Everything But the API: Evolving Methods for Impurity Hazard Identification and Risk Assessment

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Focus

- Human pharmaceuticals
  - *C.f.* veterinary pharmaceuticals, agrochemicals (pesticides/plant protection products, fertilizer *et alia*), medical devices, chemicals, consumer products (food, cosmetics, toys, ENDS), chemicals, animal feed, herbal, biological products
  - Excipients
  - (Extractables/Leachables)

Definitions

- **Impurity**: "Any component of the drug substance or drug product that is not the drug substance or an excipient." (ICH M7)
  - Actual impurity
  - Potential impurity
- **(Q)SAR and SAR:** "…refers to the relationship between the molecular (sub) structure of a compound and its mutagenic activity using (Quantitative) Structure-Activity Relationships derived from experimental data." (ICH M7)
- **Qualification:** The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. (ICH Q3A)

Origins of Impurities

- Impurities originating from synthetic process
  - Starting materials, catalysts, reagents, solvent, intermediates, reasonably expected reaction by-products, inorganic salts, heavy metals
- Impurities resulting from degradation
  - Identified and potential
- Impurities resulting from excipient and/or co-API reactions
- Impurities resulting from contamination
  - Unintentional vs intentional
  - Cleaning residues

Regulatory Guidelines on Impurities

- Regulatory environment
  - ICH Quality guidelines (ICH Q3A, Q3B, Q3C, Q3D, (Q3E*), Q6A, Q6B)
  - ICH Safety guidelines (ICH S6, ICH S9)
  - ICH Multidisciplinary (ICH M7 (c.f. ICH M7 veterinary))
  - EMA Permitted daily exposure values
  - Pharmacopoeia–provide official standards
    - US Pharmacopoeia
    - British Pharmacopoeia
    - European Pharmacopoeia

*Concept only

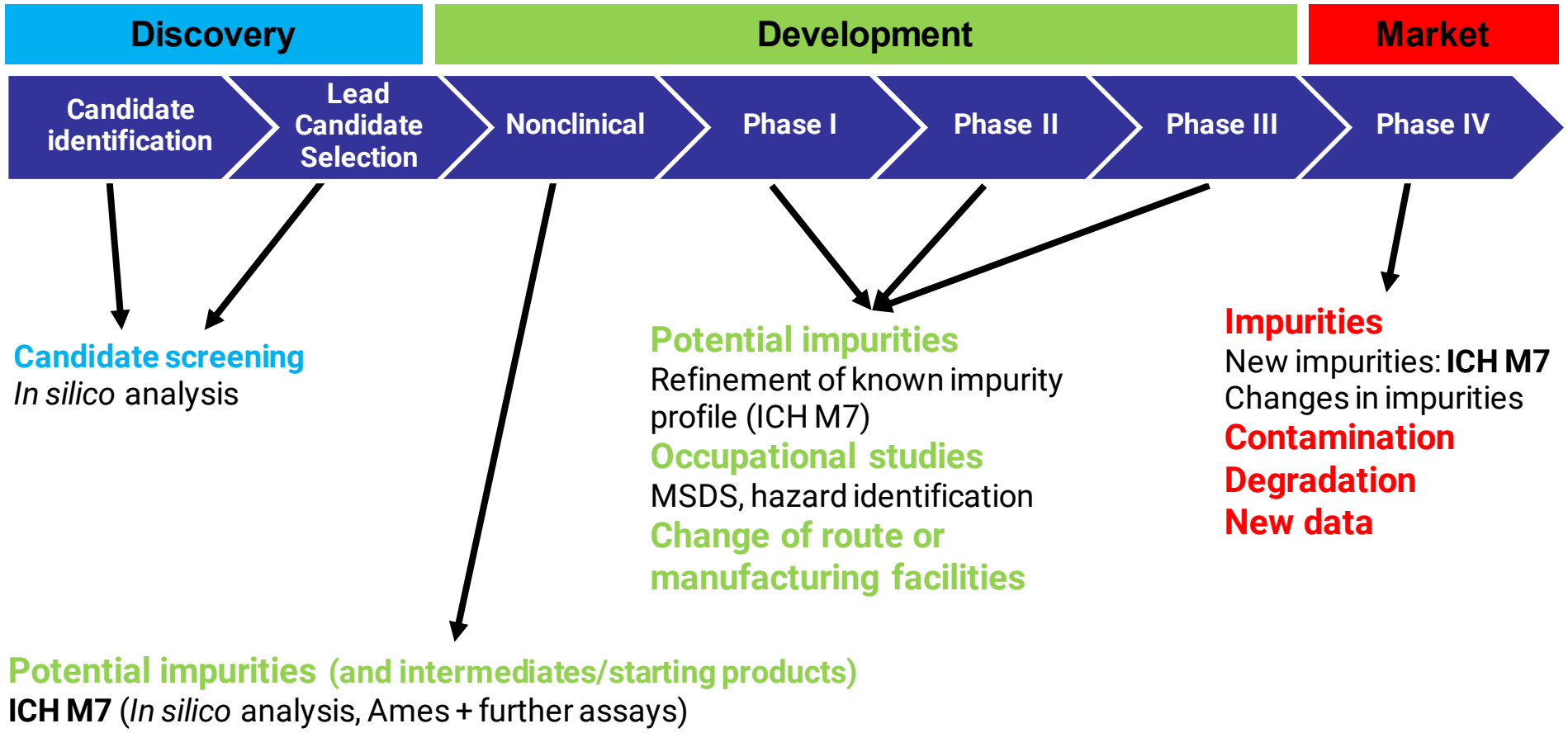
Exposed Populations

- Intended patient
  - Product indication and type
  - Duration of treatment
  - Severity of condition
- Clinician
- Non-intended patient
- Worker

Types of Substances and Data

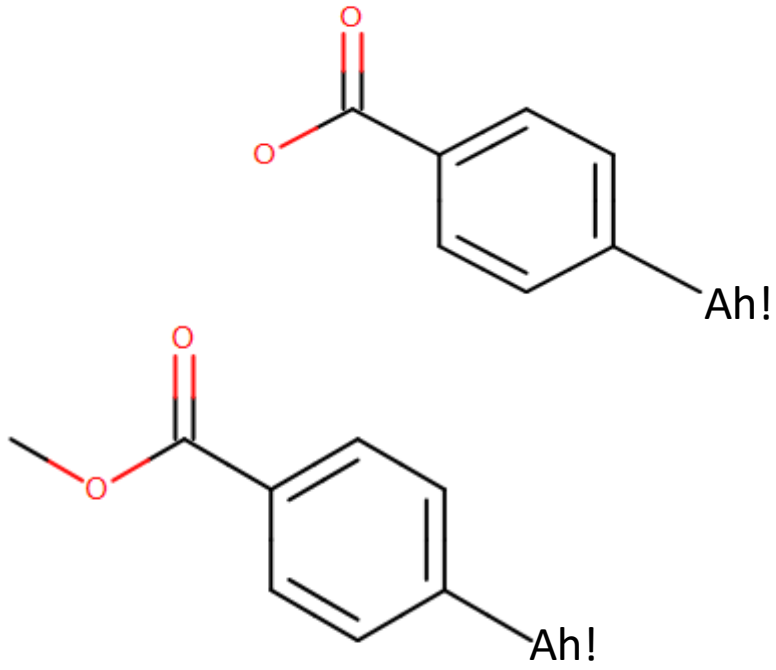
- Known substances with adequate data for evaluation
  - Reputable sources, data quality and reliability
  - Approach: Use existing literature to perform risk assessment
- Known substances with inadequate or no data for evaluation
  - Approach: Read-across from relevant substances
  - Approach: Computational modelling
- Unknown substances

When to Start



Where to Start

- Is the impurity a bacterial mutagen?
- Product indication?
- What are the predicted levels of impurity?
  - Absolute
  - Relative to parent
- What are the differences from the API?
- Duration of exposure?
- Synthetic route matters!



ICH M7

- Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk (ICH M7 (R1))
  - Focus on DNA reactive substances (usually detected with bacterial reverse mutation assay)
  - Limit of 1 mg per day
  - Covers new drug substances/products
  - Does not cover advance cancer products
- Use of (Q)SAR models
  - Expert rule-based system and statistical-based system
  - OECD validation principles
- Use of the expert

ICH M7 Classifications

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g., positive findings in *in vivo* gene mutation studies)

Bacterial mutagenicity and rodent carcinogenicity

Bacterial mutagenicity with no (or inadequate) rodent carcinogenicity data

QSAR

Consider ICH Q3A/Q3B guidelines

Negative experimental data or QSAR

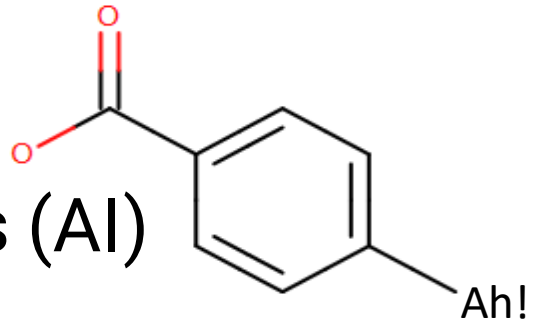
ICH M7 Audit

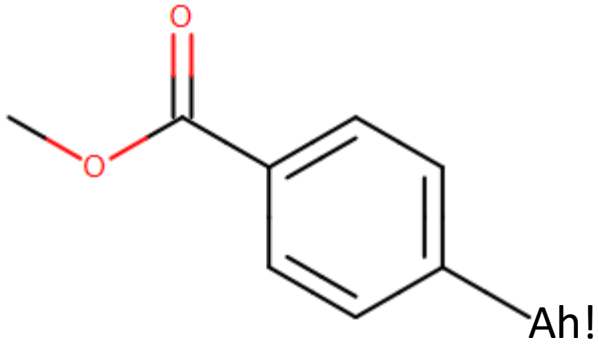
- Is the experimental Ames data appropriate for use?
  - Solvent choice?
  - Compliant with guidelines?
  - Unusual strains or forms of metabolic activation?
- Are the QSAR models used acceptable and up-to-date?
  - Have the models been correctly used?
  - Is the expert knowledge applied appropriate?
  - Is the structure adequately examined by the models?
- An out of domain prediction is not a negative prediction

Amberg, A., et al., 2019. Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses. Regul. Toxicol. Pharmacol. 102, 53–64. https://doi.org/10.1016/j.yrtph.2018.12.007

Notes on Positives

- Class 4 classifications
- Threshold of toxicological concern
- Substance and class specific acceptable intakes (AI)
  - Class 1 substances require substance specific AI
  - Alkyl chloride – reduced potency
- Less-than-lifetime limits
- Cohort of concern
  - Aflatoxin-like, N-nitroso and alkylazoxy structures
    - Nitrosamines and potency





Beyond ICH M7: ICH Q3A and ICH Q3B

- Provide guidance on the assessment of impurities in new drug substances and new drug products
- Requires reporting, identification and qualification of an impurity depending on levels identified in product
- Must also consider ICH M7

ICH Q3A and ICH Q3B

	Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
Drug Substance (ICH Q3A)	≤2g	0.05%	0.10%	0.15% or 1mg/day*
	>2g	0.03%	0.05%	0.05%
Drug Product (ICH Q3B)	<10 mg		1.0% or 5µg/day*	1.0% or 50µg/day*
	10 – 100 mg		0.5% or 200µg/day*	0.5% or 200µg/day*
	>100 mg – 2 g		0.2% or 2mg/day*	0.2% or 3mg/day*
	>2g		0.10%	0.15%

*Whichever is lower

Known: Qualification and Human Relevant Risks

- Substance specific data available
  - Does the impurity have available and relevant toxicity data?
  - Does the impurity have known limits?
  - Endogenous exposure or in food stuffs
  - Derivation of permitted daily exposure level or acceptable intake

Permitted Daily Exposure Value

The PDE will be calculated using the following formula, taken from the EMA guideline:

$$PDE = \frac{NOEL \times Weight\ Adjustment}{F1 \times F2 \times F3 \times F4 \times F5}$$

Where:

PDE: Permitted Daily Exposure
NOEL: No Observed Effect Level
F1: A factor (values between 2 and 12) to account for extrapolation between species
F2: A factor of 10 to account for variability between individuals
F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks
F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity
F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

Unknown: Qualification and Human Relevant Risks

- If no relevant data available (assuming non-mutagenic impurity)
  - Was impurity present in nonclinical studies?
  - Is the impurity a metabolite of the API?
  - If not “Consider patient population and duration of use and consider conducting:
    - Genotoxicity studies (point mutation, chromosomal aberration)
    - General toxicity studies (one species, usually 14 to 90 days)
    - Other specific toxicity endpoints, as appropriate”
  - Alternative: Use of computational models and read-across?
- Thresholds and Less-than-lifetime exposure
  - 1 mg per day

Bercu *et al*., 2019 Graham *et al*., 2021 and Harvery *et al*., 2017

Impurities in Advance Cancer Products ICH S9 and ICH Q3A/Q3B

API Genotoxic	Impurity exceeds 3A/B qualification threshold	Proposed action
Yes	No	None
	Yes	None
No	No	None
	Yes	Genotoxicity assessment of impurities should be conducted

Solvents, Elements, and Shared Facilities

- ICH Q3C (residual solvents)
- ICH Q3D (elemental impurities)
- European Medicines Agency “Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in a shared facilities” (2014)
  - Calculation derived from ICH Q3(C)
  - No initial presumption of benefit to patient
- Use and generation of Permitted Daily Exposure (PDE) values

ICH Q3C: Residual Solvents

- **Class 1 solvents:** Solvents to be avoided
  - Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
- **Class 2 solvents:** Solvents to be limited
  - Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity
- **Class 3 solvents:** Solvents with low toxic potential
  - Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day

ICH Q3D: Elemental Impurities

- **Class 1 elements:** As, Cd, Hg and Pb
- **Class 2A elements:** Co, Ni and V
- **Class 2B elements:** Ag, Au, Ir, Os, Pd, Pt, Rh, Ru, Se and Tl
- **Class 3 elements:** Ba, Cr, Cu, Li, Mo, Sb, and Sn
- Can be highly route specific

Shared Facility and Hazards

Route of administration:

Hazards Identified:

	YES	NO	UNKNOWN
Positive genotoxicant:			
Positive developmental Toxicant:			
Potential carcinogen:			
Highly Sensitising potential:			

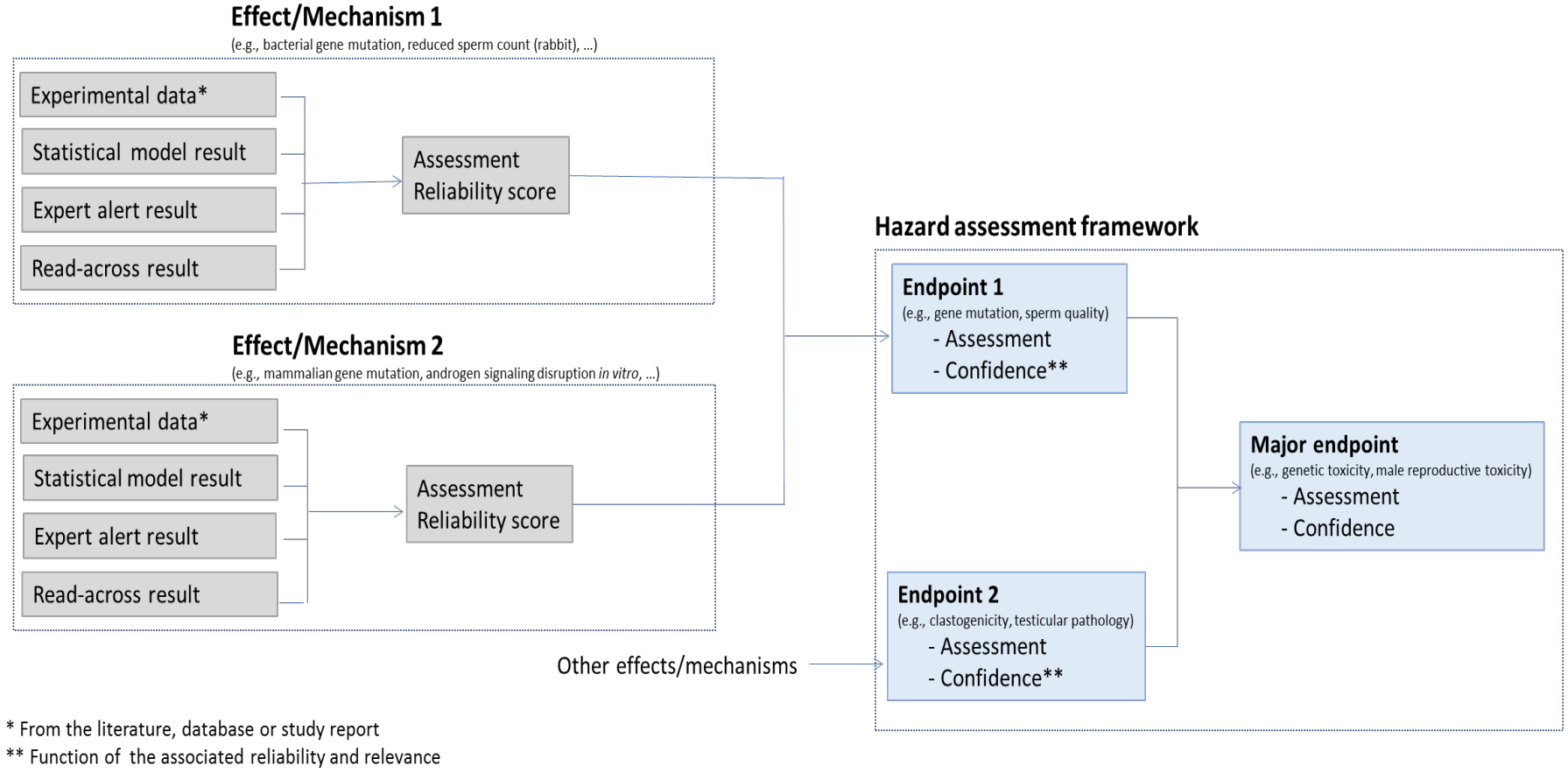
Can Animals Be Replaced by Computers?

- *Magna caveat*
  - Computational models are tools for the toxicologist to use
  - All models are wrong, but some are useful (George Box)
  - The future will not only be stranger than we suppose, it will be stranger than we can suppose (J.B.S. Haldane)

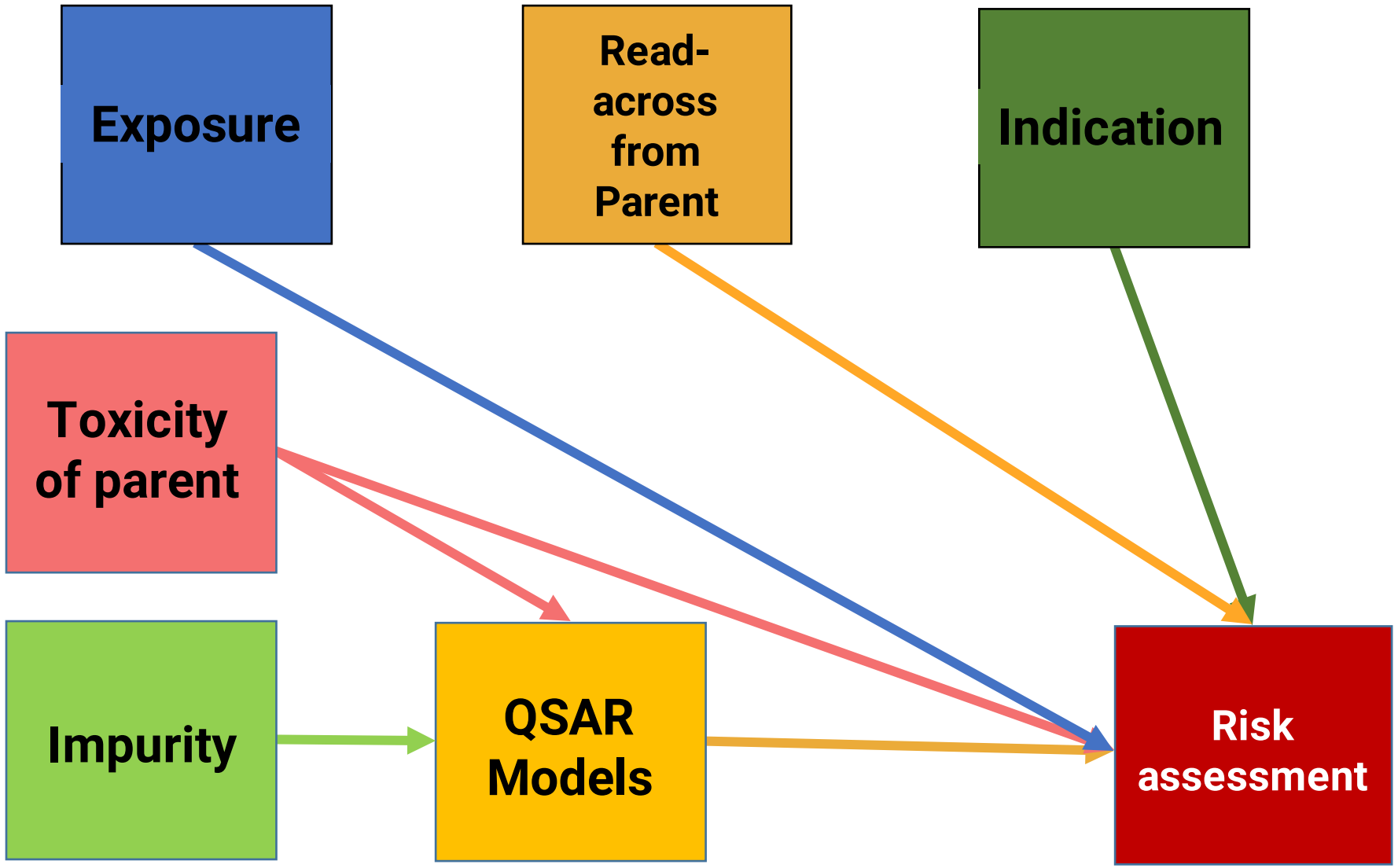
Present Tense and Future Perfect?

- Ultimate 3Rs solution?
- Resource saving
- Further acceptance for computational models and approaches
  - Reflection paper on the qualification of non-genotoxic impurities (Draft)
  - Derek Nexus/OECD QSAR ToolBox in skin sensitisation (OECD 497)
  - Use of adverse outcome pathways (Ankley *et al.*, 2010) and Quantitative adverse outcome pathways (Spinu *et al.*, 2020)
  - In silico protocols (Myatt *et al.*, 2018)
  - Next generation risk assessments (Baltazar *et al.*, 2020)

In silico Protocols



Myatt, G. J., Ahlberg, E., Akahori, Y., Allen, D., Amberg, A., Anger, L. T., ... & Hasselgren, C. (2018). In silico toxicology protocols. *Regulatory Toxicology and Pharmacology*, *96*, 1-17.


Exposure
Read-across from Parent
Indication
Toxicity of parent
Impurity
QSAR Models
Risk assessment

A General Problem?

- The problem of induction
  - Generalisation based on what we have previously observed
  - Presupposing what has happened in the past will always occur
- The Black Swan: The Impact of the Highly Improbable (Nassim Nicholas Taleb)
  - The disproportionate role of high-profile, hard-to-predict, and rare events that are beyond the realm of normal expectations in history, science, finance, and technology.
  - The non-computability of the probability of the consequential rare events using scientific methods (owing to the very nature of small probabilities).
  - The psychological biases that blind people, both individually and collectively, to uncertainty and to a rare event's massive role in historical affairs.
  - 1. Outlier; 2. Impact; 3.We make explanations to explain its occurrence

Conclusion

- Approach to impurities should be based on knowledge of appropriate guidelines and the API
- Duration and indication can be key in assessing profile
- One size does not (necessarily) fit all

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Thank you for your attention!