The Chronic Cancer Bioassay Is Frequently Conducted for Pesticides When It Is Not Always Needed to Protect Human Health

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Conflict of Interest Statement

• The presenter declares that there exists no real or perceived conflict of interest.

• I acknowledge that all animal experimentation has been carried out in accordance with the Society’s Guiding Principles in the Use of Animals in Toxicology.
Overview

• Using knowledge accumulated from intended use and class of chemistry of the proposed pesticide will focus the questions that need to be answered to protect human populations from cancer risk
• Chemical carcinogenesis: A Unified Theory of Carcinogenicity based on Contemporary Knowledge
• RISK21: A transparent systematic approach that is problem formulation based and exposure driven
• Cancer Waiver Problem Formulation
• Example
• Outcome and potential path forward
Population model of chemical carcinogenesis. Requires sufficient exposure and maintaining a sustained stress environment.

Adapted cell to maintain normal biological function

Transformed cell that survives and proliferates uncontrollably toward neoplasia

$\alpha$—Proliferation
$\mu$—Mutation
$\delta$—Death
$\rho$—Repair

Hereditary Factor
Constitutive Replication
Genotoxic Environmental Factor
Environmentally Induced Replication

Wolf et al., Reg Toxicol Pharmacol 103:86-92, 2019
Carcinogenesis

- Cancer is due to mistakes occurring in the DNA.
- More than one mistake in the DNA is necessary.
- All of the mistakes need to accumulate in a single cell (clonal origin of cancer).
- The cell population at risk is the tissue pluripotent (stem) cells.
- Every time DNA replicates, permanent mistakes could occur.
- Carcinogenesis is a stochastic process.

Doe et al., Reg Tox Pharm 103:124-129, 2019
Population model of chemical carcinogenesis. Requires sufficient exposure and maintaining a sustained stress environment.

Adapted cell to maintain normal biological function

H Hereditary Factor
R Constitutive Replication
$E_G$ Genotoxic Environmental Factor
$E_{IR}$ Environmentally Induced Replication

α—Proliferation
μ—Mutation
δ—Death
ρ—Repair

Wolf et al., Reg Toxicol Pharmacol 103:86-92, 2019
Does SAR or testing indicate mutagenic activity?

Yes

Will exposure likely exceed the mutagen TTC?

Yes

Evaluate metabolism

- Perform risk assessment
- Set permissible exposure levels

No

End cancer evaluation

No

Is there a Cramer classification?

No

Does testing indicate:
- Increased cell proliferation,
- Endocrine activity, and/or
- Immunosuppression?

Yes

Will exposure likely exceed the TTC?

Yes

End cancer evaluation

No

Is the mode of action relevant to humans?

No

End cancer evaluation

Yes

Identify toxicity endpoint NOAEL or BMD

- Perform risk assessment
- Set permissible exposure levels
RISK21 Publications

OPEN ACCESS—links at www.risk21.org

- Illustrative case using the RISK21 roadmap and matrix: prioritization for evaluation of chemicals found in drinking water
- Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans
- A framework for cumulative risk assessment in the 21st century
- Using exposure bands for rapid decision making in the RISK21 tiered exposure assessment

All in Critical Reviews in Toxicology
- 2014; 44(S3): 1–5
- 2014; 44(S3): 6–16
- 2014; 44(S3): 17–43
- 2016; 46(1): 43–53
- 2016; 46(1): 54–73
- 2016; 46(10): 835–844
- 2016; 47(2): 85–97
The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizes US EPA to register pesticides and require supporting studies. Part 158 establishes data requirements for pesticide tolerances under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA). The studies provide the scientific basis for characterizing potential risks associated with exposure. There is flexibility, however: additional data can be required (§ 158.75), alternative approaches can be accepted, and studies can be waived (§ 158.45).

These guiding principles enable focus on the information most relevant to the assessment. The goal is to ensure there is sufficient information to reliably support registration decisions that are protective of public health and the environment while avoiding the generation and evaluation of data that do not materially influence the scientific certainty of a regulatory decision. Only require data that adequately inform regulatory decision-making. Avoid unnecessary use of time and resources, data generation costs, and animal testing.
### Data Requirements for Registration of a Pesticide

**OCSPP\(^1\) Harmonized Test Guidelines - Master List**

Last Updated March 2015

The OCSPP harmonized guidelines are organized in the following series:

<table>
<thead>
<tr>
<th>Series No.</th>
<th>Series Name</th>
<th>Docket ID No.</th>
<th>Last Changed</th>
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<tbody>
<tr>
<td>835</td>
<td>Fate, Transport and Transformation Test Guidelines</td>
<td>EPA-HQ-OPPT-2009-0152</td>
<td>Nov-2008</td>
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<td>890</td>
<td>Endocrine Distruptor Screening Program Test Guidelines</td>
<td>EPA-HQ-OPPT-2009-0576</td>
<td>Aug-2009</td>
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\(^1\) OCSPP: Office of Chemical Safety and Pollution Prevention
# 40 CFR Part 158: Data Requirements for Human Health Evaluation: Acute Exposure

## Acute Testing

<table>
<thead>
<tr>
<th>OECD Guideline Number</th>
<th>US EPA Guideline Number</th>
<th>Data Requirements/Study Type</th>
<th>Use Pattern</th>
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<tbody>
<tr>
<td>401, 420, 423, 425</td>
<td>870.1100</td>
<td>Acute oral toxicity – rat</td>
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<tr>
<td>402</td>
<td>870.1200</td>
<td>Acute dermal toxicity</td>
<td>Required</td>
</tr>
<tr>
<td>403</td>
<td>870.1300</td>
<td>Acute inhalation toxicity – rat</td>
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<tr>
<td>405</td>
<td>870.2400</td>
<td>Primary eye irritation – rabbit</td>
<td>Required</td>
</tr>
<tr>
<td>404</td>
<td>870.2500</td>
<td>Primary dermal irritation</td>
<td>Required</td>
</tr>
<tr>
<td>406</td>
<td>870.2600</td>
<td>Dermal sensitization</td>
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</tr>
<tr>
<td>418, 419</td>
<td>870.6100</td>
<td>Delayed neurotoxicity (acute) – hen</td>
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</tr>
<tr>
<td>424</td>
<td>870.6200</td>
<td>Acute neurotoxicity – rat</td>
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SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

[http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title40/40cfr158_main_02.tpl](http://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title40/40cfr158_main_02.tpl)
## Data Requirements for Human Health Evaluation: Short-Term or Intermediate Exposure

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<td>870.3100</td>
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<td>21/28-day Dermal</td>
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<td></td>
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<td>Not Required</td>
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<td>411</td>
<td>870.3250</td>
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<td></td>
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<td>413</td>
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<td>90-day Inhalation – rat</td>
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## Data Requirements for Human Health Evaluation: Chronic Exposure

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<td>Food</td>
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<td><strong>Chronic (Life Long) Testing</strong></td>
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<td>452</td>
<td>870.4100</td>
<td>Chronic oral – rodent</td>
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<tr>
<td>451</td>
<td>870.4200</td>
<td>Carcinogenicity – 2 rodent species – rat &amp; mouse preferred</td>
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<td><strong>Developmental Toxicity and Reproduction</strong></td>
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<td>414</td>
<td>870.3700</td>
<td>Prenatal Developmental toxicity – rat and rabbit, preferred</td>
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<td>416</td>
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<td>Reproduction and fertility effects</td>
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<td>N/A</td>
<td>870.6300</td>
<td>Developmental neurotoxicity</td>
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SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety
### Data Requirements for Human Health Evaluation: Mutagenicity and Others

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<tr>
<th>OECD Guideline Number</th>
<th>US EPA Guideline Number</th>
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<td>471</td>
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<td>Bacterial reverse mutation assay</td>
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<td>476, 473</td>
<td>870.5300 870.5375</td>
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<td>475, 474</td>
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<td>In vivo cytogenetics</td>
<td>Required</td>
<td>Required</td>
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<td><strong>Special Testing</strong></td>
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<td>417</td>
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<td>Metabolism and pharmacokinetics</td>
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<td>N/A</td>
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<td>Companion animal safety</td>
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<td>N/A</td>
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<td>N/A</td>
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<td>Immunotoxicity</td>
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Waiving Acute Studies

Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides

Guidance Document on Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests

Pest Management Regulatory Agency
Health Evaluation Directorate
December 2013

Office of Pesticide Programs

Guidance for Waiving or Bridging of Mammalian Acute Toxicity Tests for Pesticides and Pesticide Products (Acute Oral, Acute Dermal, Acute Inhalation, Primary Eye, Primary Dermal, and Dermal Sensitization)
Waiving Repeat-Dose Studies

Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies

May 01, 2013

Office of Pesticide Programs
U.S. Environmental Protection Agency
Waiving Repeat-Dose Studies

• The US EPA allows registrants to submit waiver evaluations that document why a study normally required under Part 158 legislative mandate is unnecessary.

• Requires the presentation of a scientific rationale on why sufficient knowledge is available to inform a risk decision making the specific study unnecessary.

• The collective available data and information must be sufficient to support registration decisions that are protective of public health.

• Combines the use of existing knowledge and determination of specific data needs for consistent characterization of risk and assuring sufficiency of data for safety determinations.

• Avoids the generation of data that does not influence the regulatory decision.
Waiving Repeat-Dose Studies

• The value of a waiver is that it promotes the full use of existing knowledge to focus on scientifically sound and credible characterization of a pesticide’s risk profile.

• Through the development of a waiver document one determines data needs required to reliably support the safety of the active ingredient while still remaining protective of public health and the environment.

• A waiver can prevent delays in regulatory decisions while maintaining the delivery of health and environmental protection in support of providing access to pest management tools and safe products.

• A successful waiver avoids unnecessary use of time, data generation costs, and animal testing.
# Waiving Repeat-Dose Studies


<table>
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<th>Type of Study</th>
<th>Total # of Waiver Requests</th>
<th>Animals/study</th>
<th>Cost of study (USD)</th>
<th>Waivers Granted</th>
<th>Total animals saved</th>
<th>$ savings (USD)</th>
<th>% accepted</th>
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<tr>
<td>Inhalation</td>
<td>288</td>
<td>40</td>
<td>576K</td>
<td>222</td>
<td>8880</td>
<td>128M</td>
<td>77</td>
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<td>Neurotoxicity</td>
<td>186</td>
<td>150</td>
<td>171K</td>
<td>164</td>
<td>24600</td>
<td>28M</td>
<td>88</td>
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<td>Dermal</td>
<td>57</td>
<td>80</td>
<td>115K</td>
<td>50</td>
<td>4000</td>
<td>4M</td>
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<td>Developmental</td>
<td>48</td>
<td>1760</td>
<td>129K</td>
<td>39</td>
<td>68640</td>
<td>5M</td>
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<td>DNT</td>
<td>18</td>
<td>1760</td>
<td>772K</td>
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<td>26400</td>
<td>12M</td>
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<td>Subchronic Dog</td>
<td>14</td>
<td>32</td>
<td>260K</td>
<td>11</td>
<td>352</td>
<td>3M</td>
<td>79</td>
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<tr>
<td>Reproductive</td>
<td>38</td>
<td>3360</td>
<td>432K</td>
<td>32</td>
<td>107520</td>
<td>14M</td>
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<td>Immunotoxicity</td>
<td>223</td>
<td>32</td>
<td>70K</td>
<td>207</td>
<td>6624</td>
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<td>Chronic/Carcinogenicity</td>
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<td>560</td>
<td>887K</td>
<td>39</td>
<td>21840</td>
<td>35M</td>
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<tr>
<td>Subchronic Rat</td>
<td>12</td>
<td>40</td>
<td>150K</td>
<td>10</td>
<td>400</td>
<td>1.5M</td>
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<td>Total</td>
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<td>789</td>
<td>269,256</td>
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<td>87</td>
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Papineni et al., Toxicol Sci 156: Abstr 3491, Late Breaking Suppl 123, 2017
Problem Formulation Regarding the Chronic Rodent Cancer Bioassay

Participants included representative scientists from: US EPA, NTP, AgChem Industry, Pharmaceutical Industry, Academic Institutions, and NGOs

- The problem is …
  - Too resource intensive to get products to market
  - Are we using the right tools?
  - Inefficient assay
  - Costs are too high
  - High false positive rate
  - Human irrelevant tumors
  - Poor models for human carcinogenicity
  - Every compound has to be assessed
  - The doses aren’t relevant
  - Questionable value of information
  - Lack of harmonization of interpretation
  - Other data could be used

Problem statement: bioassay is being conducted for pesticides where it is not always needed to adequately address carcinogenicity to humans.
Key Knowledge Needs

Carcinogenicity waiver requests are most appropriate where one can provide a strong exposure argument, a lot of information on chemical class, and understanding of the Mode of Action

Criteria for food use pesticides:
• Knowledge of intended use indication and class of chemistry
• Metabolic profile
• Results of all studies, including *in vitro* and repeat-dose studies and mechanistic information
  - Genetic Toxicology Study Results
  - Special Studies and Endpoints
  - Evidence of Hormonal Perturbation
  - Evidence of Immune Suppression
  - Read-Across
• Margins of exposure based on existing data and proposed exposure scenarios
Example Waiver for Cancer Bioassay

SYN1

DRAFT Waiver based on RISK21 Approaches for Chronic/Carcinogenicity Studies

Assessment
Example Waiver for Cancer Bioassay

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Key Learnings from the Example

- Information on the exposure potential for the active ingredient
- Connect how ADME information informs the need for a rodent chronic/cancer study
- Toxicokinetic information is helpful and should relate how this chemical may behave relative to the rest of the class
- Toxicity data:
  - Relevant information that would inform whether progression of toxicity is observed and if target organs are consistently observed across studies
  - Are data consistent with what would be expected based on the ADME data?
  - Absolutely rule out in vivo genotoxicity
  - Evidence to support a lack of estrogenic or other hormonal perturbation?
  - Read-across—to other molecules in the same class
  - Margins of exposure based on existing data and proposed exposure scenarios
Summary

• A range of *in vitro* and shorter-term *in vivo* assays can be used to evaluate carcinogenic potential.
• The aim should be to identify effects that may lead directly or indirectly to DNA changes or damage, or increases in cell division.
• Health is protected by setting exposure limit values that prevent occurrence of primary effects.
• This approach protects against all adverse long-term effects, including cancer.
• The modes of action that lead to the induction of tumors are already considered under other hazardous property categories such as Mutagenicity/Genotoxicity and Target Organ Toxicity.
• A separate category for Carcinogenicity is not required and provides no additional public health protection.
• **Assessment based on this approach will allow human health to be safeguarded, far more chemicals to be fully evaluated, and innovative, safe products to become available more quickly while eliminating a costly, outmoded, and unnecessary assay.**
Conclusions

• The long-term bioassay is not required to evaluate potential for carcinogenicity in humans.
• Hazard-only classification schemes are outmoded and misleading based on the current understanding of chemical carcinogenesis.
• Utilizing mode-of-action analysis, a more direct and rational basis for human cancer risk assessment, can be performed rather than simple hazard identification.
• Avoid waste of money, time, and animals and would end up being equally health protective to prevent adverse outcomes from chronic exposure, including cancer.
References

- Doe JE, Boobis AR, Dellarco VL, Fenner-Crisp PA, Moretto A, Pastoor TP, Schoeny RS, Seed JG, Wolf DC. Chemical Carcinogenicity Revisited 2: Current Knowledge of Carcinogenesis Shows that Categorization as a Carcinogen or Non-Carcinogen is Not Scientifically Credible. Reg Toxicol Pharmacol 103:124-129, 2019
References


