

# **Appendixes**

# Appendix A

## Testing Guidelines

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### **Testing Guidelines**

Testing guidelines are developed for a variety of reasons: to allow results of various test substances or species to be easily compared, to encourage the use of certain protocols so that testing need not be repeated, and to facilitate the work of those who design and carry out tests. Many organizations have developed testing guidelines. Three such compilations have been selected for discussion.

### **FDA Guidelines Involving Whole Animal Testing**

To the extent possible, the Food and Drug Administration (FDA) makes its animal testing guidelines consistent throughout the agency and consistent with those of other agencies and organizations. However, special uses of products require special testing, and guidance is available from agency staff to help manufacturers meet those requirements. In this table, tests that generally can be considered common or standard toxicological tests usually used throughout the agency are grouped together. Those that are more specific for evaluation of the safety of certain products are identified with the FDA Center responsible for regulating that product.

- I. Agency-wide
  - A. General Toxicity
    - 1. Acute oral—rodent, nonrodent
    - 2. Acute dermal—rodent, nonrodent
    - 3. Acute inhalation—rodent
    - 4. Subchronic oral—rodent, nonrodent
    - 5. Chronic oral—rodent, nonrodent
    - 6. Carcinogenicity —rodent
    - 7. Combined chronic/carcinogenicity —rodent
  - B. Specific Effects
    - 1. Dermal sensitization—guinea pig
    - 2. Dermal irritation—rabbit
    - 3. Eye irritation—rabbit
    - 4. Teratogenicity—rodent, rabbit
    - 5. Reproduction—rodent
    - 6. Absorption, distribution, metabolism, elimination—rodent, nonrodent
    - 7. Neural-behavioral—rodent, rabbit
  - H. Center-oriented
    - A. Human Drugs
      - 1. Subchronic inhalation—rodent, nonrodent
      - 2. Subchronic dermal—rodent, nonrodent
    - 3. Vaginal and rectal administration—rodent, nonrodent
    - 4. Immunotoxicity—rodent
    - B. Food Additives/Color Additives
      - 1. Immunotoxicity—rodent
      - 2. Protein quality—rodent
      - 3. Vitamin D assay—rodent
    - C. Biologics
      - 1. All biologics administered by injection
        - a. Safety—guinea pigs, mice
        - b. pyrogenicity—rabbits
      - 2. Vaccines
        - a. Safety—mice, suckling mice, chimpanzees, monkeys, guinea pigs, rabbits
        - b. Potency—guinea pigs, mice, monkeys
        - c. Hypersensitivity—guinea pigs
        - d. Toxicity—mice
      - 3. Antitoxins
        - a. Potency—guinea pigs, mice
      - 4. Toxins
        - a. Potency—mice
      - 5. Toxoids
        - a. Potency—mice
      - 6. Immune globulins
        - a. Potency—guinea pigs
      - 7. Tuberculin
        - a. Safety—guinea pigs
        - b. Potency—mice
    - D. Devices
      - 1. Corneal metabolism—rabbit
      - 2. Biomaterial implant—rabbit, primate, cat
      - 3. U.S.P. intracutaneous—rabbit
    - E. Cosmetics
      - 1. Primary skin irritation and corrosivity - rabbit
      - 2. Phototoxicity—nude mouse, rabbit, guinea pig
    - F. New Veterinary Drugs
      - 1. Safety, efficacy—target species
      - 2. Drug tolerance—target species
      - 3. Reproduction studies—target species
      - 4. Tissue irritation—target species
      - 5. Combination drug—target species
      - 6. Drug disposition—target species
      - 7. Route of administration—target species
      - 8. Intramammary infusion-dairy cows, goats

## **OECD Guidelines Involving Whole Animal Testing**

The Organization for Economic Cooperation and Development (OECD) guidelines have wide acceptance in the United States and abroad because of the Mutual Acceptance of Data Decision (I). Under the terms of this decision, member countries of OECD must accept data generated in other countries if done so according to these guidelines. Animal tests contained in the guidelines are listed below.

1. Effects on Biotic Systems
  - 202 Daphnia, acute immobilization test and reproduction test
  - 203 Fish, acute toxicity test
  - 204 Fish, prolonged toxicity test: 14 day study
  - 205 Avian dietary toxicity test
  - 206 Avian reproduction test
2. Degradation and Accumulation
  - 305A Bioaccumulation: Sequential Static Fish Test
  - 305B Bioaccumulation: Semi-static Fish Test
  - 305C Bioaccumulation: Test for the Degree of Bioconcentration in Fish
  - 305D Bioaccumulation: Static Fish Test
  - 305E Bioaccumulation: Flow-through Fish Test
3. Health Effects
 

Short-Term Toxicology

  - 401 Acute oral toxicity
  - 402 Acute dermal toxicity
  - 403 Acute inhalation toxicity
  - 404 Acute dermal irritation/corrosion
  - 405 Acute eye irritation/corrosion
  - 406 Skin sensitization
  - 407 Repeated dose oral toxicity—rodent: 14/28 day
  - 408 Subchronic oral toxicity—rodent: 90 day
  - 409 Subchronic oral toxicity—nonrodent: 90 day
  - 410 Repeated dose dermal toxicity: 14/28 day
  - 411 Subchronic dermal toxicity: 90 day
  - 412 Repeated dose inhalation toxicity: 14/28 day
  - 413 Subchronic inhalation toxicity: 90 day
  - 414 Teratogenicity
  - 415 One-generation reproduction toxicity study
  - 416 Two-generation reproduction toxicity study
  - 417 Toxicokinetics
  - 418 Acute delayed neurotoxicity of organophosphorous substances
  - 419 Subchronic delayed neurotoxicity of organophosphorous substances: 90 day

Long-Term Toxicology

  - 451 Carcinogenicity studies

- 452 Chronic toxicity studies
- 453 Combined chronic toxicity/carcinogenicity studies

### Genetic Toxicology

- 474 Genetic toxicity: micronucleus test
- 475 In vivo mammalian bone marrow cytogenetic test—chromosomal analysis
- 478 Rodent dominant lethal test

## **Pesticide Assessment Guidelines Involving Whole-Animal Testing**

The Office of Pesticide Programs of the Environmental Protection Agency (EPA) has developed guidelines for testing required under the Federal Insecticide, Fungicide, and Rodenticide Act. These Pesticide Assessment Guidelines contain standards for conducting acceptable tests, guidelines for the evaluation and reporting of data, guidelines as to when additional testing might be required, and examples of acceptable protocols (2). Similar guidelines have been developed by EPA's Office of Toxic Substances (OTS) for testing required under the Toxic Substances Control Act (3).

### Subdivision E: Hazard Evaluation: Wildlife and Aquatic Organisms

#### Series 70: General Information and Requirements

#### Series 71: Avian and Mammalian Testing

- 71-1 Avian single-dose oral LD<sub>50</sub> test
- 71-2 Avian dietary LC<sub>50</sub> test
- 71-3 Wild mammal toxicity test
- 71-4 Avian reproduction test
- 71-5 Simulated and actual field tests for mammals and birds

#### Series 72: Aquatic Organism Testing

- 72-1 Acute toxicity test for freshwater fish
- 72-2 Acute toxicity test for freshwater aquatic invertebrates
- 72-3 Acute toxicity test for estuarine and marine organisms
- 72-4 Fish early life-stage and aquatic invertebrate life-cycle studies
- 72-5 Life-cycle tests of fish
- 72-6 Aquatic organism accumulation tests
- 72-7 Simulated or actual field testing for aquatic organisms

### Subdivision F: Hazard Evaluation: Humans and Domestic Animals

#### Series 80: Overview, Definition, and General Requirements

#### Series 81: Acute Toxicity and Irritation Studies

- 81-1 Acute oral toxicity study

- 81-2 Acute dermal toxicity study
- 81-3 Acute inhalation toxicity study
- 81-4 Primary eye irritation study
- 81-5 Primary dermal irritation study
- 81-6 Dermal sensitization study
- 81-7 Acute delayed neurotoxicity of organophosphorous substances
- Series 82: Subchronic Testing
  - 82-1 Subchronic oral toxicity (rodent and nonrodent): 90 day study
  - 82-2 Repeated dose dermal toxicity: 21 day study
  - 82-3 Subchronic dermal toxicity: 90 day study
  - 82-4 Subchronic inhalation toxicity: 90 day study
  - 82-5 Subchronic neurotoxicity: 90 day study
- Series 83: Chronic and Long-Term Studies
  - 83-1 Chronic toxicity studies
  - 83-2 Oncogenicity studies
  - 83-3 Teratogenicity study
  - 83-4 Reproductive and fertility effects
  - 83-5 Combined chronic toxicity/oncogenicity studies
- Series 84: Mutagenicity
  - 84-1 Purpose and general recommendations for mutagenicity testing
  - 84-2 Mutagenicity tests (described in very general terms, with reference to the OTS guidelines)
- Series 85: Special Studies
  - 85-1 Metabolism study
  - 85-2 Domestic animal safety testing
- Subdivision G: Product Performance**
- Series 95: Efficacy of Invertebrate Control Agents
  - 95-1 General considerations
  - 95-8 Livestock, poultry, fur and wool-bearing animal treatments
  - 95-9 Treatments to control pests of humans and pets
- Series 96: Efficacy of Vertebrate Control Agents
  - 96-1 General considerations
  - 96-2 Fish control agents
  - 96-3 Aquatic amphibian control agents
  - 96-4 Terrestrial amphibian and reptilian control agents
  - 96-5 Avian toxicants
  - 96-6 Avian repellents
  - 96-7 Avian frightening agents
  - 96-8 Mole toxicants
  - 96-9 Bat toxicants and repellents

- 96-10 Commensal rodenticides
- 96-11 Rodenticides in orchards
- 96-12 Rodenticides on farm and rangelands
- 96-13 Rodent fumigants
- 96-14 Rodent repellents on tree seeds
- 96-15 Rodent repellents on cables
- 96-16 Rodent reproductive inhibitors
- 96-17 Mammalian predacides
- 96-18 Domestic dog and cat repellents
- 96-19 Browsing animal repellents
- 96-30 Methods and protocols

#### **Subdivision M: Biorational Pesticides**

(This subdivision duplicates many of the provisions of other subdivisions, and is therefore not described in detail.)

- Series 150: Overview, Definitions, and General Provisions
- Series 152: Toxicology Guidelines
  - Subseries 152A: Toxicology Guidelines
  - Subseries 152B: Toxicology Guidelines for Microbial Pest Control Agents
- Series 154: Nontarget Organism Hazard Guidelines
  - Subseries 154A: Nontarget Organism Hazard Guidelines for Biochemical Agents
  - Subseries 154B: Nontarget Organism Hazard Guidelines for Microbial Agents
- Series 157: Experimental Use Permit Guidelines
- Subdivision N: Environmental Fate**
- Series 165: Accumulation Studies
  - 165-4 Laboratory Studies of Pesticide Accumulation in Fish
  - 165-5 Field Accumulation Studies of Aquatic Nontarget Organisms

### **Appendix A References**

1. Organization for Economic Cooperation and Development, *Guidelines for Testing of Chemicals*, and addenda (Paris: 1981).
2. U.S. Environmental Protection Agency, *Pesticide Assessment Guidelines* (Springfield, VA: National Technical Information Service, 1984).
3. U.S. Environmental Protection Agency, *Office of Toxic Substances Health and Environmental Effects Test Guidelines* (Washington, DC: update October 1984).