



# Historical Control Data for Sub-chronic Toxicity Testing for GM Crops

*Ad hoc meeting with EFSA*

October 18, 2021

# Interpretation of Mammalian Toxicology Data

Data Generation

Statistical and Nonstatistical Analysis

## Expert Interpretation:

- Statistically significant differences occur independent of treatment due to random sampling (Kluxen et al., 2021).
- Statistically significant differences do NOT always indicate biologically-relevant findings (Lewis et al., 2002; EFSA, 2011).

## Weight-of-Evidence Approach

Evaluate for patterns and inter-relationships of differences in multiple response variables suggestive of target organ or systemic toxicity:

- Magnitude and direction of differences from control
- Dose-response (if there are multiple treated groups)
- Observed differences consistent across sex
- Data ranges established by concurrent reference groups (when available)
- Historical Control Data

# Regulatory Framework on the Use of HCD (1)

*“Ideally, all historical control data submitted for consideration are obtained from the laboratory at which the study being assessed was carried out, and relate to animals of the same strain, age and sex, and obtained from the same supplier, as those used in the study. They should come only from studies conducted within 5 years, or two to three years on either side, of the study under review.” – OECD, 2002 (for chronic toxicity and carcinogenicity studies)*

*“Historical control data can help interpret results in a number of situations. It has been suggested that... only historical data collected over the last 5 years should be used.” – OECD, 2011 (for chronic toxicity and carcinogenicity studies)*

*“Historical background data on variations in endpoint values should primarily be obtained from databases available at the actual testing facility or in the public domain.” – EFSA Sci Com, 2011 (on 90-day)*

*“Information on the background variability in a given parameter may be obtained by the applicant from data from other animals of the same species/strain tested in the same or other experiments, or from internationally harmonised databases.” – Implementing Regulation 503/2013*

# Regulatory Framework on the Use of HCD (2)

“Where available, historical control data shall be provided routinely. The data shall be for endpoints that could represent critical adverse effects, and shall be strain-specific and from the laboratory which carried out the study. They shall cover a five-year period, centered as closely as possible on the data of the index study.” – Regulation (EU) No 283/2013 (for plant protection products)



HCD extensive information requirements are specified only for: “Long-term toxicity and carcinogenicity” and “Reproductive toxicity studies” and not for other toxicity studies, including “short-term” toxicity studies (i.e., 28- and 90-day studies).

*“Whenever possible, information on natural variation of test parameters shall be derived from historical background data ...” “The use of historical background data should be considered on a case-by-case basis, if needed (for example to justify sporadic observations in single individuals).” – EFSA, 2014 (90-day for GMO assessment)*

*“HCD are necessary to follow changes in the biology of the used test species and to differentiate the way to evaluate test results. HCD represent a summary of the observations made on the untreated or control groups from individual studies and a complete assessment of their relevance should be provided by the applicant in the dossier based on the **criteria as set out in Commission Regulation (EU) No 283/2013:**” – EFSA, 2019 (submission of dossiers for pesticide active substances)*

# Regulatory Framework on the Use of HCD (3)



*“The experts also agreed upon the need to have a clear guidance on the use of historical control data to ensure that such data is used in a consistent and structured way in the peer review process. A workshop can be organized to start the preparation of such guidance.” – EFSA, 2020 (outcome of pesticides peer review meeting)*



# Recent EFSA Requests Regarding HCD for Sub-chronic Toxicity Testing for GM



## Increasing inconsistent requests for additional information/details

- Description of methodology used to select studies
- Full list of studies composing each HCD
- Dates of each individual study
- Strain, supplier, age, diet, fasting status, analysis methods, euthanasia method, “other” unspecified information
- Individual study mean values and range of means
- Individual study median values and range of individual values
- Standardized Effect Size (SES) graphs

## Temporal relationship of HCD to the study

- Inconsistent across multiple requests, and across applicants
  - Recent HCD requests range from 1-4 years PRIOR to a subject study to 2-3 years AFTER a subject study
  - Typically includes dates that occur after a study has been finalized and/or submitted for regulatory review

## Addressing these EFSA questions for HCD has not resulted in any change to study conclusions

# Challenges with HCD Availability

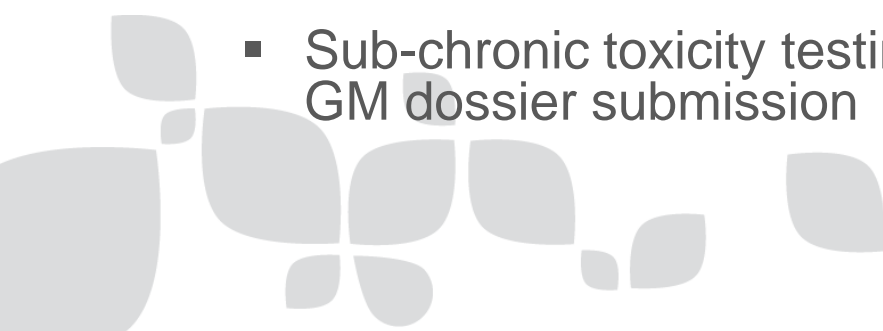


## Many studies are conducted at outside labs (CROs)

- CROs update HCD on a routine basis; typically, annually
- Some CRO HCD come from other companies' studies (may create intellectual property issues)
- CRO software systems may not allow for generation of requested data (e.g., median)

## Temporal constraints

- Depends on the number of similar study types at the test facility
- May require flexibility, with appropriate justification
- Most applicants cannot delay study finalization in anticipation of *post hoc* test facility control data for dossier submission
  - Sub-chronic toxicity testing is typically the rate-limiting step for GM dossier submission



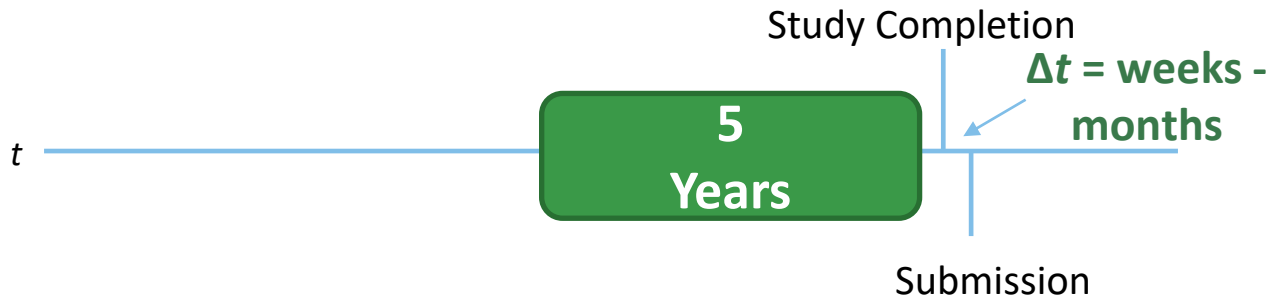
# Sub-chronic Toxicity Testing is the Rate-Limiting Step for GM Dossier Submission

...“should come only from studies conducted within 5 years, or two to three years on either side, of the study under review.” – OECD, 2002 (for chronic toxicity and carcinogenicity studies)

...“It has been suggested that... only historical data collected over the last 5 years should be used.” – OECD, 2011 (for chronic toxicity and carcinogenicity studies)

...“shall cover a 5-year period, centered as closely as possible on the date of the index study.” – Regulation (EU) No 283/2013 (for plant protection products)

GM Submission: Rate-Limiting Study



# CLE Proposal Regarding HCD for GM



## HCD selection criteria

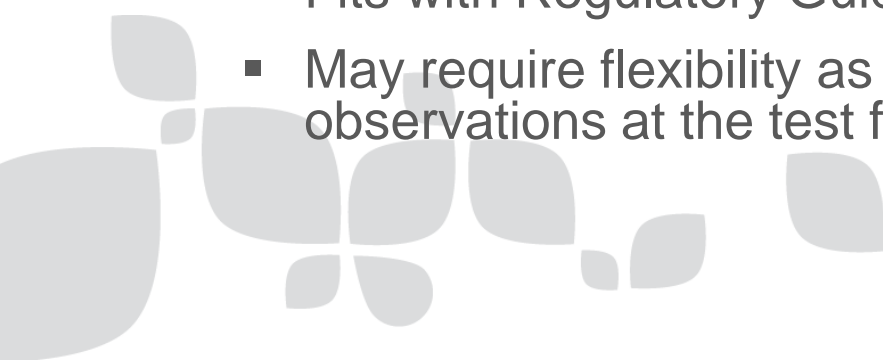
- Species and strain, sex, animal supplier, approximate age of animals at the beginning of the study, comparable diet/nutrition, and route of administration

## HCD information/details to be provided

- Summary of HCD selection criteria
- Total number of studies and overall range of study dates
- Overall mean and min/max of reference range
  - Consistent with the information provided by the test facility

## Temporal relationship of HCD to the study

- Minimum of 5 years prior to study completion
  - Fits with Regulatory Guidance (EFSA and OECD)
  - May require flexibility as the number of appropriate studies or observations at the test facility may be limited



# Citations



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