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Regulatory Toxicology

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Regulatory Toxicology

In the crop protection business:

Regulatory Toxicology ⇔ Risk Assessment

Are there risks associated with recommended uses?

Are these risks acceptable?

Risk Assessment Framework: **RISK = TOXICITY X EXPOSURE**

- ❑ Hazard identification
- ❑ Dose-response assessment
- ❑ Exposure assessment
- ❑ Risk characterization

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Hazard Identification – Data Requirements

- Characterization of adverse toxic effects
- US EPA Data Requirements for Pesticides

Code of Federal Regulations (CFR), Title 40, Part 158

a case-by-case basis, submission of product performance data for any pesticide product registered or proposed for registration.

2. [Reserved]

Subpart F—Toxicology

§ 158.500 Toxicology data requirements table.

(a) *General*. Sections 158.100 through 158.130 describe how to use the data table in paragraph (d) of this section to determine the toxicology data requirements for a particular pesticide product.

(c) *Key*. R=Required; CR=Conditionally required; NR=Not required; MP=Manufacturing-use product; EP=End-use product; TGAI=Technical grade of the active ingredient; PAI=Pure active ingredient; PAIRA=Pure active ingredient radiolabeled; Choice=Choice of several test substances depending on study required.

(d) *Table*. The following table lists the toxicology data requirements. The table notes are shown in paragraph (e) of this section.

TABLE—TOXICOLOGY DATA REQUIREMENTS

Guideline Number	Data Requirements	Use Pattern		Test substance to support		Test Note No.
		Food	Nonfood	MP	EP	
Acute Testing						
870.1100	Acute oral toxicity - rat	R	R	TGAI and MP	TGAI, EP, and possibly diluted EP	1, 2
870.1200	Acute dermal toxicity	R	R	TGAI and MP	TGAI, EP	1, 2, 3
870.1300	Acute inhalation toxicity - rat	R	R	TGAI and	TGAI and	4

Identified hazards not a cut-off

Used for risk determination together with exposure

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Hazard Identification – Bridging or Waiving

- US EPA guidance - Acute toxicity studies
  - e.g. granular pesticide products composed of > 90% inert carriers
  - e.g. not possible to generate respirable atmosphere
  - e.g. end-use products of similar composition

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)

US Environmental Protection Agency
Office of Pesticide Programs

Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis

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Hazard Identification – Bridging or Waiving (cont.)

- US EPA guidance – Other studies
  - Neurotoxicity battery
  - Subchronic inhalation
  - Subchronic dermal
  - Immunotoxicity
    - e.g. no evidence of neurotoxicity or immunotoxicity in the database of toxicology studies
    - e.g. weight-of-evidence (WOE) approach considering hazard and exposure: physical-chemical properties, overall toxiciyt profile, exposure scenarios, margins of exposure

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: February, 2013

SUBJECT: A Retrospective Analysis of the Immunotoxicity Study (OCSPP Test Guideline No. 870.7800)

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

Office of Pesticide Programs
U.S. Environmental Protection Agency

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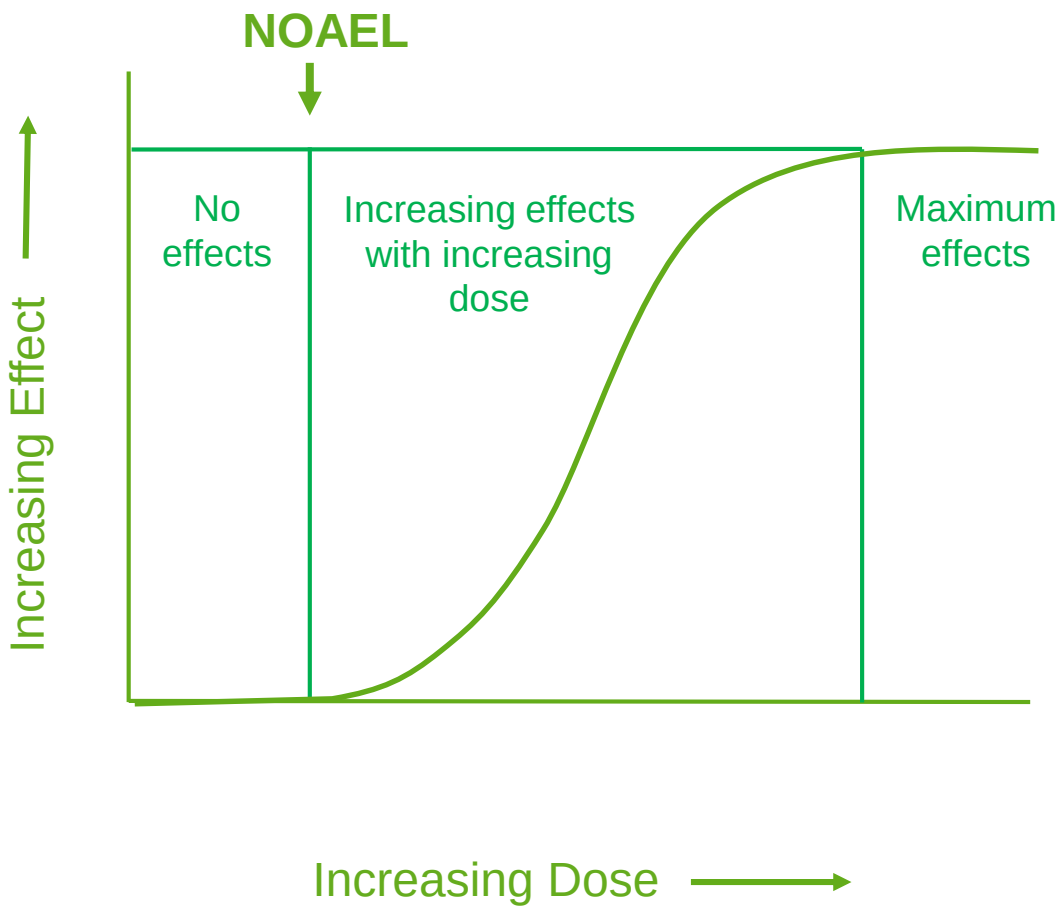
Dose-Response Assessment

- The ultimate goal for toxicology studies is to identify a dose that will not cause any adverse effects
- **No Observed Adverse Effect Level (NOAEL)**
- **LOAEL = Lowest Observed Adverse Effect Level**



Acute Toxicity Classification

- ❑ Toxicity Categories
- ❑ Signal Words
- ❑ Precautionary Statements
- ❑ First Aid
- ❑ Worker Protection

Office of Pesticide Programs

Label Review Manual

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Acute Toxicity Classification (cont.)

	CATEGORY I	CATEGORY II	CATEGORY III	CATEGORY IV
Oral LD50 (mg/kg)	≤ 50	> 50 thru 500	> 500 thru 5000	> 5000
Dermal LD50 (mg/kg)	≤ 200	> 200 thru 2000	> 2000 thru 5000 g	> 5000
Inhalation LC50 (mg/L)	≤ 0.05	> 0.05 thru 0.5	> 0.5 thru 2	> 2
Skin Irritation	Corrosive	Severe irritation at 72 hours	Moderate irritation at 72 hours	Mild or slight irritation at 72 hours
Eye Irritation	Corrosive	eye irritation clearing in 8-21 days	eye irritation clearing in 7 days or less	Minimal effects clearing in less than 24 hours
Signal Words	DANGER	WARNING	CAUTION	CAUTION

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Acute Toxicity Classification (cont.)

Headline®
fungicide

For use in disease control and plant health in the following c
barley, citrus fruit, corn (all types), cotton, dried shelled peas
edible-podded legume vegetables, grass grown for seed, mi
crops (flax seed, rapeseed, safflower, sesame, sunflower), pe
rye, sorghum, soybean, succulent shelled peas and beans, s
tuberous and corm vegetables (includes potato), and wheat

Active Ingredient*:
pyraclostrobin: (carbamic acid, [2-[[[1-(4-chlorophenyl)-1*H*-pyrazol-3
yl]oxy]methyl]phenyl]methoxy-, methyl ester) . . . . . .
Other Ingredients:** . . . . . .
Total: . . . . . .
* Equivalent to 2.09 pounds of pyraclostrobin per gallon.
** Contains petroleum distillates.

EPA Reg. No. 7969-186 **EPA Est. N**

KEEP OUT OF REACH OF CHILDREN

WARNING/AVISO

Si usted no entiende la etiqueta, busque a alguien para que se la expl
details. (If you do not understand this label, find someone to explain it

See inside for complete **First Aid**, **Precautionary Statements**, **Di**
Use, **Conditions of Sale and Warranty**, and state-specific crop a
restrictions.

In case of an emergency endangering life or property involvi
call day or night 1-800-832-HELP (4357).

FIRST AID

If swallowed	• Call a poison control center or doctor immediately for treatment advice. • **DO NOT** give any liquid to the person. • **DO NOT** induce vomiting unless told to do so by a poison control center or doctor. • **DO NOT** give anything to an unconscious person.
If on skin or clothing	• Take off contaminated clothing. • Rinse skin immediately with plenty of water for 15 to 20 minutes. • Call a poison control center or doctor for treatment advice.
If in eyes	• Hold eyes open and rinse slowly and gently with water for 15 to 20 minutes. • Remove contact lenses, if present, after first 5 minutes; then continue rinsing eyes. • Call a poison control center or doctor for treatment advice.
If inhaled	• Move person to fresh air. • If person is not breathing, call 911 or an ambulance; then give artificial respiration, preferably by mouth to mouth, if possible. • Call a poison control center or doctor for further treatment advice.

Note to Physician: Probable mucosal damage may contraindicate the use of gastric lavage.

HOTLINE NUMBER

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact BASF Corporation for emergency medical treatment information: 1-800-832-HELP (4357).

Precautionary Statements

Hazards to Humans and Domestic Animals

WARNING. May be fatal if swallowed. Causes substantial but temporary eye injury. Causes skin irritation. Harmful if absorbed through skin. Avoid contact with eyes, skin or clothing.

Personal Protective Equipment (PPE)
Some materials that are chemically resistant to this product are listed below. For more options, refer to **Category A** on an EPA chemical-resistance category selection chart.

USER SAFETY RECOMMENDATIONS

Users should:
- Wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.
- Remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing.
- Remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.

Carcinogenicity Classification

- 2005 Classification of pesticides
  - Carcinogenic to humans – strong evidence of human carcinogenicity based on convincing epidemiological evidence or lesser epidemiological evidence in combination of strong evidence in animals
  - Likely to be carcinogenic in humans – plausible association between human exposure and cancer or strong evidence in animals
  - Suggestive evidence of carcinogenic potential – Suggestion of carcinogenicity in animals, concern for potential carcinogenic effects in humans
  - Inadequate information to assess carcinogenic potential
  - Not likely to be carcinogenic to humans – no basis for human concern

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Carcinogenicity Assessment

- Threshold effects – no response over a range of low doses that include zero (e.g. non genotoxic carcinogens)
  - Non-linear assessment
    Reference Dose (RfD)
    RISK = TOXICITY X EXPOSURE
- Non-threshold effects – responses at all doses above zero (e.g. genotoxic carcinogens)
  - Linear assessment
    Linear Low-Dose Extrapolation (q1*)
    RISK = TOXICITY X EXPOSURE

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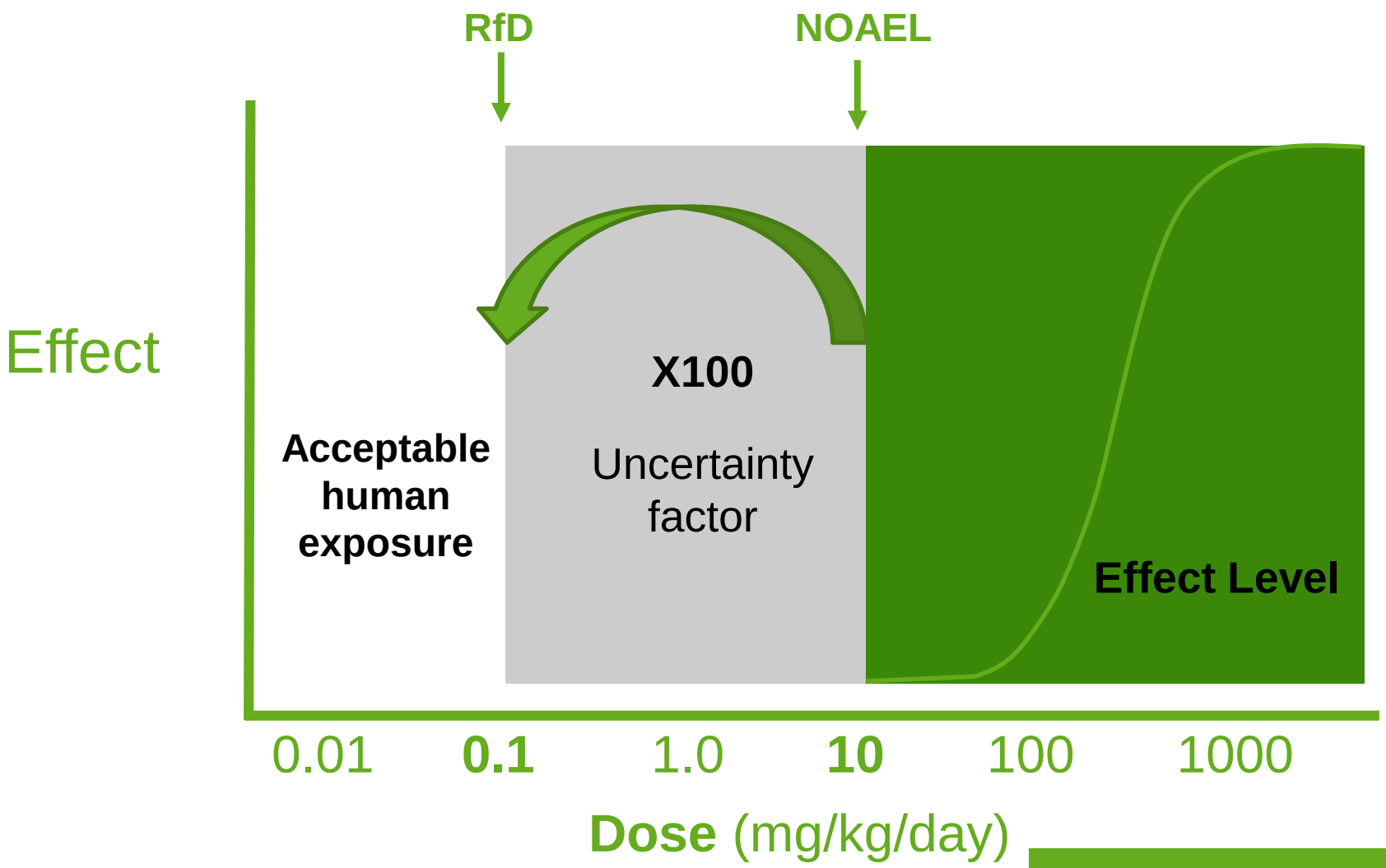
Reference Dose (RfD)



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Uncertainty Factors

Safety/Uncertainty Factor	Reason	Value
Interspecies	Most humans aren't rats	10X
Intraspecies	All humans aren't the same	10X
FQPA (Food Quality Protection Act)	Young may be more sensitive than adults	1, 3, 10X
Database	Study database not acceptable	3-10X
Maximum		10000 X but most not greater than 3000X

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Dietary Risk Assessment

RfD= NOAEL/ UF (uncertainty factor)

Lowest NOAEL of most sensitive species/ endpoint

- ARfD (acute reference dose) – estimate of daily oral exposure for an acute duration (24h or less) to human population without appreciable risk of deleterious effects during a lifetime. Derived form NOAEL/ LOAEL
- CRfD (chronic reference dose) – estimated of daily oral exposure for chronic duration (lifetime) to human population without appreciable risk of deleterious effects during a lifetime. Derived from NOAEL/ LOAEL

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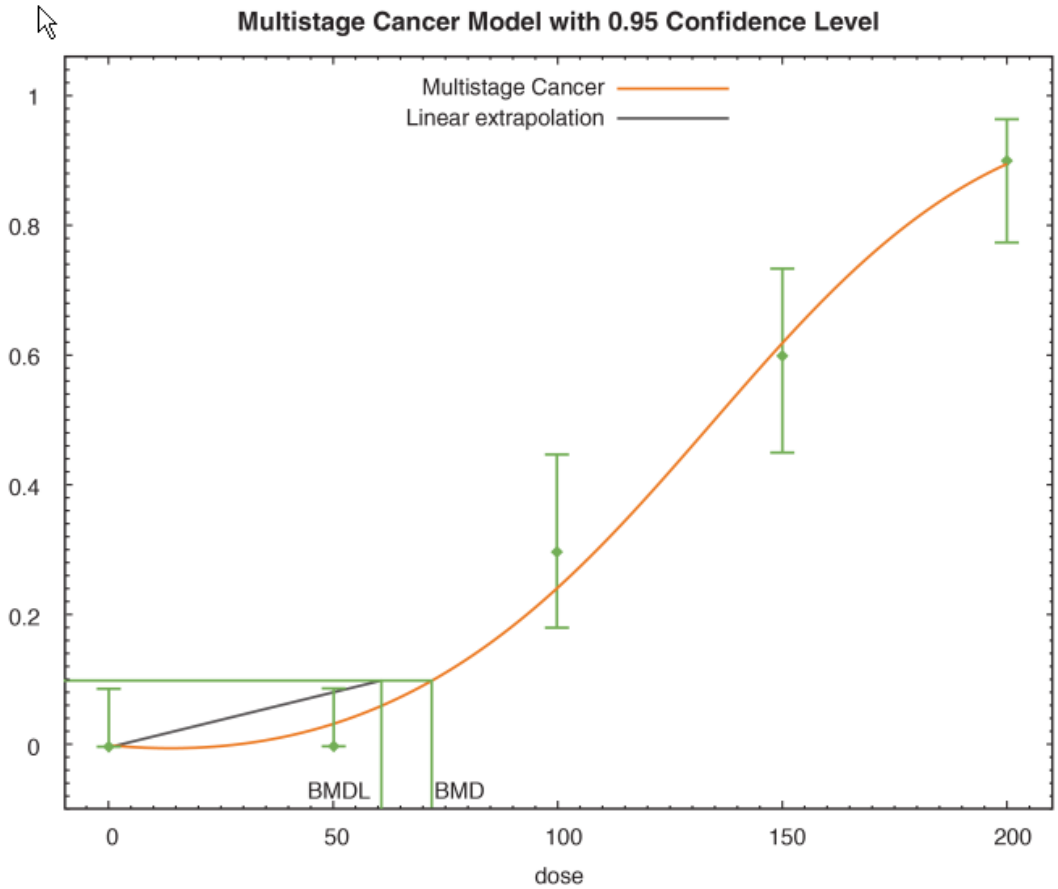
Linear Low Dose Extrapolation



- Linear extrapolation through zero threshold dose from upper confidence level of lowest dose that caused cancer
- Yields a cancer slope factor (q1*) used to predict cancer risk at a specific dose
- Used to calculate individual lifetime cancer extra risk

EXTRA RISK = q1* x lifetime exposure

- Acceptable extra risk set at 10^{-6} (1 in a million)

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