CURRENT STATE-OF-PLAY: OECD DISCUSSIONS ON DOSES SELECTION IN CHRONIC TOXICITY STUDIES

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BACKGROUND - 2018

- Some European member countries implementing the UN GHS reported that some chronic studies reviewed were conducted at doses not allowing *adverse effects* to be observed, and no hazard classification (GHS) could be established;
- Range-finding study justified higher doses in main study, but no explanation provided in examples shown;

- WNT agreed, as an *interim solution*, to add some language in TGs to ensure study results can be used to satisfy regulatory needs of member countries (see next slide).

- WNT acknowledged that:
  - guidance is needed at OECD on dose selection and determination of top dose in chronic toxicity studies;
  - Role/utility/limitations of TK data in dose selection/data interpretation needs further discussion and guidance.

WNT decision in 2018: Text added in chronic, reproductive and developmental tox studies (e.g. TG 443)

Dose selection

20. Normally, the study should include at least three dose levels and
appropriate dose levels, the investigator should consider all ava
information from previous studies, **TK data** from pregnant or n
lactational transfer, and estimates of human exposure. If TK data
dependent saturation of TK processes, care should be taken to avoid high dose
saturation, provided of course, that human exposures are expected to be well below the point of saturation. In such cases, the highest dose level should be at, or just slightly above the inflection point for transition to nonlinear TK behaviour.

All elements seem to be there to accommodate flexibility in dose selection, but guidance in using these elements in an agreeable way is missing or insufficient.

21. In the absence of relevant **TK data**, the dose levels should be based on toxic effects, unless limited by the physical/chemical nature of the test chemical. If dose levels are based on toxicity, the highest dose should be chosen with the aim to induce some systemic toxicity, but not death or severe suffering of the animals.

22. In the dose selection the investigator should also consider and ensure that data generated is adequate to fulfil the regulatory requirements across OECD countries as appropriate (e.g., hazard and risk assessment, classification and labelling, ED assessment, etc.) *[added in 2018]*

23. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs or doses near the limit of detection that would allow for derivation of a benchmark dose for the most sensitive endpoint(s). To avoid large dose spacing between NOAELs and LOAELs, two- or four-fold intervals are frequently optimal. The addition of a **fourth test group** is often preferable to using a very large interval (e.g. more than a factor of 10) between doses.

What about the Test Report?

Test report

Test conditions:

- rationale for dose level selection;

TG 416 (2-Gen)

Test report

Test conditions:

- Rationale for dose level selection;

TG 443 (EOGRTS)

Test report

Test conditions:

– rationale for route of administration and dose selection;

TG 452-452-453 (Chr-Carc.)

Justification should be provided in the study report in all cases to support the choice of the doses selected for the main study (range-finding study, use of other data e.g. TK, analogue data…)

CONTEXT IN THE UN GHS TEXT (e.g. Chapter 3.7 on reproductive toxicity)

3.7.2.5.7 There is general agreement about the concept of a limit dose, above which the production of an adverse effect may be considered to be outside the criteria which lead to classification. However, there was no agreement within the OECD Task Force regarding the inclusion within the criteria of a specified dose as a limit dose. Some Test Guidelines specify a limit dose, other Test Guidelines qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure would not be achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

3.7.2.5.8 In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would not normally lead to classification, unless other information is available, e.g. toxicokinetics information indicating that humans may be more susceptible than animals, to suggest that classification is appropriate. Please also refer to the section on Maternal Toxicity for further guidance in this area.

3.7.2.5.9 However, specification of the actual "limit dose" will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1000 mg/kg, unless expected human response indicates the need for a higher dose level, has been recommended as a limit dose.

3.7.2.5.10 Further discussions are needed on the inclusion within the criteria of a specified dose as a limit dose.

CONTEXT IN THE UN GHS TEXT (e.g. Chapter 3.9 Repeated Exposure STOT)

3.9.2.9.5 The guidance values proposed refer basically to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment should be done on a case-by-case basis; e.g. for a 28-day study the guidance values below would be increased by a factor of three.

3.9.2.9.6 Thus for Category 1 classification, significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals and seen to occur at or below the (suggested) guidance values as indicated in Table 3.9.1 would justify classification:

Table 3.9.1: Guidance values to assist in Category 1 classification

Route of exposure	Units	Guidance values (dose/concentration)
Oral (rat)	mg/kg bw/d	≤ 10
Dermal (rat or rabbit)	mg/kg bw/d	≤ 20
Inhalation (rat) gas		
Inhalation (rat) vapour		
Inhalation (rat) dust/mist/fume		

Note: *"bw" is for "body weight", "h" for" hour" and*

Table 3.9.2: Guidance values to assist in Category 2 classification

Route of exposure	Units	Guidance value range (dose/concentration)
Oral (rat)	mg/kg bw/d	10 < C ≤ 100
Dermal (rat or rabbit)	mg/kg bw/d	20 < C ≤ 200
Inhalation (rat) gas	ppmV/6h/d	50 < C ≤ 250
Inhalation (rat) vapour	mg/litre/6h/d	0.2 < C ≤ 1.0
Inhalation (rat) dust/mist/fume	mg/litre/6h/d	0.02 < C ≤ 0.2

Note: *"bw" is for body weight,"h" for" hour" and "d" for "day".*

3.9.2.9.8 The guidance values and ranges mentioned in 3.9.2.9.6 and 3.9.2.9.7 are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decisions about classification. They are not intended as strict demarcation values.

RELEVANT OECD GUIDANCE 116 on Chr-Carc studies (2011) - (extracts)

76. In selecting appropriate dose levels for long-term bioassays (e.g., TG 451, TG 452, TG 453), a balance has to be achieved between hazard identification/characterization on the one hand and characterization of low-dose responses and their relevance on the other. This is particularly relevant in the situation where a combined chronic toxicity and carcinogenicity study (TG 453) is to be carried out.

- The highest dose level should be chosen to identify toxic effects including the principal target organs while avoiding severe toxicity, morbidity, or death (OECD 2000, GD No.19). It should be noted that the severity of toxicity and survival in a two year study may be underestimated from the short-term study; for this reason, Test Guidelines indicate that a top dose lower than the dose providing evidence of toxicity in a short-term study may be chosen. When there is no toxicity in shorter-term studies it is recommended to consult with the relevant regulatory authorities.
- Dose levels should be selected to reflect the purpose of the study. In most cases, dose levels and dose level spacing may be selected to establish a dose-response and to derive a point of departure (e.g., BMDL or NOAEL).

RELEVANT OECD GUIDANCE 116 (2011) (extracts)

83. Available toxicokinetic data (ADME) should always be taken into account when selecting dose levels for a chronic toxicity or carcinogenicity study, although such data may not be readily available for all chemicals, as they are not required under all regulatory schemes. Many toxicokinetic processes influencing absorption, distribution, elimination and metabolic activation or detoxication may become saturated at higher doses, resulting in systemic exposures to parent compound or metabolites that would not be expected in the real life human exposures for which risk assessments are needed. The effect of repeated exposures on the pattern of absorption, metabolism, detoxification, and clearance of a compound will provide information on the internal dose achieved during chronic exposure under conditions of the bioassay. The importance of having data on toxicokinetics in reaching a decision on the design most suitable for a chronic toxicity or carcinogenicity study is stressed in this guidance and the use of such data are discussed in more detail in Chapter 3, Section 3.4 of this Guidance Document.

84. Physiologically-based toxicokinetic (PBTK) modelling is also a valuable tool for defining doses where non-linear toxicokinetics may occur, thus allowing this to be considered in selecting the highest and other dose levels in the study. The use of PBTK modelling is explored in more detail in Section 3.4. Finally, specific mechanistic studies (where available) may provide useful information regarding target tissues affected by the test substance and the doses associated with effects on key events, and should be taken into account when selecting doses for a chronic toxicity or carcinogenicity study.

RELEVANT OECD GUIDANCE 116 (2011) (extracts)

3.1.2.2 Selection of the top dose

88. The selection of the highest dose level to be used i
study has long been a matter of controversy. At the time whe
be routinely used to assess the qualitative potential of a test su
cancer, the emphasis was on testing at high levels in order to ma
detect effects. The concept of the Maximum Tolerated Dose (MTD),
highest dose to produce toxic effects without causing death and to decrease bo
more than 10% relative to controls (OECD 2002, GD No. 35) became well est
often used in the assessment of a chronic toxicity or a carcinogenicity study to decide whether the top dose tested was adequate to give confidence in a negative result. This Guidance Document focuses on the selection of the top dose, rather than attempting to define an MTD.

90. If the main objective of the study is to identify a cancer hazard, there is broad acceptance that the top dose should ideally provide some signs of toxicity such as slight depression of body weight gain (not more than 10%), without causing e.g., tissue necrosis or metabolic saturation and without substantially altering normal life span due to effects other than tumours. Excessive toxicity at the top dose level (or any other dose level) may compromise the usefulness of the study and/or quality of data generated. Criteria that have evolved for the selection of an adequate top dose level include: (in particular) toxicokinetics; saturation of absorption; results of previous repeated dose toxicity studies; the MOA and the MTD.

Has the knowledge and experience increased in the last decade to develop more specific/informed/documented guidance on the "do/don't" in the top-dose selection?

Are there other options?

- Re-allocate total number of animals across at least 4 dose groups+control group
  - no change in animal number
  - lower group size, risk of missing (rare) effects

- Add a 4th treatment group
  - No impact on power of study to detect an effect
  - Increase in total number of animals

Would any of these options solve the issue of the top-dose?

WEBINARS ON REGULATORY FRAMEWORKS

- 29 August 2019: Australia
- 16 October 2019: United States + Canada
- 18 December 2019: Japan
- 15 January 2020: European Union

Presentations of data requirements for chronic toxicity studies across regulatory frameworks and how data is used for hazard id, classification, risk assessment, and followed by exchange and discussions.

Next steps at OECD

- Invite the US to report back outcome of KMD workshop in an OECD webinar format (Q4 2020)
- Project from NL on study design could resume (?)
- Member countries to decide on scope of further work:
  - Re-discuss the determination of Maximum Tolerated Dose?
    - Is there scientific consensus today?
  - Modification of study design?
    - Need statistical analysis to inform possible changes
  - Development of specific guidance on the use of additional information like e.g. TK,
    - to inform dose selection, dose spacing, number of doses?
    - to inform the GHS on limit dose for classification purposes?
  - Who to lead this effort? Creation of a dedicated OECD Expert Group?
    - Probably yes