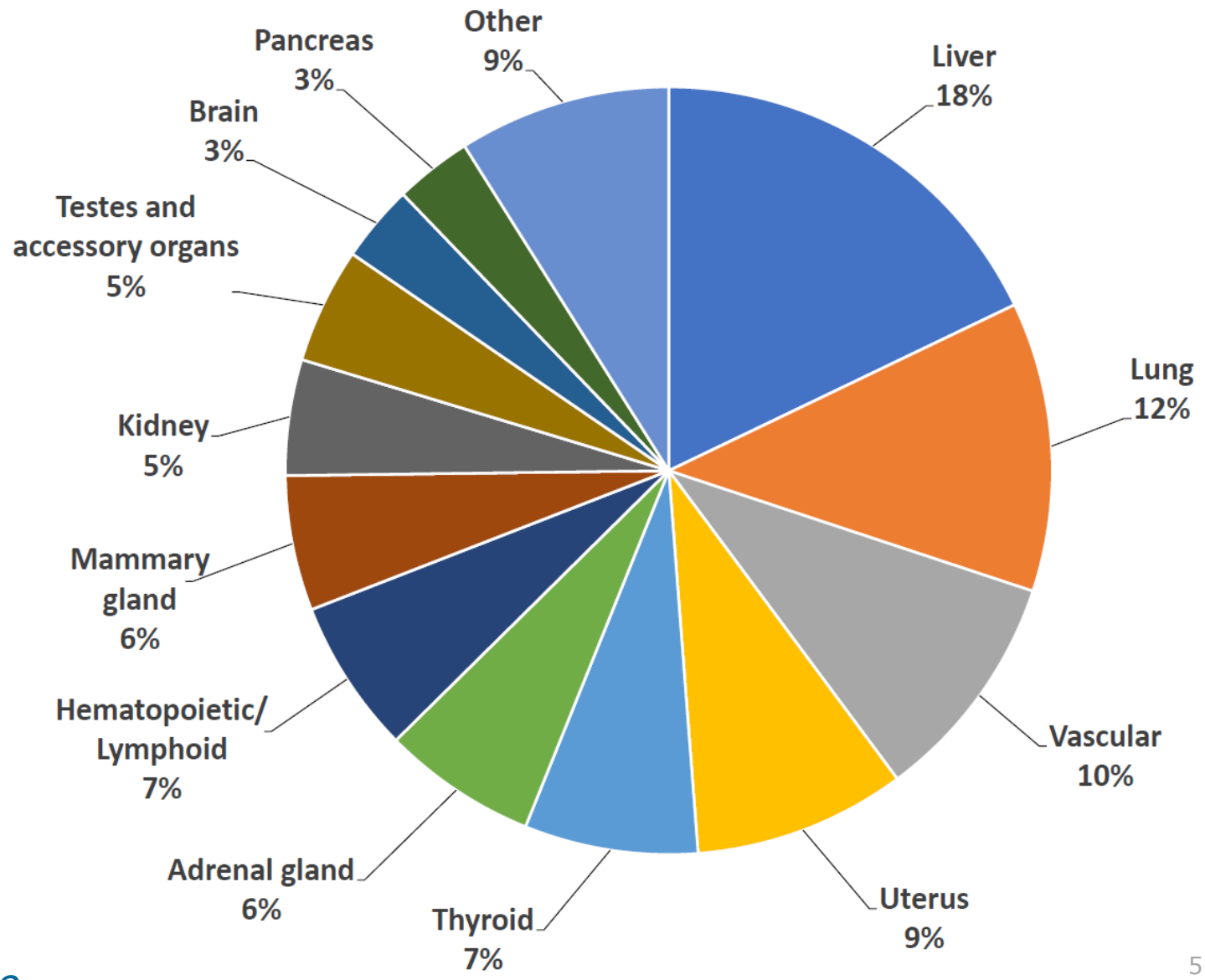
MOAs identified

MOA/MOA network[a]	Description	Organs	# Tumor cases	# Substances
Nuclear receptor (CAR and/or PXR) activation leading to induction of enzymes involved in xenobiotic metabolism	Sustained enzyme induction leading to hepatocellular adenoma/carcinoma	Liver	58	55
	Hepatic thyroid-hormone catabolism leading to sustained thyroid hormone production leading to follicular cell adenoma/carcinoma	Thyroid	42	40
	Hepatic steroid hormone catabolism leading to sustained hormone production leading to Ley	Testes	5	5
	Hepat sus to		7	7
Sustained cytotoxicity	Sustai pro	bladder and intestine	61	45
Sustained cytotoxicity–oxidative stress	Oxidative stress leading to sustained cytotoxicity and increased cell proliferation leading to tumor formation	Various including: liver, spleen and lymphoid system	7	4
Endocrine-related MOAs	Sustained disruption of hormonal signaling leading to imbalance in hormone production leading to overstimulation of hormone sensitive tissue leading to tumor formation.	Various including: mammary gland, uterus, ovaries and testes	29	11
PPARα activation	PPARα activation leading to increased cell proliferation leading to hepatocellular adenoma /carcinoma	Liver	11	11
Thyroid Peroxidase inhibition	Thyroid peroxidase inhibition leading to sustained TSH production leading to sustained thyroid hormone production leading to follicular cell adenoma/carcinoma	Thyroid	4	4

In addition: 114 tumors cases, related to 72 chemicals, with unknown MOA

Tumors with unidentified MOA – ‘known unknowns’

- 72 substances
- 114 occurrences of tumour formation
- 19 different organs/organsystems
- Lung and adrenals putative MOAs identified



Heusinkveld et al, Crit Rev Toxicol, 2020

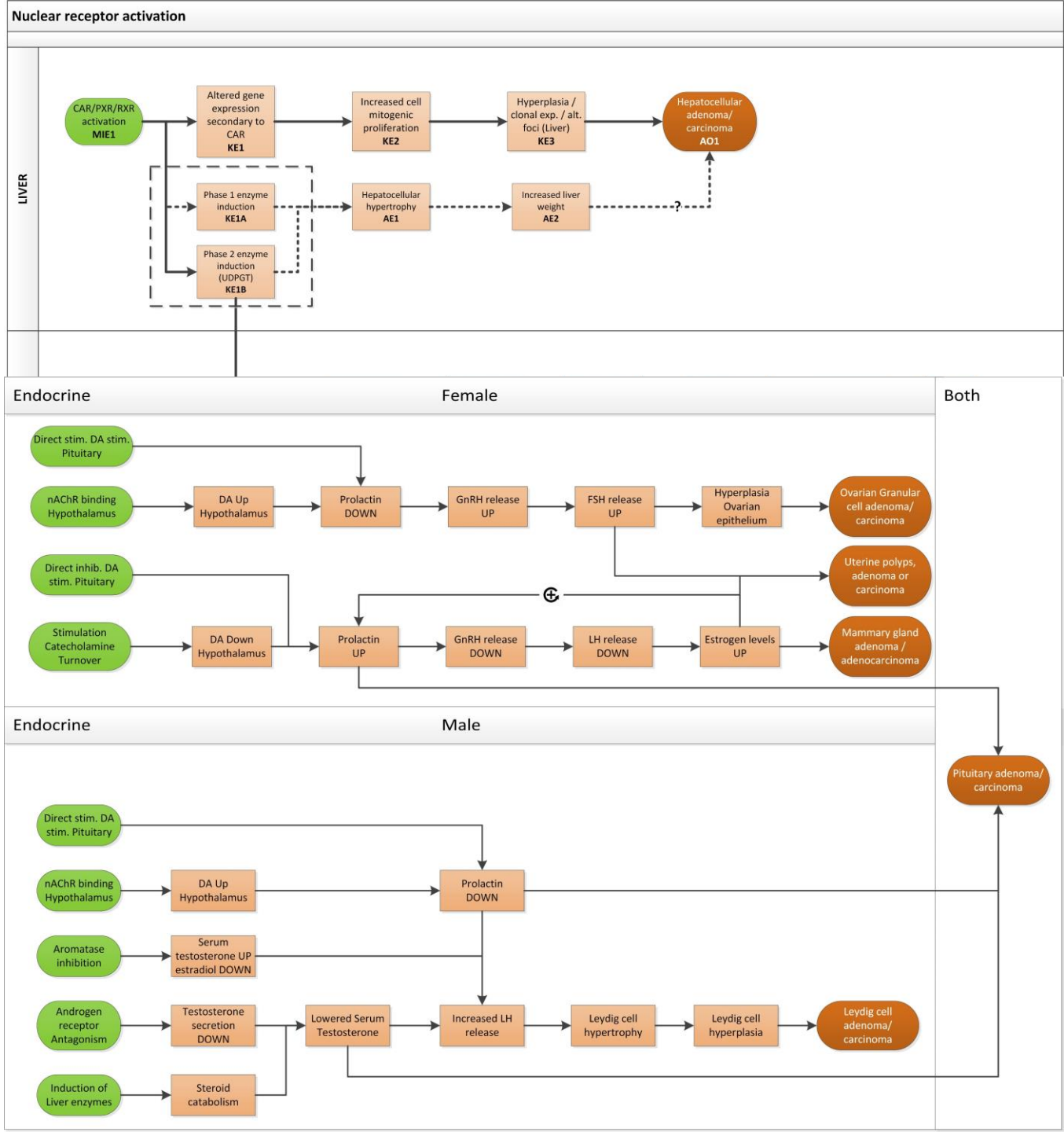
Issues to be solved

- MOAs identified in rodents
- Missing human MOAs e.g. immunosuppression
- Which MOAs should be considered?
  - Who determines relevance
  - Define relevance
  - Criteria for relevance

- Know your biology
  - Human (tumour) biology
  - Homology of tissues/cell types
- Mechanism-based
- Quantitative relationship

Mechanistic approach

- Mechanisms outlined -> AOPs
- Define NAMs for relevant KEs
  - Many NAMs out there
  - Criteria for NAMs to be met for regulatory use? Tech readiness levels?
  - Characterization of models
  - Relevance unknown or uncertain



Heusinkveld et al, Crit Rev Toxicol, 2020

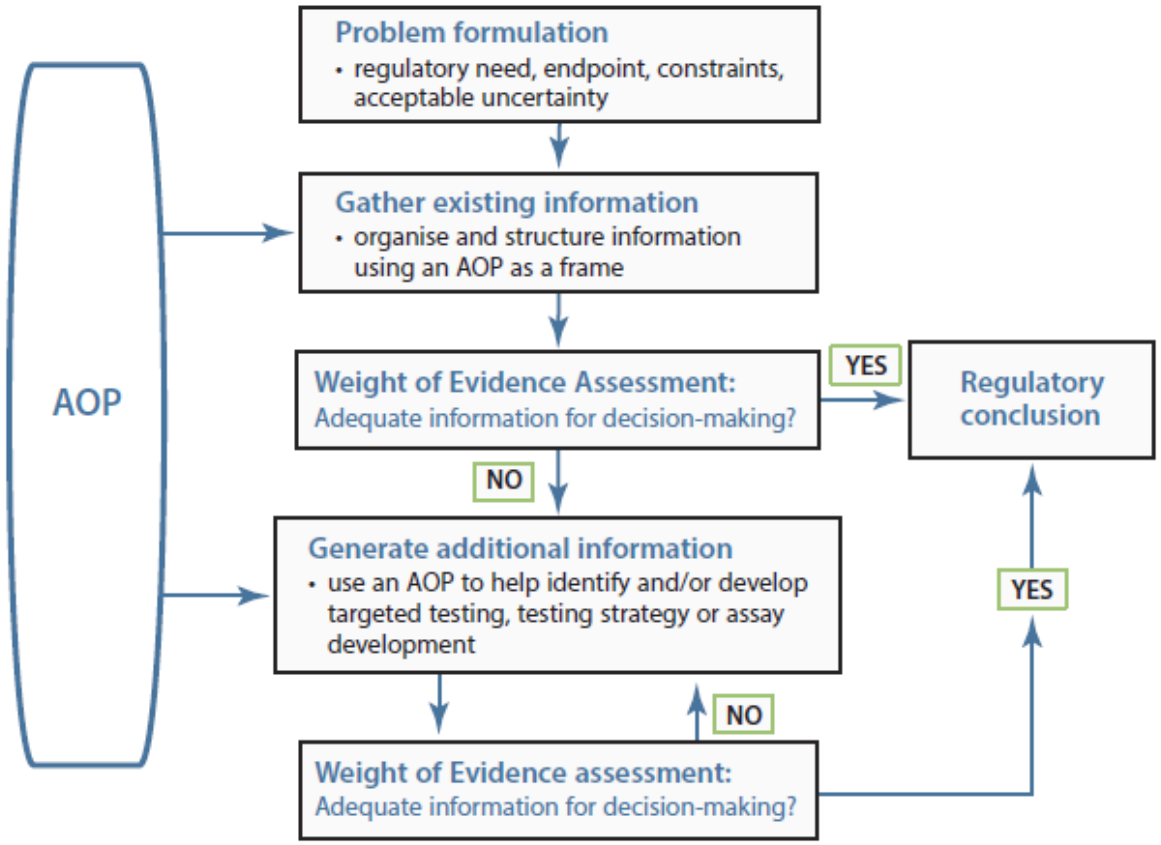
Integrated Approaches to Testing & Assessment

IATA definition

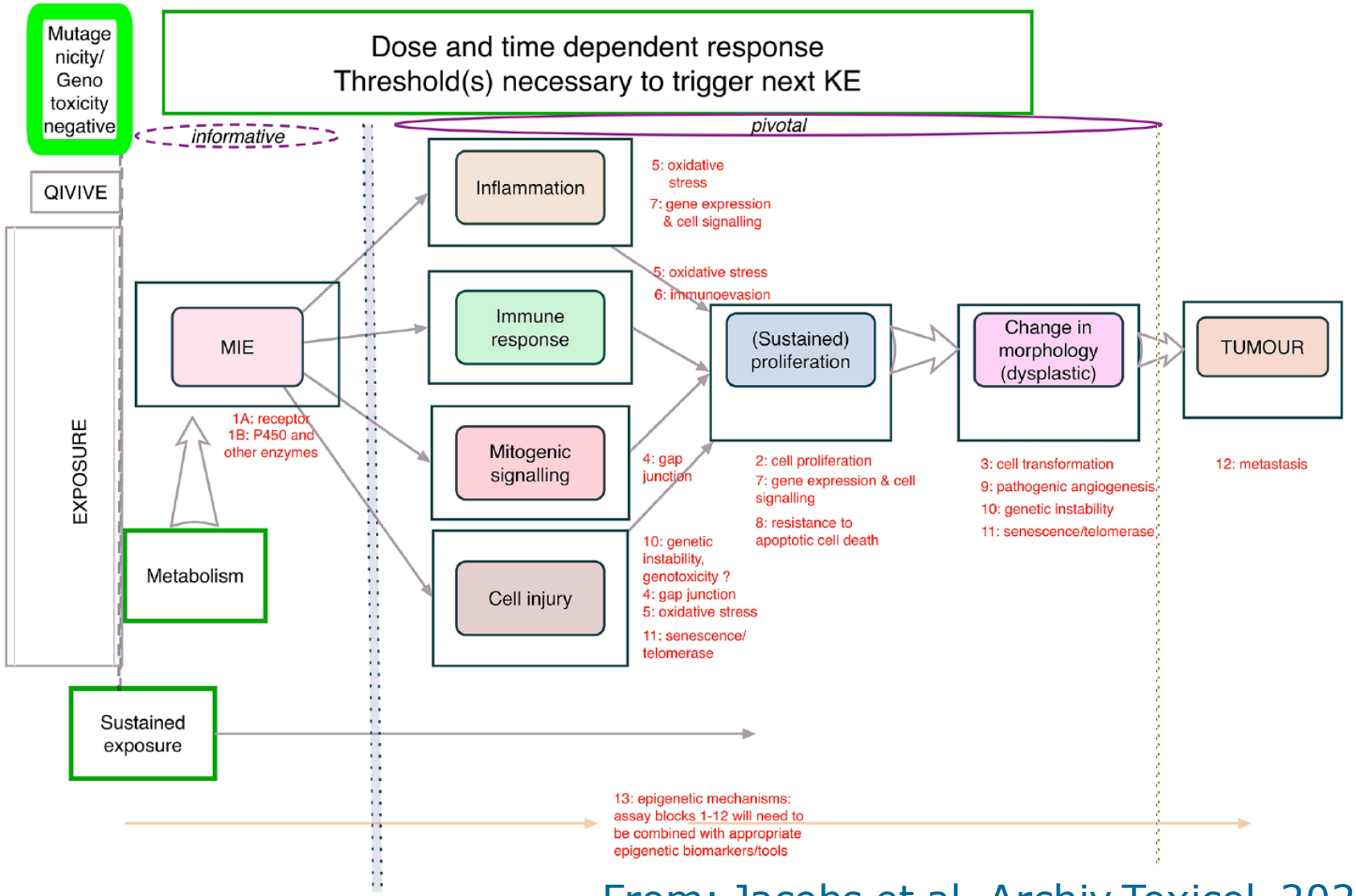
- **Integrating** results from one or many methodological **approaches**,
- using existing information and generating new information using **testing** strategies

- Iterative approach to answer a defined question (**assessment**)

Figure 4. **Framework for how an AOP can be applied to inform and structure IATA in a decision context**



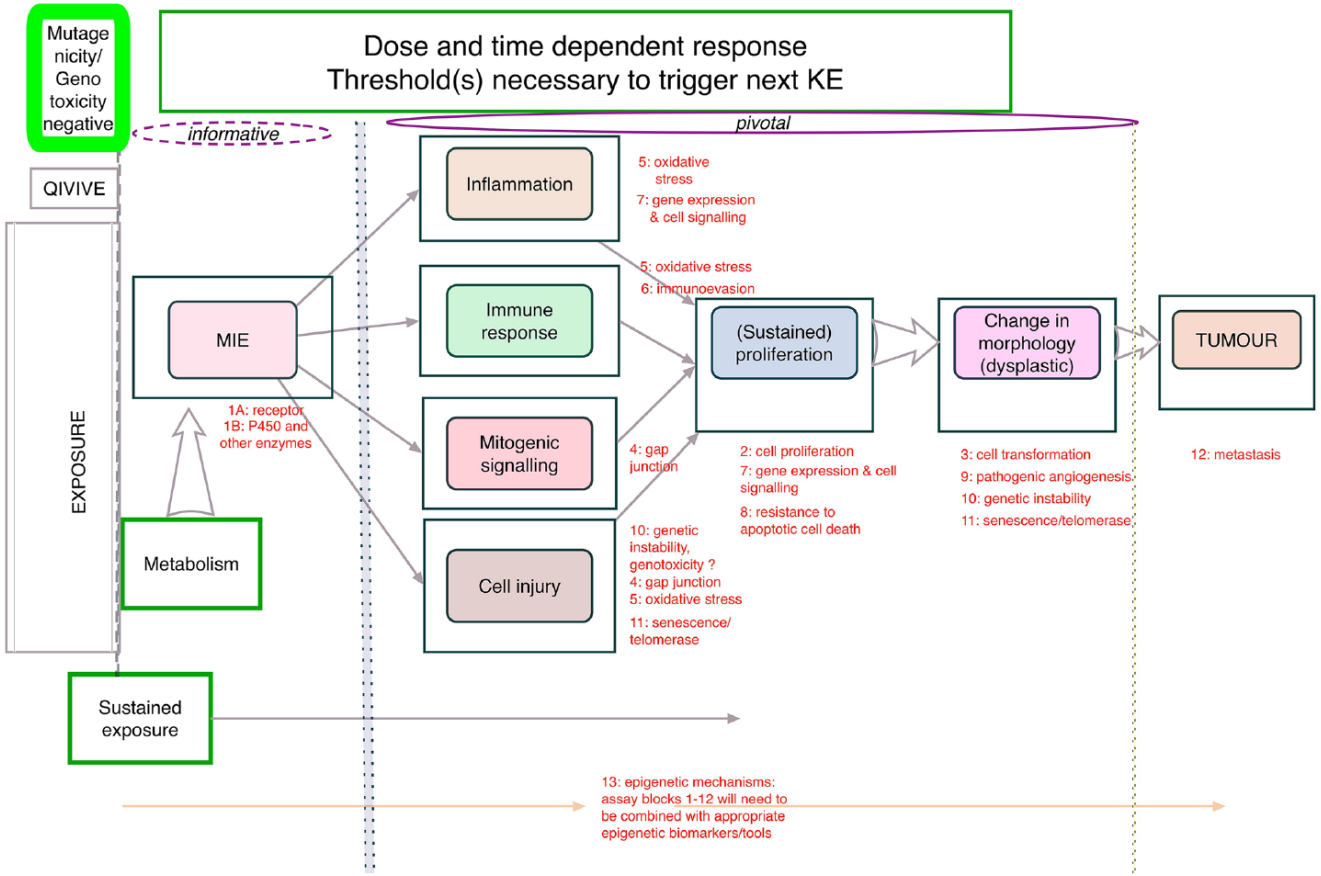
IATA for non-genotoxic carcinogens



From: Jacobs et al, Archiv Toxicol, 2020

IATA for non-genotoxic carcinogens

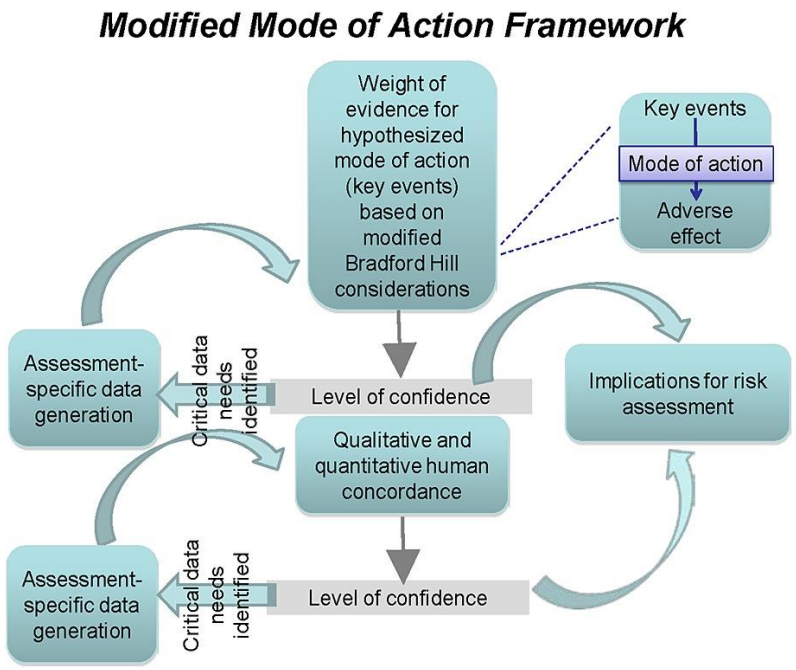
Work in progress:
Review of available NAMs/Assays in terms of robustness and appropriateness



From: Jacobs et al, Archiv Toxicol, 2020

Human relevance assessment

- Should be done in a structured and transparent fashion, using well-defined criteria based on WHO/IPCS framework
- Should be done for both toxicological pathways (MOA/AOP) **AND** associated NAMs
- Should be done for pathways as a whole, not for single elements of a pathway



From: Meek et al., J Appl Toxicol 2014

Are we there yet?

YES

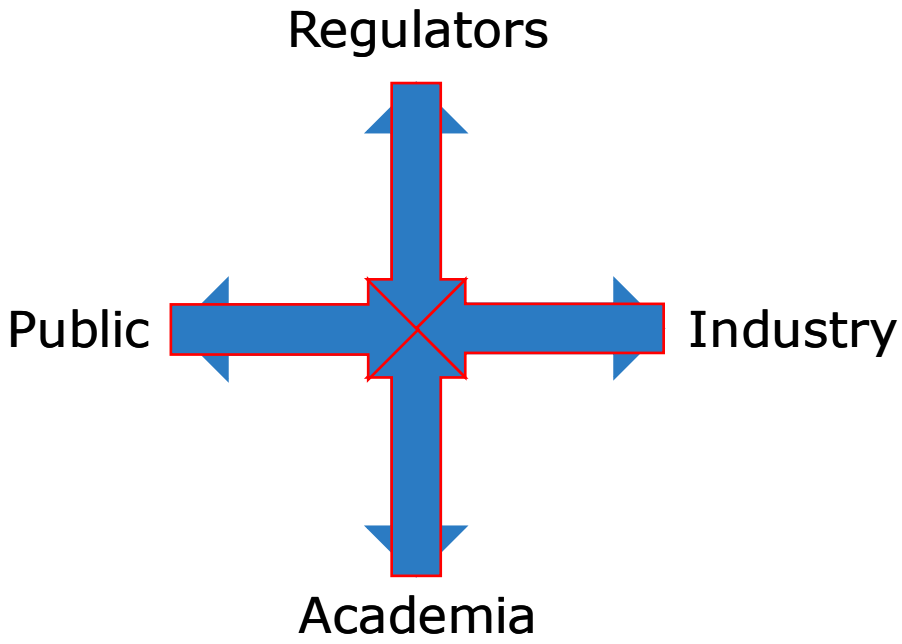
- Assays available for MIE and 1st KE in many mechanisms
- Absence of GenTox
- PBPK models available extrapolation well underway

NO

- Elephant in the room: Proliferation assay in vitro
- Missing higher tier endpoints
- Quantitative approach required!
- Build test strategy
  - Cell models
  - Whole organism models
  - Short term in vivo?
- How not to end up overly conservative?

Facilitation through policy

- Start talking
- Development of NAMs
  - Trust
  - Quality criteria
  - Reliability
  - Reproducibility
  - Technological readiness
- Encourage data sharing
- Transition period



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Thank you for your attention

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