

§ 158.340 Toxicology data requirements.

(a) Table. Sections 158.50 and 158.100 through 158.102 describe how to use this table to determine the toxicology data requirements and the substance to be tested.

Kind of data required	(b) Notes	General use patterns										Test substance		Guide-lines reference No.		
		Terrestrial		Aquatic		Greenhouse		Forestry	Domestic outdoor	Indoor	Data to support MP	Data to support EP				
		Food crop	Nonfood	Food crop	Nonfood	Food crop	Nonfood									
Acute testing																
Acute oral toxicity—rat	(1)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	MP and TGAI.	EP* or EP dilution* and TGAI.	81-1
Acute dermal toxicity	(1), (2)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	MP and TGAI.	EP* or EP dilution* and TGAI.	81-2
Acute inhalation toxicity—rat.	(16)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	MP and TGAI.	EP* and TGAI.	81-3
Primary eye irritation—rabbit.	(2)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	MP	EP*	81-4
Primary dermal irritation	(1), (2)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	MP	EP*	81-5
Dermal sensitization	(3)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	MP	EP*	81-6
Acute delayed neurotoxicity—hen.	(4)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	TGAI	TGAI	81-7
Subchronic testing																
90-day feeding studies—rodent and nonrodent.	(17)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	TGAI	TGAI	82-1
21-day dermal	(18)	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	TGAI	TGAI and EP*	82-2
90-day dermal	(5), (19)	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	TGAI	TGAI	82-3
90-day inhalation—rat	(6)	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	TGAI	TGAI	82-4
90-day neurotoxicity: Hen	(7)	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	TGAI	TGAI	82-5
Mammal	(8)	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	TGAI	TGAI	82-5
Chronic testing																
Chronic feeding—2 spp. rodent and nonrodent.	(9), (13), (20)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	TGAI	TGAI	83-1
Oncogenicity study—2 Spp. rat and mouse preferred.	(9), (21)	R	R	R	R	R	R	R	R	R	R	R	R	TGAI	TGAI	83-2
Teratogenicity—2 species Reproduction, 2-generation.	(10), (15), (11), (14)	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	[R]	TGAI	TGAI	83-3

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		Terrestrial		Aquatic		Greenhouse		Forestry	Domestic outdoor	Indoor	Data to support MP		Data to support EP
		Food crop	Nonfood	Food crop	Nonfood	Food crop	Nonfood						
Mutagenicity testing													
Gene mutation	(22) [R]	R	[R]	R	[R]	[R]	R	R	R	R	TGAI	TGAI	84-2
Structural chromosomal aberration.	(22) [R]	R	[R]	R	[R]	[R]	R	R	R	R	TGAI	TGAI	84-2
Other genotoxic effects	(22) [R]	R	[R]	R	[R]	[R]	R	R	R	R	TGAI	TGAI	84-4
Special testing													
General metabolism	(23)	R	CR	R	CR	R	CR	CR	CR	CR	PAI or PAIRA.	PAI or PAIRA.	85-1
Dermal penetration	(24)	CR	CR	CR	CR	CR	CR	CR	CR	CR	Choice	Choice	85-2
Domestic animal safety	(12)	CR	CR	CR	CR	CR	CR	CR	CR	CR	Choice	Choice	86-1

AAKey: R=Required data; CR=Conditionally required; []=Brackets (ie [R], [CR]) indicate data requirements that apply when an experimental use permit is being sought; MP=Manufacturing-use product; EP=End-Use Product; (asterisk identifies those data requirements that end-use applicants (i.e., "formulators") must satisfy, provided that their active ingredient(s) is (are) purchased from a registered source); TGAI=technical grade of the active ingredient; PAI="Pure" active ingredient; PAIRA="Pure" active ingredient, radio-labeled; Choice=choice of several test substances, depending on studies required.

(a) NOTES: The following notes are referenced in column two of the table contained in paragraph (a) of this section.

(1) Not required if test material is a gas or highly volatile.

(2) Not required if test material is corrosive to skin or has pH less than 2 or greater than 11.5; such a product will be classified as toxicity category I on the basis of potential eye and dermal irritation effects.

(3) Required unless repeated dermal exposure does not occur under conditions of use.

(4) Not required unless test material is an organophosphate, or a metabolite or degradation product thereof which causes acetyl cholinesterase depression or is structurally related to a substance that causes delayed neurotoxicity.

(5) Required if use involves purposeful dermal application to, or prolonged exposure of, human skin.

(6) Required if use may result in repeated inhalation exposure at a concentration likely to be toxic. A test with duration of 21 days is required if pesticide is used on tobacco.

(7) Required if acute delayed neurotoxicity test showed neuropathy or neurotoxicity or if closely related structural to a compound which can induce these effects.

(8) Required if acute oral, dermal, or inhalation studies showed neuropathy or neurotoxicity.

(9)(i) Studies designed to simultaneously meet the requirements of both the chronic feeding and oncogenicity studies (i.e., a combined study) can be conducted.

(ii) Minimum acceptable test durations for chronic feeding and oncogenicity studies are as follows:

(A) Chronic rodent feeding study (food use pesticides)—24 months.

(B) Chronic rodent feeding study (non-food pesticides)—12 months is usually sufficient.

(C) Chronic nonrodent (i.e., dog) feeding study—12 months.

(D) Mouse oncogenicity study—18 months.

(E) Rat oncogenicity study—24 months.

(10) Required to support products intended for food uses and to support products intended for non-food uses if significant exposure of human females of child bearing age may reasonably be expected.

(11) Required to support products intended for food uses and to support products intended for non-food uses if use of the product is likely to result in human exposure over a portion of the human lifespan which is significant in terms of the frequency of exposure, magnitude of exposure, or the duration of exposure (for example, pesticides used in treated fabrics for wearing apparel, diapers, or bedding; insect repellents applied directly to human skin; swimming pool additives; constant-release indoor pesticides which are used in aerosol form).

(12) Required on a case by case basis.

(13) In most cases, where theoretical maximum residue contribution (TMRC) exceeds 50 percent of the maximum permitted intake (MPI), a one year (or longer) interim report on a chronic feed study is required to support a temporary tolerance.

(14) In most cases, where theoretical maximum residue contribution (TMRC) exceeds 50 percent of the maximum permitted intake (MPI), a first generation (or longer) interim report on a multigeneration reproduction study is required to support a temporary tolerance.

(15) A teratology study in one species is required to support a temporary tolerance.

(16) Required if the product consists of, or under conditions of use will result in, an inhalable material (e.g., gas volatile substances, or aerosol/particulate).

(17) Required if intended use(s) of the pesticide product is expected to result in human exposure to the product, under the following conditions:

(i) Human exposure is via the oral route.

- (ii) Expected human exposure is over a limited portion of the human lifespan, yet is significant in terms of the frequency of exposure, magnitude of exposure, or the duration of exposure (for example, products requiring a temporary tolerance to support an experimental use permit or emergency exemption).
- (18) Required if intended use(s) of the pesticide product is expected to result in human exposure to the product, under the following conditions:
 - (i) Human exposure is via skin contact.
 - (ii) Expected human skin contact is not purposeful, and such exposure is of limited frequency and duration (for example, such exposure could result from use of certain disinfectant, liquid fumigant or agricultural or home/garden pesticide products, and other circumstances where the Agency determines that more than acute dermal exposure is involved).
 - (iii) Data from a subchronic 90-day dermal toxicity study are not required.
- (19) Required if pesticidal use will involve purposeful application to the human skin or will result in comparable human exposure to the product, (e.g., swimming pool algaecides, pesticides for remagnetizing clothing), and if either of the following criteria are met:
 - (i) Data from a subchronic oral study are not required.
 - (ii) The active ingredient of the product is known or expected to be metabolized differently by the dermal route of exposure than by the oral route, and a metabolite of the active ingredient is the toxic moiety.
- (20) Required if either of the following criteria are met:
 - (i) Use of the pesticide product is likely to result in repeated human exposure to the product, over a significant portion of the human life-span (for example, products intended for use in and around residences, swimming pools, and enclosed working spaces or their immediate vicinity).
 - (ii) The use requires a tolerance for the pesticide or an exemption from the requirement to obtain a tolerance, or requires issuance of a food additive regulation.
- (21) Required if any of the following criteria are met:
 - (i) The active ingredient(s) or any of its (their) metabolites, degradation products, or impurities:
 - (A) is structurally related to a recognized carcinogen.
 - (B) is a substance that cause mutagenic effect as demonstrated by *in vitro* or *in vivo* testing.
 - (ii) Produces in subchronic studies a morphologic effect (e.g., hyperplasia, metaplasia) in any organ that may lead to neoplastic change.
 - (iii) The use requires a tolerance for the pesticide or exemption from the requirement to obtain a tolerance, or requires the issuance of a food additive regulation.
 - (iv) Use of the pesticide product is likely to result in human exposure over a portion of the human lifespan which is significant in terms of either the time the exposure occurs or the duration of exposure (for example, pesticides used in treated fabrics for wearing apparel, diapers, or bedding; insect repellents applied directly to human skin; swimming pool additives; constant-release floor pesticides which are used aerosol form).
- (22)(i) The required battery of mutagenicity tests must include tests appropriate to address the following three categories in accordance with the objectives set forth in § 158.202:
 - (A) Gene mutations.
 - (B) Structural chromosomal aberrations.
 - (C) Other genotoxic effects as appropriate for the test substance, e.g., numerical chromosome aberrations, direct DNA damage and repair, mammalian cells transformation, target organ/cell analysis.
- (ii) Currently recognized tests for each of these categories are listed with the National Technical Information Service (NTIS). Applicants shall explain their reasons for selecting specific tests from the battery or currently recognized tests. Because of the rapid improvements in this field, applicants are encouraged to discuss with the Agency: test selection, protocol design and results or preliminary testing.
- (iii) Not required if the pesticide use pattern precludes human exposure (e.g., nonvolatile pesticides packaged and used in enclosed bait boxes).
- (23) Required if chronic feeding or oncogenicity studies are required.
- (24) Dermal absorption studies required for compounds having a serious toxic effect as identified by oral or inhalation studies, for which a significant route of human exposure is dermal and for which the assumption of 100 percent absorption does not produce an adequate margin of safety. Registrants should work closely with the Agency in developing an acceptable protocol and performing dermal absorption studies.

[49 FR 42881, Oct. 24, 1984. Redesignated and amended at 53 FR 15993, 15999, May 4, 1988; 58 FR 34203, June 23, 1993]

§ 158.390 Reentry protection data requirements.

(a) *Table.* Sections 158.50 and 158.100 through 158.102 describe how to use this table to determine the reentry protection data requirements and the substance to be tested.

Kind of data required	(b) Notes	General use patterns										Test substance		Guideline reference No.	
		Terrestrial		Aquatic		Greenhouse		Forestry	Domestic outdoor	Indoor	Data to support MP	Data to support EP			
		Food crop	Nonfood	Food crop	Nonfood	Food crop	Nonfood								
Foliar dissipation	(1)	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	132-1
Soil dissipation	(1), (4)	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	CR	132-1