# ECHA-EFSA Workshop: Implementing the EC Roadmap on Phasing Out Animal Testing in Pesticides and Biocides

## Key Agronomic and Safety Characteristics Concept (key-ASCs or «need to know» approach):

## Examples with *Carcinogenicity, Biopesticides and AI*



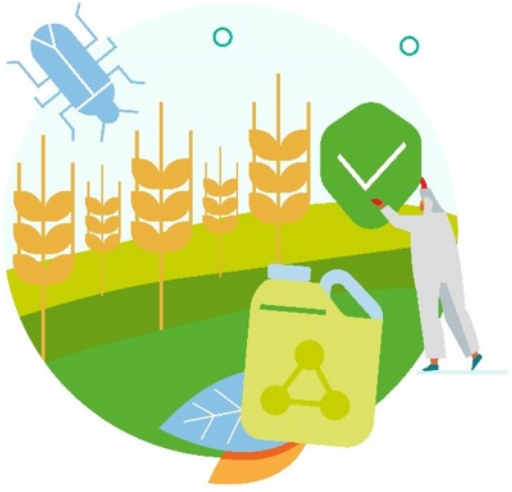
***SESSION 2.2*** **- REFLECTIONS FROM STAKEHOLDERS – 2 – ROADMAP SPECIFIC (TECHNICAL) OPPORTUNITIES AND CHALLENGES FOR PESTICIDES AND BIOCIDES**

***DR TINA MEHTA*****, GLOBAL HEAD OF HUMAN HEALTH, ADAMA**

**21 OCTOBER 2026**

# Farmers' Toolbox

Current agricultural paradigm is shifting to include a variety of integrated agronomic solutions.



**CONVENTIONAL PESTICIDES**



**BIOPESTICIDES**



**PLANT BIOTECHNOLOGY**



**DIGITAL AND PRECISION AGRICULTURE**

A new approach will integrate the best tools and latest advances in chemical testing methods to ensure robust human and environmental safety and risk assessments, across different agronomic product platforms.

# Key ASCs – Efficacy and Protection Goals Attributes

HESI TEA (Transformation of Evaluation of Agrochemicals) concept paper proposed the concept of
- **"good enough toolkit"** to promote efficient decision-making: *Wolf et al, 2023)*

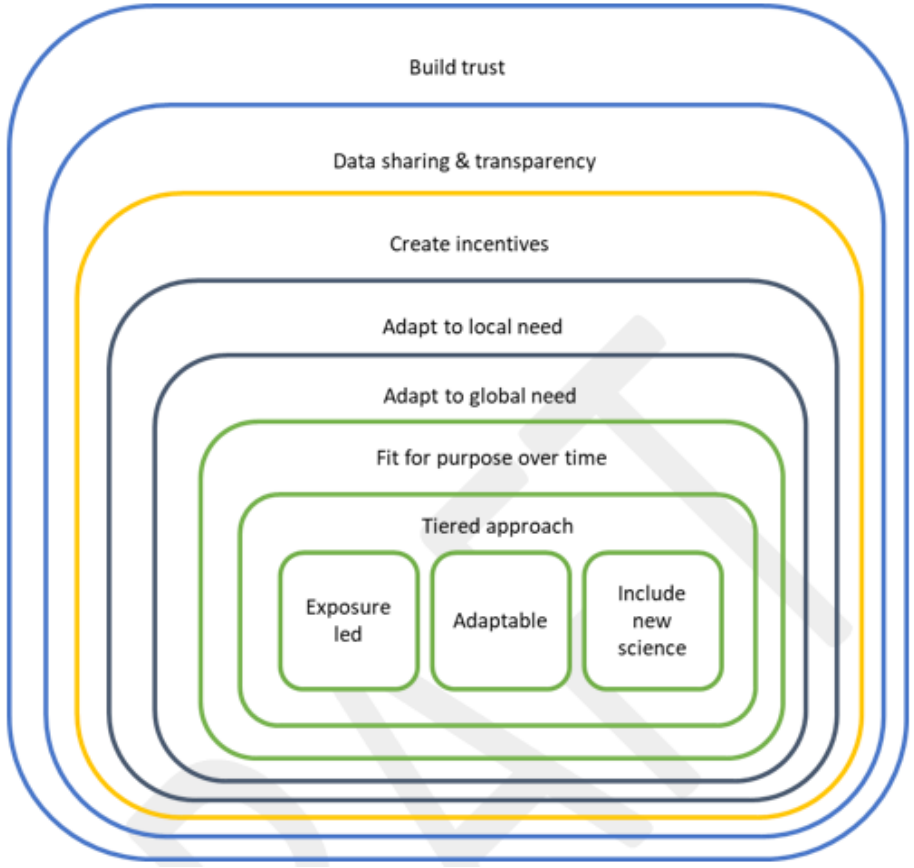
**Why are the Key ASCs important for Regulators, CLE and all stakeholders**:

- Allow prioritisation for farmers' toolbox solutions
- Improve Farming and Food industry competitiveness
- Risk Assessment approach proportionate to agronomic solution, ensuring equivalent or higher level of protection
- Reduce assessment times and increase transparency, associated to staged and modular assessment
- More comprehensive risk assessment, particularly at renewals
- Investment planning security (industry) and resource planning (all stakeholders)

➢ Meeting the EU Comm (ENV) concept of *« safe and sustainable by design »*

**Why are the Key ASCs important for Animal Testing?**

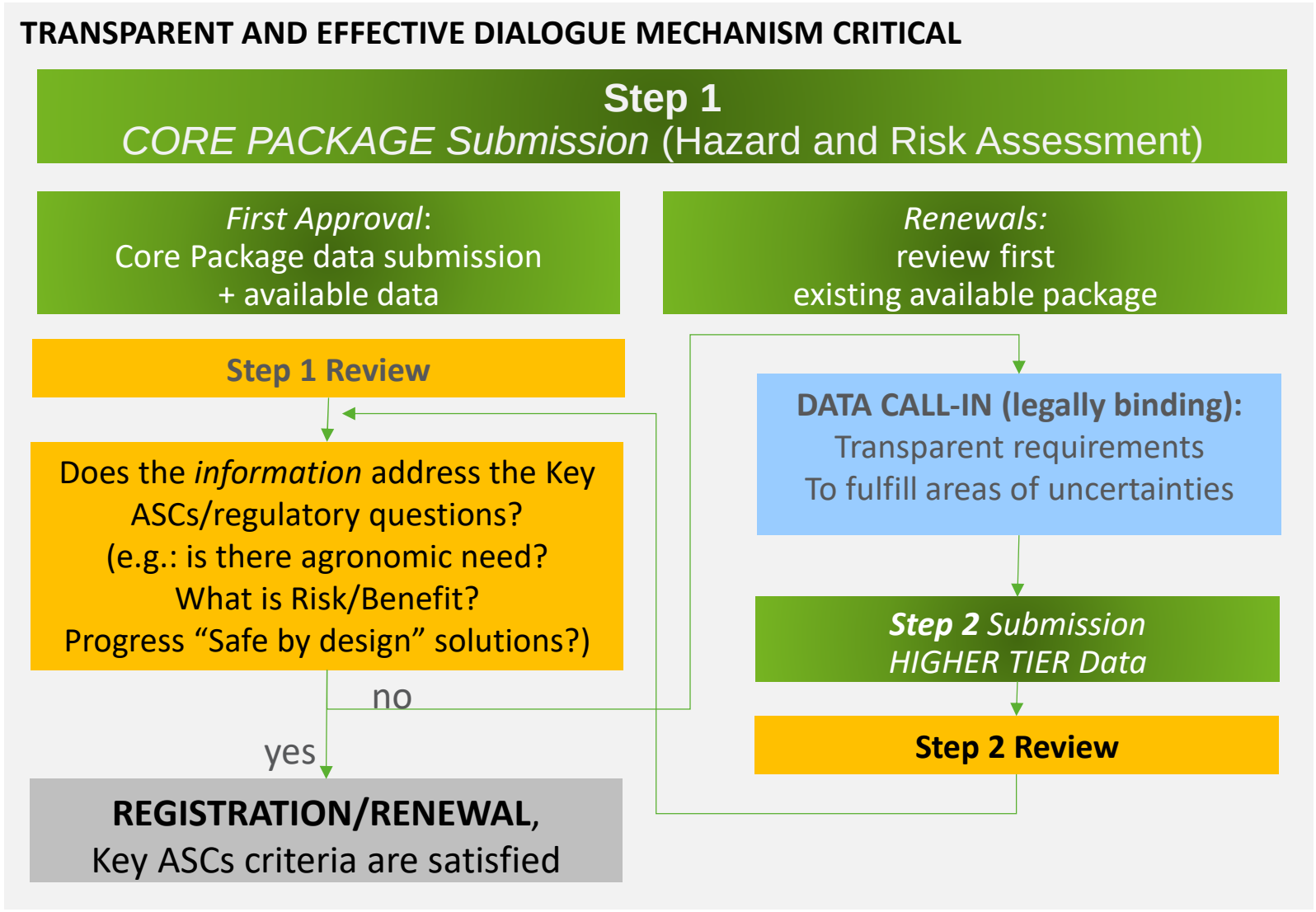
- With a problem formulation approach and associated tiered strategies, it will be possible to:
  - phase in New Approach Methodologies (NAMs)
  - progressively reduce reliance on vertebrate studies




*Inspired by HESI TEA conceptual model*
*With permission from Bhuller et al et al. 2025, submitted*

# Key ASCs – Paradigm Shift 1

**Process *adaptation for transparent & tiered approach*, with *targeted data call-in* system**




**Advantages when clearly identifying "Key ASCs" (policy goals) in Regulation + relevant Tiered Approaches in Guidance**

**Regulators advantages:**
Shorter assessment time
Resource effectiveness
Effective public consultation

**Applicant advantages:**
Staged investment
Investment security
Fewer moving targets

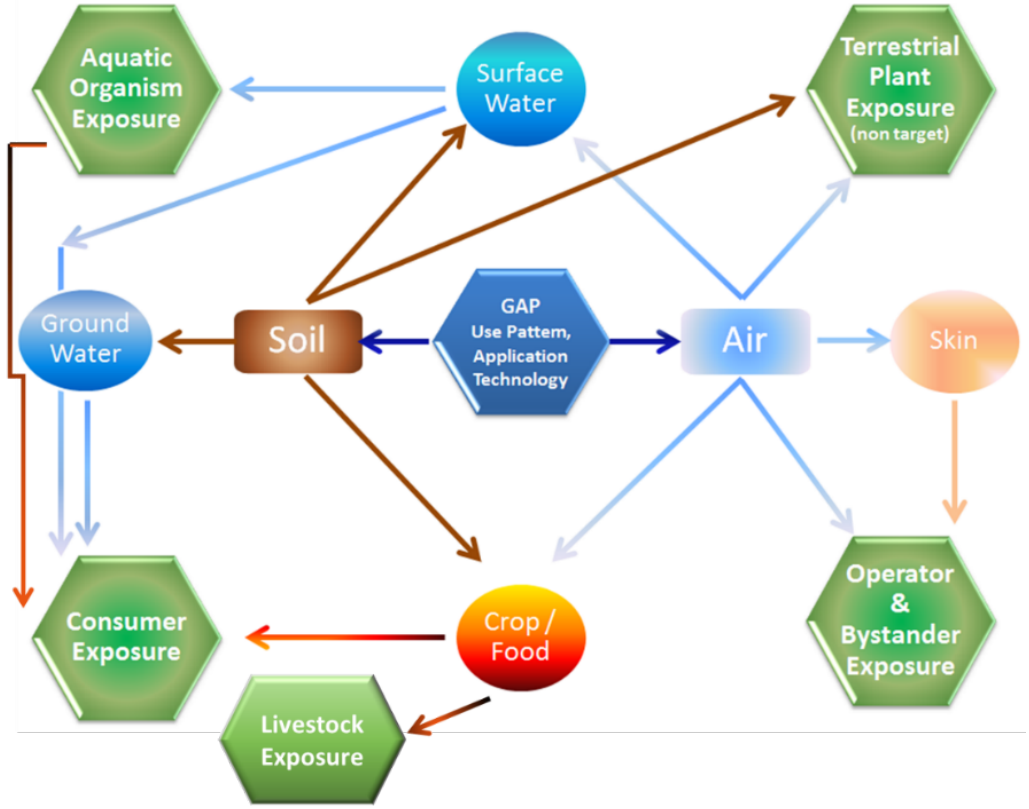
**Advantages for everyone:**
Earlier regulators engagement
More innovation to the market
Higher transparency of decision

# Key ASCs – Paradigm Shift 2

## Defining the "*safety attributes/questions*" instead of the "data requirement" in regulation & relevant guidance

**What are we trying to address?**

Numerous exposure pathways need addressing in agricultural products safety assessment




*From HESI TEA conceptual model, from Bhuller et al. 2025, submitted*

EU: 1107/2009, 283& 284/2013; most tests in 2 species

| *Mammalian use for conventional pesticide registration (common global requirements)* | *1st species (anim. No.)* | *2nd species (anim. No.)* |
|---|---|---|
| ADME | Rat (30) | (occasional) |
| Acute "6-pack" | Rat/Mouse/Rabbit (60) ??? | - |
| Oral Sub-chronic (Range Finder/28d+90-day) | Rat (60+100) | Dog (/mouse) (10+40 /60+100) ??? |
| Oral Chronic (1-year)/cancer | Rat (500) | Mouse (450) ??? |
| Other exposure routes | Usually, Rat (100) | - |
| Oral Development (Screen/main) | Rat (310+1100) | Rabbit (210+900) ??? |
| Oral Reproduction (Screen/2-gen) | Rat (950 + 3100) | - |
| Immunological | Rat (50) ??? | - |
| Neurological (acute/repeated) | Rat (80+200) ??? | - |
| ED & Mechanistic | Usually, Rat (variable) | - |
| Metabolites (genotox/repeated/DART) | Usually, Rat (assumed 500) | |
| ***TOTAL ANIMAL USE*** | ***Ca. 9000 Mammals*** ??? | |

*Example of animal use; adapted from Henriquez et al. 2025, ATLA accepted*

*There is a more efficient way to use animals....*

# Key ASCs - Today's Human Safety Requirements

WHY

Current *protection* goal in Reg (EC) 1107/2009:
*« No unacceptable effect on human health and environment »*

WHAT

Fulfil HH CLP for Risk Management
Hazard classes: CMR, ED/new hazards (STOT; acute)

What are we trying to answer

Conduct HH Risk Assessment
1. Dietary/Non-Dietary
2. For use approval
3. For monitoring
4. For food trade
5. For environmental risk assessments

HOW

List of Data Requirements Reg (EC) 283&284/*2013*

*Ca*. 50 studies;
Extensive animal use;
Traditional toxicology tools

>50 Guidance Documents/ Scientific opinions (EC comm. C 344 2023)

Explain how to use old technologies to fulfill agricultural, societal & regulatory demands

Perspective

Received: 11 May 2022 Revised: 15 July 2022 Accepted article published: 26 August 2022 Published online in Wiley Online Library: 14 September 2022

(wileyonlinelibrary.com) DOI 10.1002/ps.7148

# Transforming the evaluation of agrochemicals

Douglas C Wolf,[a] Yadvinder Bhuller,[b] Rhian Cope,[c] Marco Corvaro,[d] Richard A Currie,[e] John Doe,[f] Adriana Doi,[g] Gina Hilton,[h] Jyotigna Mehta,[i] David Saltmiras,[j] Fiona Sewell,[k] Maria Trainer[c] and Sandrine E Déglin[l*]

**Abstract**

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2021.1987384

Taylor & Francis

REVIEW ARTICLE

OPEN ACCESS Check for updates

# Using existing knowledge for the risk evaluation of crop protection products in order to guide exposure driven data generation strategies and minimise unnecessary animal testing

Paul Parsons[a], Elaine Freeman[b], Ryan Weidling[b], Gary L. Williams[a], Philip Gill[a] and Neil Byron[a]

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Regulatory Toxicology and Pharmacology 162 (2025) 105889

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

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# Transforming the Evaluation of Agrochemicals: A Conceptual Model

Bhuller Yadvinder[a], Bishop Patricia[b], Cope Rhian[c], Corvaro Marco[d], Richard A. Currie[e], Gina M. Hilton[f], Mehta Jyotigna[g], Puglisi Raechel[h], Douglas C. Wolf[i], Sandrine E. Deglin[h,*]

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ARTICLE I

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Guiding principles

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https://doi.org/10.1007/s00204-026-04411-1

GENOTOXICITY AND CARCINOGENICITY

# The use of cultured human hepatocytes as a test system to evaluate cell proliferation as a key event in nongenotoxic carcinogenesis

David E. Cowie[1] · Samuel M. Cohen[2] · Manuela Goettel[3] · Brian G. Lake[4] · Stephanie Nadzialek[5] · Uku Rooni[6] · Maaike E. Schutte[7] · Helen Tinwell[8] · Josh Turicchi[1] · Tomoya Yamada[9] · Christian Strupp[10]

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Regulatory Toxicology and Pharmacology

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# Towards achieving a modern science-based paradigm for agrochemical carcinogenicity assessment

Gina M. Hilton[a,*], Raffaella Corvi[b], Mirjam Luijten[c], Jyotigna Mehta[d], Douglas C. Wolf[e]

[a] PETA Science Consortium International e.V., Stuttgart, Germany
[b] European Commission, Joint Research Centre (JRC), Ispra, Italy
[c] National Institute for Public Health and the Environment, Netherlands
[d] ADAMA Agricultural Solutions Ltd, Reading, United Kingdom
[e] Syngenta, United States

# Key ASCs: Defining the « *HOWs* » *Today's Mindset*

## *Evolution from the 1960's?*

Agrochemicals Data Requirements: Reg (EC) 283&284/2013

*Timeframe for conduct, analysis and follow-up work: >5 years*

**No Meaningful Change in recent draft 283 Annex revisions**

***IF NON-GENOTOXIC…***

**OECD TG 453:**
**COMBINED CHRONIC TOXICITY/CARCINOGENCITY STUDY**
**(2018)**
**RAT 2 YEAR**

Originated **1981**

Precursor studies: 7/28 D-R Study & 90 Day Tox Study OECD TG 408

**OECD TG 451:**
**CARCINOGENCITY STUDY**
**(2018)**
**MOUSE 18 MONTH**

Originated **1981**

Precursor studies: 14/28 D-R Study & 90 Day Tox Study OECD TG 408

**OECD GD 116:**
**CONDUCT AND DESIGN OF CHRONIC TOXICITY AND CARCINOGENICITY STUDIES**
**(2012; 2ND ED.)**

Originated **1997** (Dose-selection guidance only)

2002: Guidance Notes

2008: OECD broaden scope to include MoA and HRF (2010 1st Ed.)

**FOLLOW-UP MODE OF ACTION WORK TO ADDRESS HUMAN RELEVANCE FRAMEWORK/ CLASSIFICATION**

Implications for metabolite assessment and testing leading to **increased *in vivo* testing**

Bioassay - very poor predictivity of human relevant non-genotoxic carcinogens
See analysis from EPAA Mechanism-based Carcinogenicity Waiver project (Heusinkveld *et al.*, 2020; Critical Reviews in Toxicology, DOI: 10.1080/10408444.2020.1841732)

# EPAA and EU Comm. Roadmap: *It's time for change! We can do this!!*

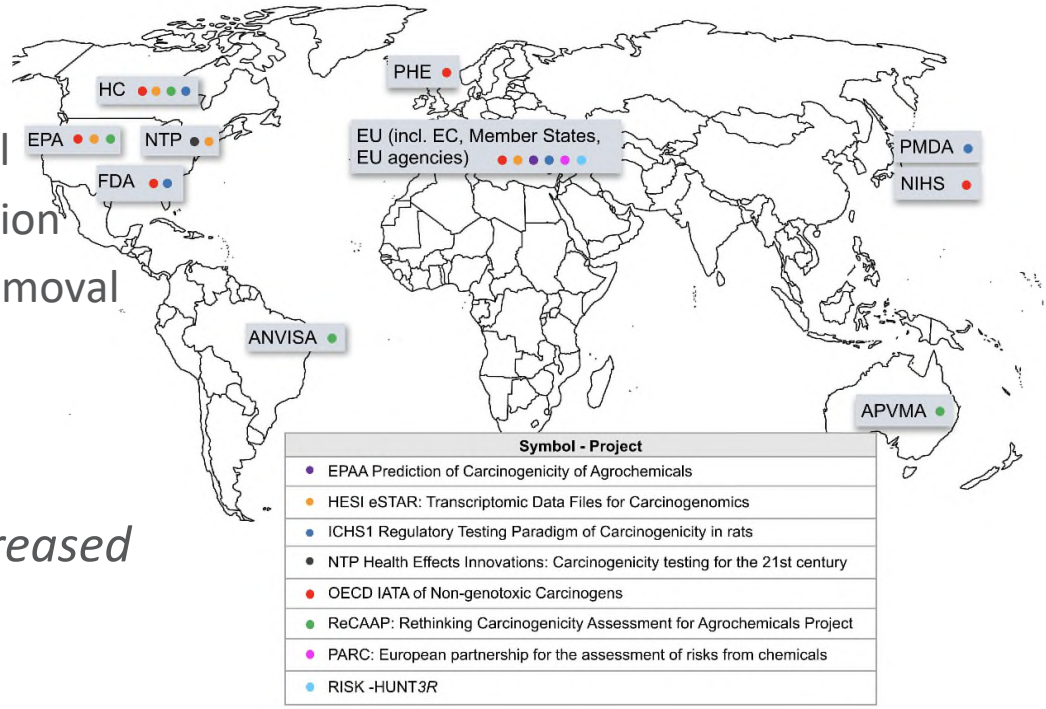
Chapter outlining consensus approach for implementation included in Roadmap…***publication submitted to NAMs Journal (*Corvi *et al*. 2026*) with key actions (short-mid-long term) and accountabilities***

**Mapping of Global Carcinogenicity Activities**: Project leaders gathered to create **forum of experts**…

- Reviewed commonalities, duplication, learnings, incompatibilities, science gaps, showed interconnections
- Identified & aligned science building blocks to **build a new assessment framework, adaptable for all sectors**
- Delivered a harmonised **Problem Formulation and Science-based approach**

for carcinogenicity safety assessment with **regulatory alignment**

- **Focus** on exclusion of genotoxicity, identification of toxicological targets, cell transformation, cell proliferation and immunomodulation
- **Reduce reliance on animal testing**, including more imminent removal of 2nd species (mouse) and **phase-in relevant NAMs**…

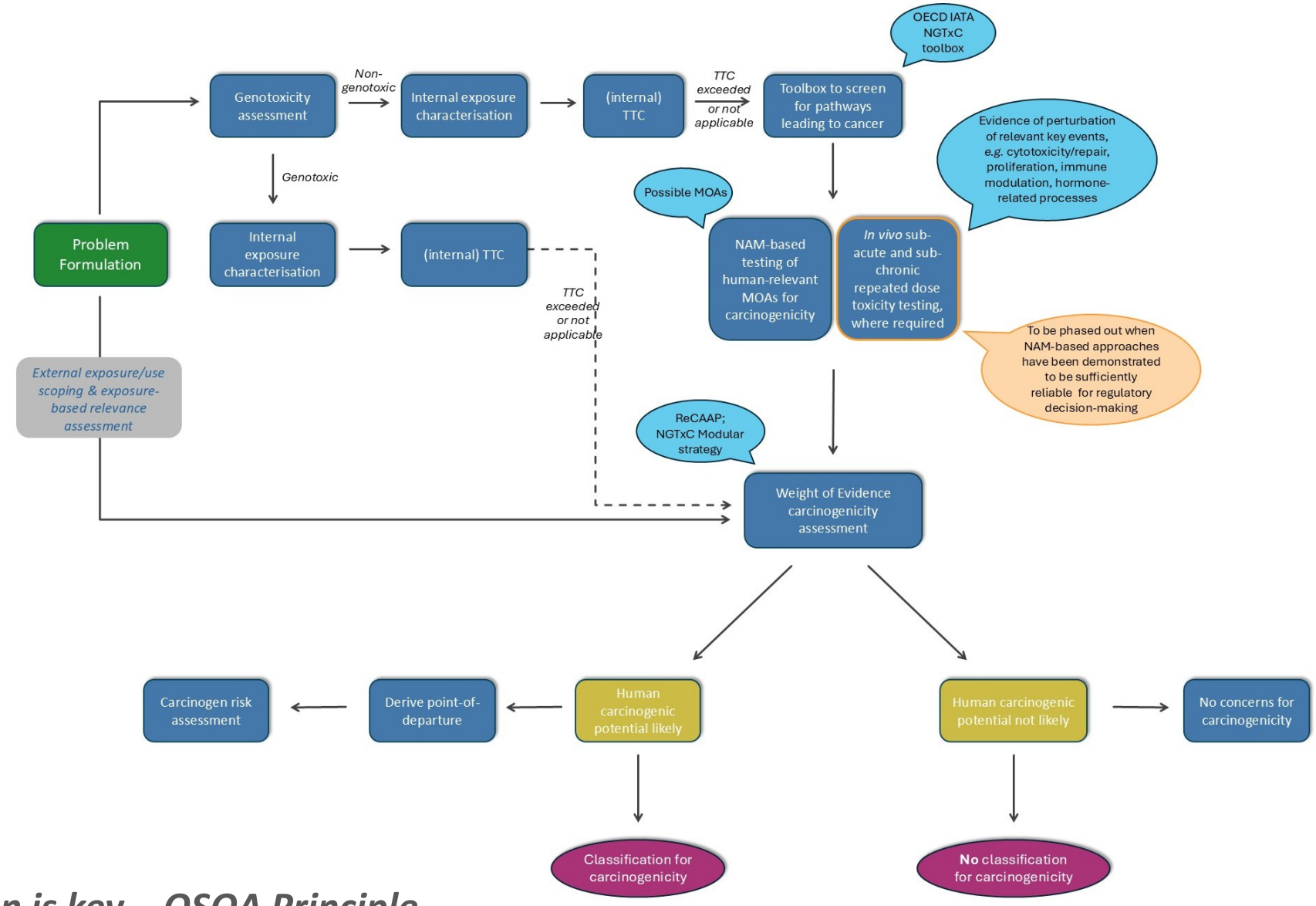



**Critical to Success** - *Change Management requirements*

- *Evolving regulatory landscape for agrochemicals, with an increased emphasis on societal driven protection enhancement*

(EPAA: Carc. Project leads: Mirjam Luitjen (RIVM), Raffaella Corvi (EU COMM JRC) and Tina Mehta (ADAMA))

# Global Carcinogenicity Assessment Framework for Chemicals




***Global dimension is key – OSOA Principle***

# Key ASCs: Defining the «*WHATs/HOWs*» Tomorrow's Mindset

***WHY:*** Current protection goal in 1107/2009:
*« No unacceptable effect on human health and environment »*

Have Key ASCs (instead of data requirements) in Reg (EC) 283&284/2013

**The underpinning regulatory questions (Key Safety ASCs)**

Define Likelihood of carcinogenic hazard *According to classification schemes*

Is there a carcinogenic risk? If applicable, *define carcinogenic safety value (PoD)*

Is there a chronic exposure risk? If so, *define chronic exposure threshold (PoD)*

***WHAT (unchanged)***
What are we trying to address

Fulfil CLP need

Fulfil Risk Assessment needs

***HOW***
Guidance Docs
Assessement scheme

**Option 1** (today; short-term solutions):
- Use 2 year rat + 18 month mouse

**Option 2** (mid-term solutions):
- Use 90d NOAEL + Pathway analysis
- *In vivo* waiving criteria (*e.g.* for low bioactivity/low bioavailability)

**Option 3** (long-term solutions):
- OECD NGTxC IATA *in vitro* testing battery (immune, proliferation, transformation...)

**Option 1** (today; short-term solutions):
- Use 2 year rat + 18 month mouse
- Exposure considerations (OUS-EU)

**Option 2** (mid-term solutions):
- Use 90d NOAEL + appropriate duration extrapolation factor

**Option 3 (**long-term solutions):
- PBK + *In vitro* battery (omics) to derive an *in vitro* PoD

**Option *n*...**: accomodate new science

Downstream actions

Carc CLP NC,2,1B,1A

Cut-off Labelling Monitoring

Safety thresholds

Risk assess

# Key ASCs - Paradigm Shift 3

## Design Key ASCs that are *modular, adaptable and future-proof*, allowing new (agricultural and safety) technologies to be introduced

Example of Problem Formulation driven by Key ASCs, for different Regulatory scenarios

| Assessment Scenario | Acute Systemic Toxicity Hazard | Skin Sensitization Hazard & Risk | Mutagenicity | Carcinogenic Hazard | Carcinogenic Risk |
|---|---|---|---|---|---|
| **The pesticide active is a Conventional chemical pesticide** | Yes, *In silico*/*in vitro* | Yes, tiered (*in vitro*/*in vivo*) | Yes, tiered (*in vitro*/*in vivo*) | Yes, tiered | Yes, tiered |
| **The pesticide active is a Microorganism** | Adaptations; Pathogenicity | Assume positive | No; secondary metabolites | Assess secondary metabolite | Assess secondary metabolite |
| **The pesticide active is Biopesticide, sub-type Peptide** | Consider *in vitro*/ Adaptations | Yes, Investigate *in vitro* or *in vivo* | Generally, not deemed necessary | **Generally, not deemed necessary** | **Generally, not deemed necessary** |
| **Precision & Digital Applications** | Follow the active hazard scheme but consider needs based on reduced/negligible exposure scenarios | | | | |
| **Plant Biotechnology product (cis-genic seed changes)** | *In silico* assessment of *cis*-genetic changes | Consider endogenous allergens/Allergenicity | Generally, not deemed necessary | Generally, not deemed necessary | Generally, not deemed necessary |
| **Technology X...** | ... | ... | ... | ... | ... |

# Biopesticide example – *Problem Formulation driven…*



Environment International 203 (2025) 109675

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journal homepage: www.elsevier.com/locate/envint

Review article

A Scheme for Safety Testing and Assessment of Biochemicals under the EU Plant Protection Products Regulation (BiochemPPP-STAS)

Rosa Criollo [a], Marie-Noëlle Douaiher [b], Orçun Gürkan [c], Julie Montagnac [d], Hanno Bothe [e], Siân Ellis [c], Sara Lamperti [f], Jyotigna Mehta [g], Benjamin Rignall [h], Ursula G. Sauer [i], Christian Strupp [j], Seamus Taylor [k], Michael Werner [l,*]

[a] FMC Corporation, Frankfurt am Main, Germany
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[c] Corteva Agriscience, Abingdon-on-Thames, United Kingdom
[d] Corteva Agriscience, Paris, France
[e] Bayer AG – R&D, Crop Science Division, Monheim, Germany
[f] Corteva Agriscience, Varese, Italy
[g] ADAMA Agricultural Solutions Ltd., Reading, United Kingdom
[h] BASF SE, Limburgerhof, Germany
[i] Scientific Consultancy – Animal Welfare, Neubiberg, Germany
[j] Gowan Crop Protection Ltd, Harpenden, United Kingdom
[k] ADAMA Agricultural Solutions Ltd., Köln, Germany
[l] Syngenta Crop Protection AG, Basel, Switzerland

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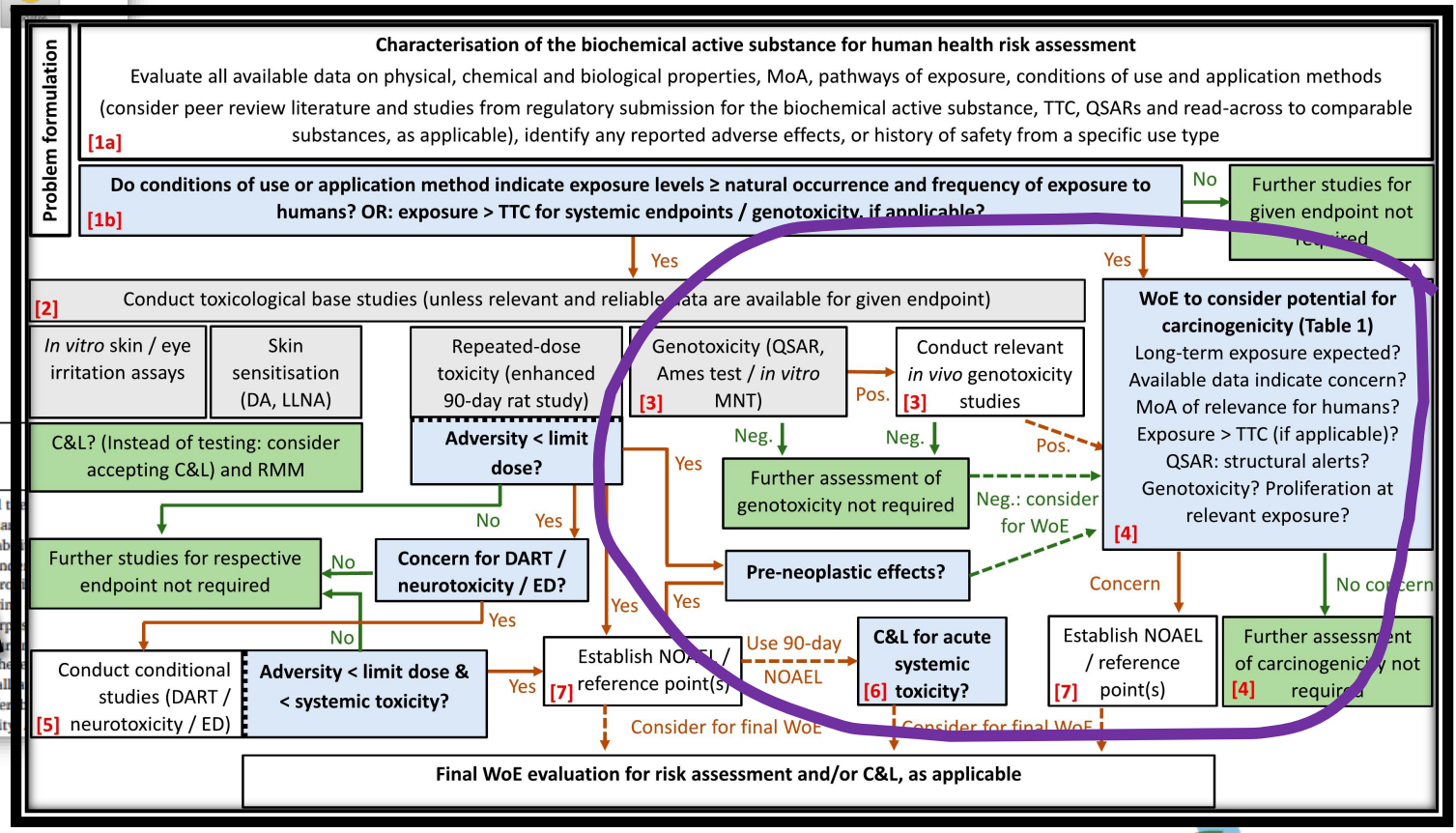
journal homepage: www.elsevier.com/locate/envint

Full length article

Reduced regulatory testing of biochemical plant protection products: an evaluation using three case studies

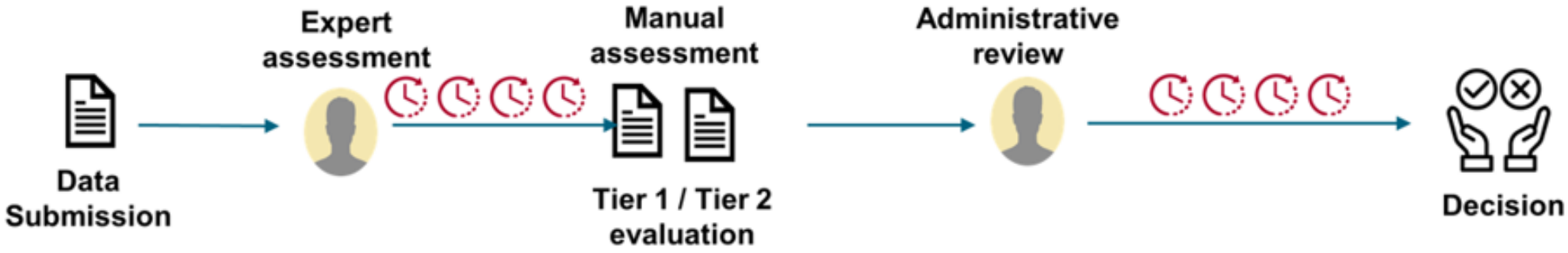
Siân Ellis [a], Hanno Both [b], James Courtney [c], Marie Noelle Douaiher [d], Jorrell Fredericks [e], Orçun Gürkan [a], Sara Lamperti [f], Monika Maleri [g], Jyotigna Mehta [h], Christian Strupp [e], Seamus Taylor [h], Michael Werner [i], Bennard van Ravenzwaay [j]

***Example conclusion**: Long-Term Toxicity and Carcinogenicity: as XXX is not genotoxic (in vitro data), and 90-day studies have shown that it is essentially devoid of significant organ toxicity as well as any ED potential, long term and carcinogenicity studies are considered not necessary. **No study needed**.* (Ellis *et al* (2026); doi: https://doi.org/10.1016/j.envint.2026.110549)

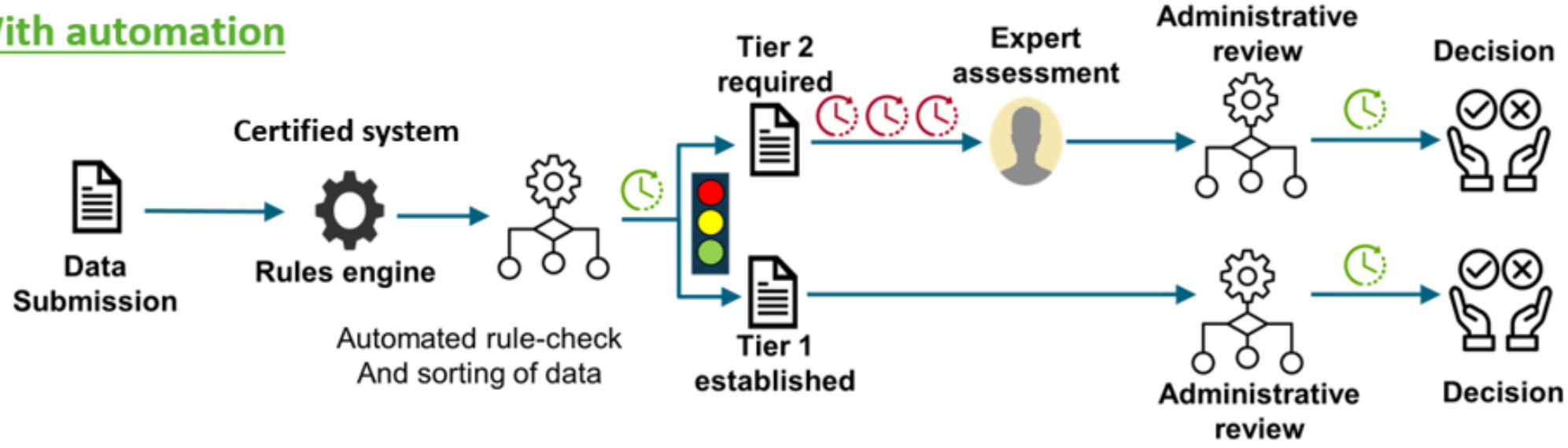


# Key ASCs: Rule-Coded Automation - Regulatory Assessment of Non-Dietary Operator Exposure Risk: "*Minimal Viable Product*" Pilot

**Current situation:** ***Inefficient use of limited regulatory resources creates barriers to innovation***



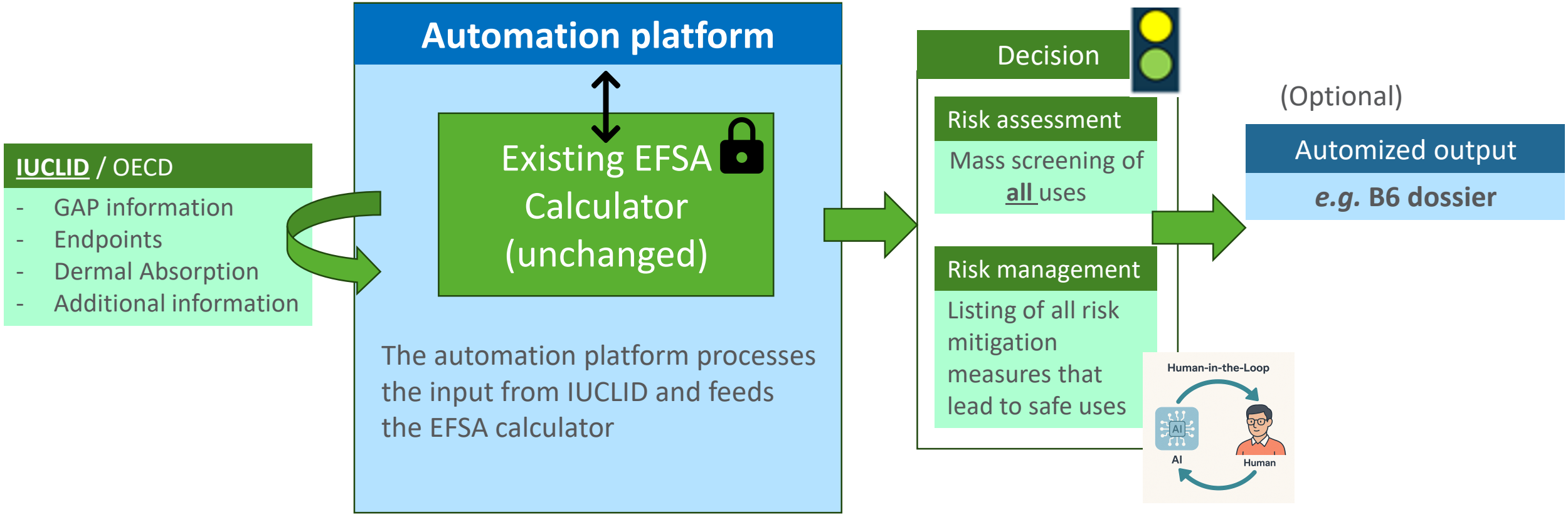

**With automation**




**Subteam:** Christian Kuester, Christiane Wiemann, Sian Wright-Williams, Alexander Gregory, Kathrin Buerling, Edgars Felkers, Zahra Shokribousjein

# Proposed approach… *…towards Regulatory Simplification:*

- Accelerated regulatory evaluation time
- Improved planning certainty with more consistent RA outcome
- Building trust by collaborating with regulators




OPEX as an example: ***translate science into effective tools!***

# Conclusion: *the keyASCs Concept can work…*

Key Safety ASCs focusses on the **"need to know" to characterize relevant hazards & safety**…

Paradigm shifts incorporate:

1. Process adaptation for transparent & tiered approach with targeted data call-in system
2. Defining the "safety attributes/questions" to address in regulations/guidance
3. Design modular, adaptable and future-proof characteristics, enabling new technologies

**Carcinogenicity** - **demonstrates a viable approach,** addresses risk management goals for different contexts of use, & regulatory questions for both cancer hazard (inc. CLP regulation) and human-relevant risk assessment – ***also applicable for other complex end-points***

- Incorporates **tiered elements** starting with problem formulation - understanding the external exposure/use scenarios to evaluate the exposure-based relevance for risk to humans
- Provides a **more efficient, innovative, effective and humane approach** to assessment
- Framework is **applicable uniformly across sectors and globally** – with tiering & decision criteria adaptable to specific legislative requirements

KeyASCs are exemplified by the **Biopesticides scheme** – **fit-for-purpose assessments** possible

Regulatory simplification shown by **ND RA automation** - tiered assessment efficiencies - **creating enablers**

CropLife EUROPE

# THANK-YOU!

Are we missing something fundamental to achieve risk management goals?
Is there an elephant in the room?



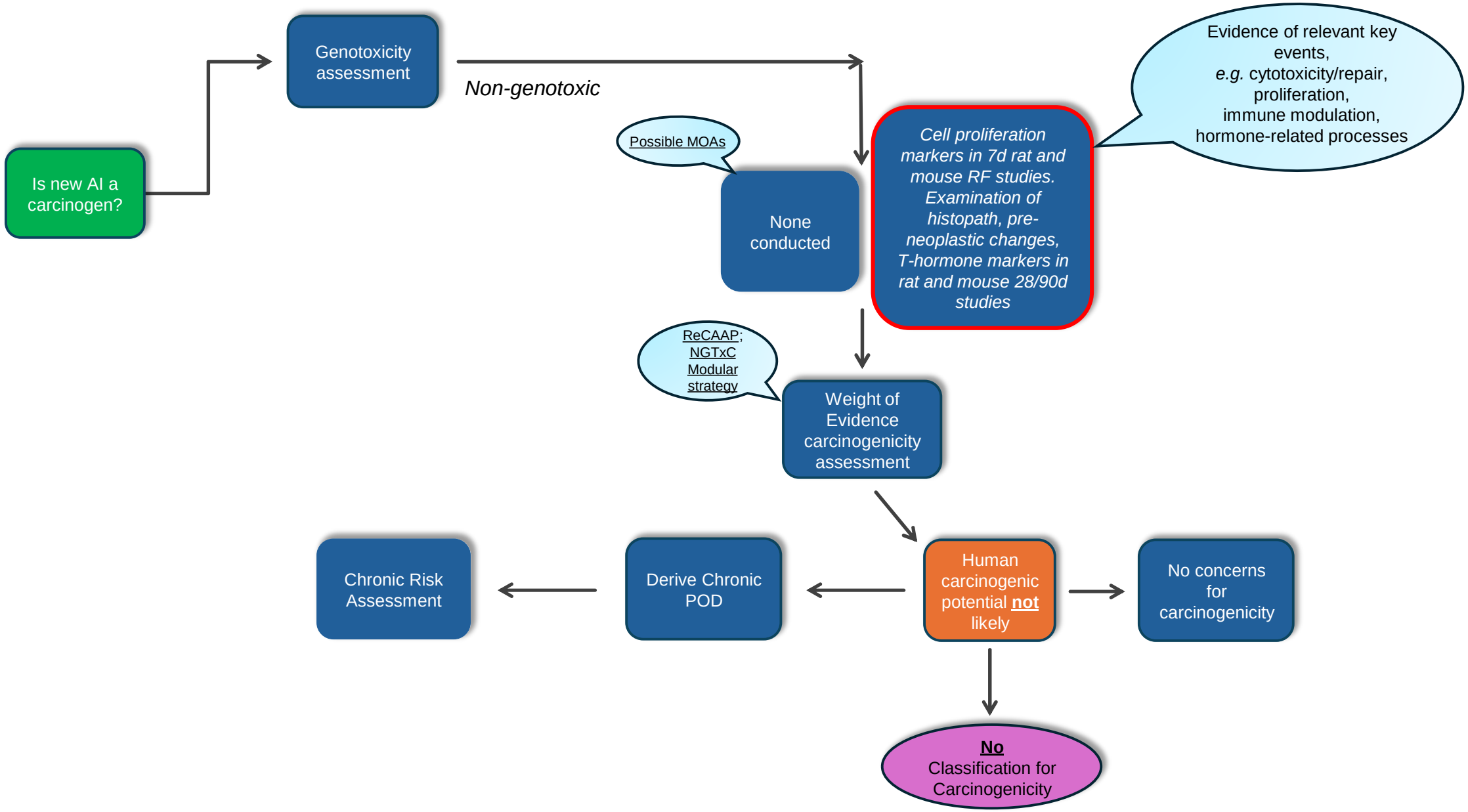
FOR MORE INFORMATION
Name Tina Mehta
tina.mehta@adama.com

# Extra slides – hyperlinked to main part

# Key ASCs – A new tiered information requirement

| DRAFT - Possible approach for a conventional new active substance | | | |
|---|---|---|---|
| Current data requirement | Future Key ASC | Tier 1 (+ Step1 assessment) | Tier 2 (Regulator data call-in) |
| • ADME | **Characterize human A, D, M, E** | HT-PBK based on GI abs, Dermal abs, comparative metabolism, Plasma protein binding, microsome clearance.<br>+ phys-chem (Solub.; Kow; bioaccumulation) | Higher tier *in vitro*: Km/Vmax, tissue partitioning....<br>+ Refined PBK |
| • Acute 6-pack | **Provide acute classification, relevant for risk management (PPE, package, transport etc.)** | Battery: *in silico* / *in vitro* OECD TG | *In vivo* for skin sensitization (only if quantitative risk assessment is needed) |
| • Sub-chronic toxicity studies | **Provide estimate of:**<br>• **systemic toxicity/STOT-RE potential**<br>• **short term TRV** | Initially: RAT 90d, integrated NTx, ITx, TK, GTx<br>→ Short term-omics or<br>→ PBK + battery of *in vitro* tests | Is 2° species necessary?<br>Any additional study for STOT? |
| • Mutagenicity | **Define Mutagenic hazard/CLP Muta** | *In vitro* core package (or integrated design) | Any other study triggered for M hazard? |
| • **Chronic/Carcinogenesis studies** | **Define:**<br>• **Carcinogenic hazard/CLP Carc**<br>• **Carcinogenic TRV, chronic TRV** | Initially: 90d studies with Mechanistic evidence (EPAA, in prep) and/or OECD sequential testing strategy). | Higher tier *in vitro* - 2y rat/18m mouse<br>Any additional study for C Hazard + chronic PoD? |
| • Developmental studies | **Define:**<br>• **DART hazard/CLP Repro**<br>• **Life stage sensitivity TRV** | Rat Dev Tox (414) | Triggered (?) Rabbit Dev Tox (414)<br>Any additional study for R Hazard + life stage sensitivity? |
| • Reproduction studies | | Rat enhanced 2-gen/EOG (416/443) | |
| • ED/Neurotox./Immunotox. | **Define new hazard classes** | Low tier *in vitro* ED, DNT/NT, DIT/IT tests | High tier *in vitro* tests + PBK |
| • Metabolite studies | **Fulfill requests for**<br>- **Crop (livestock) metabolites assessment**<br>- **Water metabolite assessments** | Biological Read-Across;<br>**TTC**; Battery of *in vitro* tests + HT-PBK | Higher tier for read-across or independent assays. |
| • Future need (adaptable).... | • **Societal/scientific need X…** | | |

# Example: Applying the Assessment Framework for New Active Substance



# Change Management for Implementation – Snapshot!

**Short-term:**

- Get **buy-in from EU Commission** for new framework for carcinogenicity assessment
- Develop **communication** roadmap
- Define early on and secure required **funding for translational activities**, *e.g.* validation, case studies, CRO-readiness, dialogue. Define Funding models and resources
- Establish **safe spaces to stimulate dialogue** between industry and regulators on data assessment, as a pre-submission consultation → make this mandatory on the mid-term

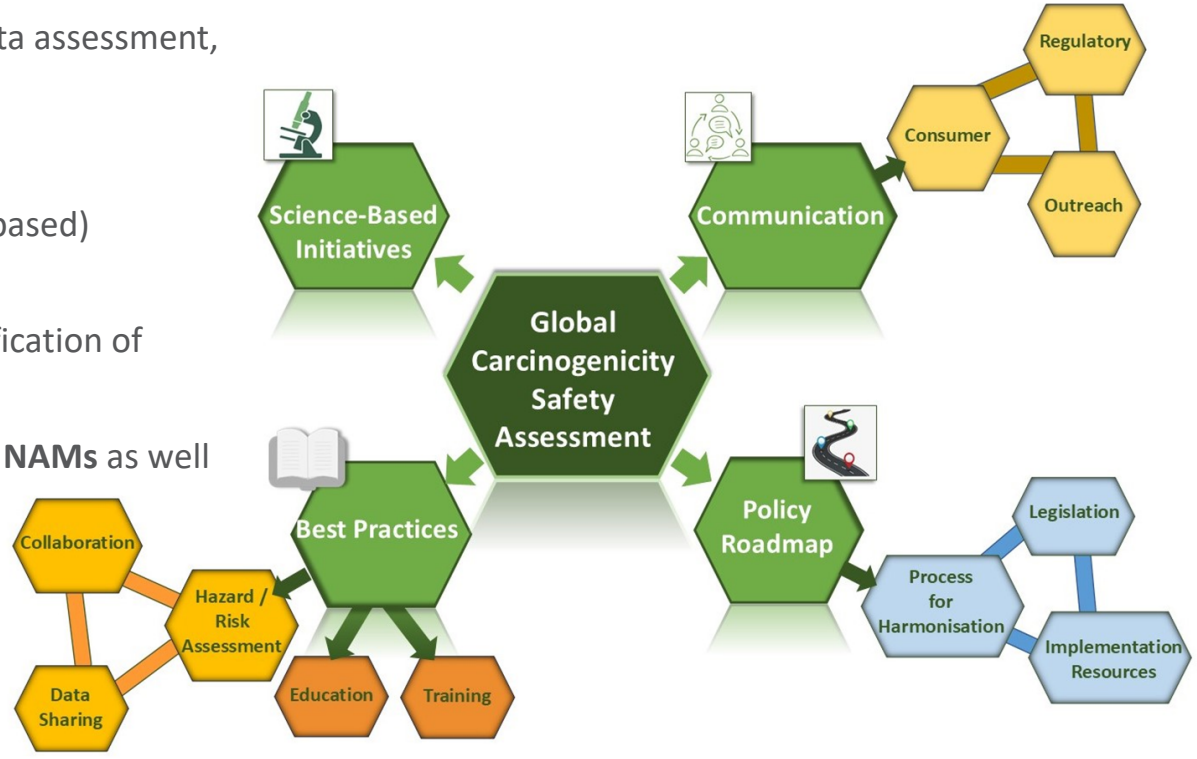
**Mid-term:**

- Adapt **regulatory processes in different sectors** to allow mechanism-based (NAM-based) carcinogenicity assessment
- Start **adapting CLP/GHS criteria** in line with NAMs-based approach; consider modification of hazard classes (muta/carc) on the longer-term?
- Identify gaps / secure funding for the development of missing **(e.g. more complex) NAMs** as well as for translational activities

**Long-term: Implement…**

- the **new, entirely non-animal, framework for carcinogenicity assessment**
- **modified CLP/GHS criteria** and possibly also modified hazard (muta/carc) classes
- **training/education of next generation professionals** on new concepts and methods for carcinogenicity assessment

*More details are in the Publication!*



# Biopesticide example – Carcinogenicity: *conditional data*

| Endpoint | Test method | CropLife Europe proposal for adaptations to mammalian toxicity data requirements for biochemical active substances and biochemical PPPs |
|---|---|---|
| **5.5: Long-term toxicity and carcinogenicity** | QSAR<br>Generally, no new testing | **Conditional data requirement, considerations for tiered testing and assessment approach to evaluate long-term toxicity and carcinogenicity:**<br>Note: This approach serves to determine whether the biochemical may mediate carcinogenicity by a genotoxic or non-genotoxic MoA; however, cell proliferation, oestrogenicity and immunosuppression (reflecting non-genotoxic carcinogenicity) should only be considered relevant when they drive the NOAEL.<br><br>**Is long-term exposure expected** due to expected use(s) of the biochemical active substance/PPP?<br>**Evaluate available data**: history of safe use / health benefit / literature incl. regulatory databases / ToxCast<br>Does the **biochemical's MoA have relevance for humans**?<br>**Exposure > TTC when threshold for carcinogenicity can be defined** / has been defined by regulators?<br>**QSAR: Are there structural alerts for carcinogenicity** that are of relevance to humans?<br>**Waive rodent cancer bioassays based on (a) absence of genotoxicity; (b) absence of (proliferative) findings at human relevant exposure levels; (c) non-relevance to humans of MoA**<br>**If new testing data are necessary, due to triggers of concern:** conduct the enhanced rodent 90-day repeated dose toxicity study and/or mechanistic studies to support the postulated MoA (see Hilton et al., 2022)) |
| ***Case Examples: Publication in preparation*** | **Example conclusion:** *Long-Term Toxicity and Carcinogenicity: as XXX is not genotoxic (in vitro data), and 90-day studies have shown that it is essentially devoid of significant organ toxicity as well as any ED potential, long term and carcinogenicity studies are considered not necessary. No study needed.* | |