Requirements and challenges for genotoxicity risk assessment in BPR and REACH legislations

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Disclaimer

This presentation includes a description of the current practice and reflections of the author.

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Risk Assessment and Regulations under ECHA's remit

- Biocidal Products Regulation - **BPR**
- Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals – **REACH**
- Occupational Exposure Limit - **OEL setting**
- Scope of REACH and BPR [article 1]:
  - ensure a high level of protection of human health and the environment.
  - Underpinned by the precautionary principle.

REACH provisions on genotoxicity

- Substances classified as Muta 1A, 1B should be included in the Authorisation list to ensure that they are progressively replaced.

BPR provisions on genotoxicity

- Substances classified as Muta 1A, 1B shall not be approved unless derogation is possible.
- Products classified as Muta 1A, 1B shall not be authorized for use by the general public; no derogation possible.

Risk assessment for genotoxic carcinogens

- **REACH** [Annex I]

  "*For some hazard classes, especially germ cell mutagenicity and carcinogenicity, the available information may not enable a toxicological threshold, and therefore a DNEL, to be established".*

- **BPR** [Annex VI]

  "*For mutagenicity and carcinogenicity, a non-threshold assessment should be carried out if the active substance or substance of concern is genotoxic and carcinogenic*".

Risk assessment for genotoxic carcinogens

- Unless a threshold mechanism of action is **clearly demonstrated** (e.g. aneugenicity), it is generally considered prudent to assume that thresholds **cannot** be identified in relation to mutagenicity, genotoxicity, and genotoxic carcinogenicity, although a dose-response relationship may be shown under experimental conditions.

- For genotoxic carcinogens, the risk assessment is done **qualitatively** and/or in a **semi-quantitative** approach which provides a means to assess the efficiency of risk management measures which aim to reduce exposure as much as possible.

[BPR Guidance Human Health Assessment & Evaluation, section 4.3.1]
[REACH Guidance R.8 Characterization of dose-response for HH, R.8.2]

Risk assessment for genotoxic carcinogens

- A **qualitative** risk assessment should **always** be performed, and this should lead to identification of strict risk mitigation measures (RMMs) to be used.

- If the data is of sufficient quality, a semi-quantitative risk assessment can be performed to provide quantitative information on the residual exposure levels after the application of RMMs to decide whether the exposure is tolerable or should be further reduced.

[BPR Guidance Human Health Assessment & Evaluation, section 2.4.1.1]

[REACH R.8 Guidance Characterization of dose-response for Human Health]

Approaches of semi-quantitative risk assessment

1. The 'linearised' approach referring to the lifetime cancer risk and assuming a linear dose response for the carcinogenic effect.
2. The 'Large Assessment Factor' approach as originally proposed by EFSA (EFSA, 2005)

- Approaches result in derivation of Dose of Minimum Effect Level – DMEL or BMDL10.
- In the linearised approach, if exposure levels are below the DMEL → cancer risk may be of low concern.

[BPR Guidance Human Health Assessment & Evaluation, section 2.4.1.1]
[REACH Guidance R.8 Characterization of dose-response for HH, R.8.2]

Linearised approach

- DMEL is derived for a specified cancer risk level by a linear high to low dose extrapolation and using further assessment factors if necessary.
- There are no agreed tolerable lifetime cancer risk levels in EU legislations
- No derivation of DMEL in technical scientific opinions of restriction or authorisation under REACH
- The level of low concern has to be decided on a policy level (in different contexts within and outside EU, levels of 10^{-5} and 10^{-6} for workers and general population have been considered)

[BPR Guidance Human Health Assessment & Evaluation, section 2.4.1.1]

[REACH Guidance R.8 Characterization of dose-response for Human Health]

Example: Ethylene oxide (disinfectant) assessment for possible approval under derogation

	Study	NOAEL/ LOAEL	Overall assessment factor	Value
DMEL (inhalation) for professionals	NTP TR 326, Mouse inhalation, Long term duration (Comparable to OECD guideline 451)	$BMDL_{10}$ calculation for alveolar/ broncheolar adenomas and carcinomas in female mice resulted in a value of 35.5 ppm. Corrected dose descriptor: **28,65 ppm**. [*Differences between exposure conditions mice (6h/day, 5 days/week) and human (8h/day, 5 days/week)*] and	High to low extrapolation: 10,000 (*linearised approach 1:100,000; basis for dose descriptor was $BMDL_{10}$*)	28,65 ppm/10,000 = 0.00287 ppm ≈ **3 ppb**

Example: Ethylene oxide (disinfectant)

Derivation / Identification of the relevant dose descriptor for carcinogenicity	
Based on the results of an inhalational mice carcinogenicity study (whole body exposure) a $BMDL_{10}$ of 35.5 ppm in female mice is assumed.	
	"Linearised approach"
Relevant dose descriptor	35.5 ppm (female mice, inhalation)
Modification of the relevant dose descriptor	
	"Linearised approach"
Differences between exposure conditions mice (6h/day, 5 days/week) and human (8h/day, 5 days/week)	6/8 x 5/5
Difference between activity level: at rest (5.3 m^3) versus light activity (10 m^3)	5.3/10
Differences between occupational and lifetime exposure conditions	52/48 x 75/40
Calculation of corrected dose descriptor	35.5 x 6/8 x 5/5 x 5.3/10 x 52/48 x 75/40 x
Corrected Dose Descriptor	28,65 ppm
Calculation of DMEL for professionals (corrected BMD divided by overall assessment factor)	28,7 ppm/10,000 = 0.00287 ppm ≈3 ppb

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Example: Ethylene oxide, risk characterisation for industrial user

Actual exposure monitoring data from 4 EtO sterilisation plants in Europe was compared with the DMEL-value. Even the minimum value from the submitted data set results in an exceedance of the DMEL-value of 400%. Thus, no acceptable risk for industrial workers involved in EtO disinfection could be demonstrated, based on an elevated lifetime cancer risk of 1×10^{-5} .

Task/ Scenario	Tier/ PPE	DMEL (ppb)	Measured exposure (8-hour TWA) (ppb)	Measured exposure/ DMEL (%)	Acceptable (yes/no)
Overall max. value		3	888	29600%	No
Overall average		3	190	6333%	No
Max value country 9		3	888	29600	No
Average country 9		3	324	10792	No
Min. value country 9		3	56	1850	No
Max value country 3		3	28.5	950%	No
Average country 3		3	18	600%	No
Min value country 3		3	12	400%	No

Threshold of Toxicological Concern - TTC

- It can be used in the absence of data
- TTC values are derived from extensive databases of toxicity data by the oral route
- Applicable only to **oral** route of exposure
- Used in the assessment of impurities in BPR
- May be used in REACH for low tonnage substances to derive DMEL.

[BPR Guidance Human Health Assessment & Evaluation, Appendix 1-4]
[REACH Endpoint specific guidance R.7c, Appendix R.7-1]

Challenge in the assessment of Muta 2, BPR

- For Muta 2 non carcinogenic substances, a qualitative risk assessment should be conducted to ensure that exposure is as low as to be considered acceptable.
- How to improve the certainty on the assessment?
- Can the proposed quantitative risk assessment for genotoxic substances help?

Missing elements and Uncertainties in the hazard assessment of genotoxicity

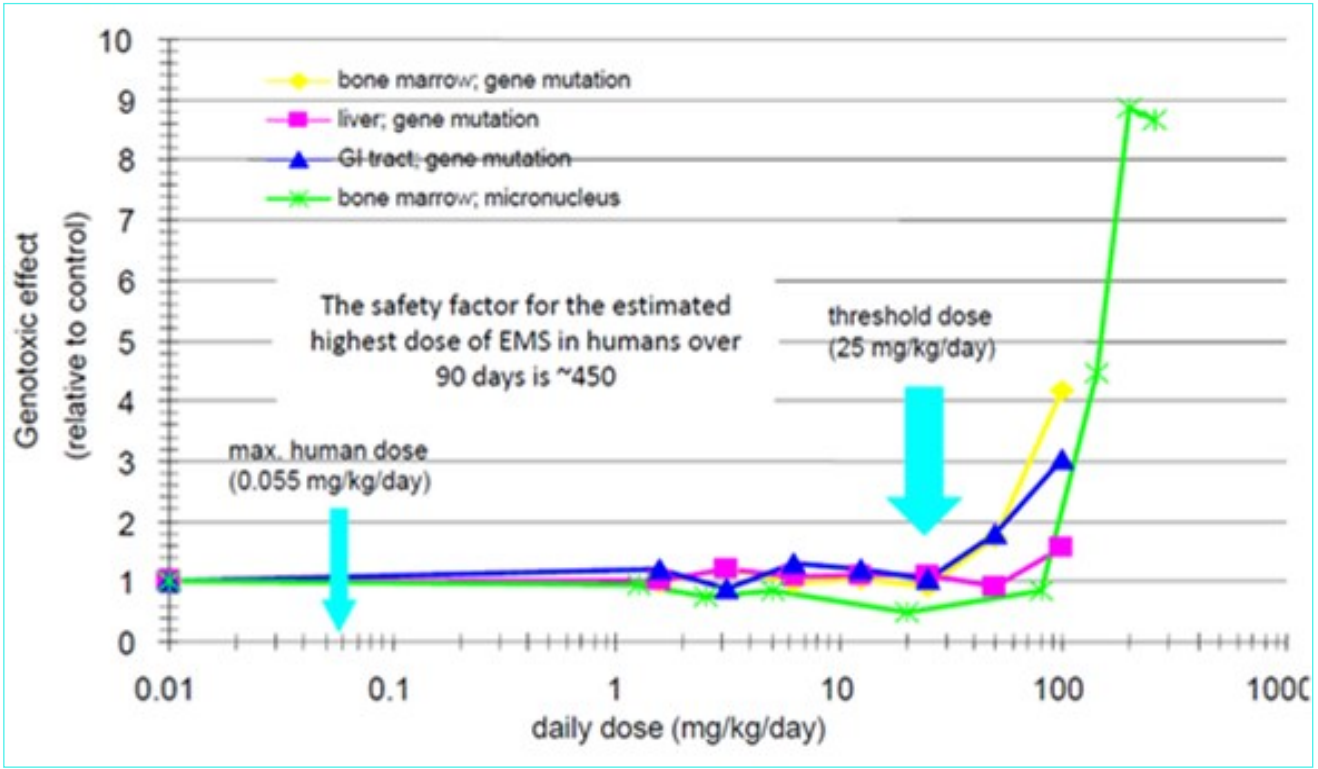
Some important:

- Data gap for information on local chromosomal damage in *in vivo* genotoxicity testing (gut micronucleus assay under development)
- Limited data to demonstrate availability of test substance in bone marrow. Micronucleus in bone marrow appears to be of lower sensitivity than *in vivo* comet or TGR.
- No test method for female germ cells.

Questions on the risk assessment

- Is *in vivo* testing using one study and 3 doses, 5 animals/sex/dose enough?
- Is the statistical power of the *in vivo* genotoxicity assays sufficient to be used as Point of Departure?
- What duration of exposure Health Based Guidance Values (HBGV) can be set? Acute, subacute?
- What a comprehensive risk assessment for genotoxicity should include? More tissues and different assays?
- Can risk assessment be performed when there are missing elements in the hazard assessment of genotoxicity?

Viracept example from pharmaceuticals

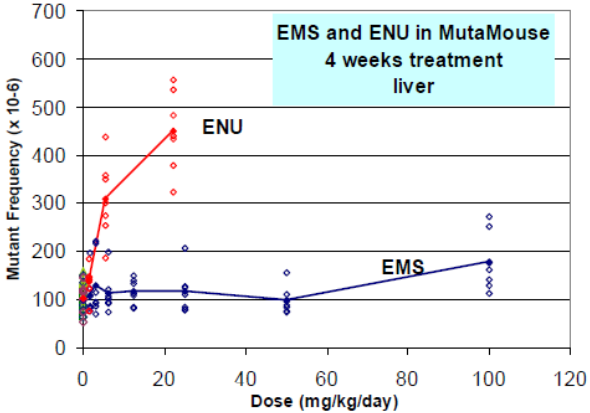


"EMS toxicity in Viracept—A comprehensive human risk assessment based on threshold data for genotoxicity": https://doi.org/10.1016/j.toxlet.2009.04.003

Case by case

EMS: threshold dose-response

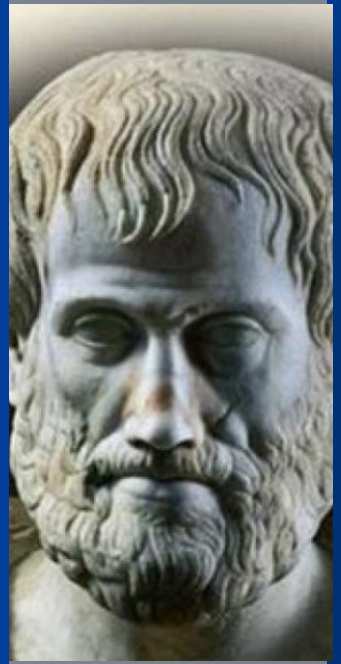
ENU: linear dose-response



"MNT and Muta™Mouse studies to define the in vivo dose response relations of the genotoxicity of EMS and ENU": https://doi.org/10.1016/j.toxlet.2009.03.021

Example and way forward

- The example shows the extensive testing to be undertaken.
- In which situations should this be done?
- Per example, for substances to which the exposure is unavoidable? E.g. food contaminants?
- Will NAM increase the feasibility of quantitative assessment for genotoxic substances in the future?



ΝΟΜΟΣ ΝΟΥΣ ΑΝΕΥ ΟΡΕΞΕΩΣ

The law is mind free of appetite

Aristotle, Politics, 4th century BC.

A regulatory toxicologist should have **scientific and regulatory reasoning** as the only driver of the assessment and a mind **free of prejudice and desire**.

Thank you

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