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Figure 5. Influence of route of exposure and vehicle on pyrethroid toxicity. The first panel (panel A) on top shows the variation in potency observed by using different routes to administer allethrin in mice. Apparently equipotent, highly-effective doses (expressed in mg/kg bw) administered by each route are compared (Nishimura et al. 1984). Panel B shows the evident influence of dosing vehicle on deltamethrin potency in rats. Deltamethrin dissolved in corn oil was observed to be up to ~200-fold more potent in producing a motor activity decline than other vehicles (i.e., ED_{50} from 5.1 to >1,000 mg/Kg). A similar trend is observed for LOEL estimates. Oral LOEL and ED_{50} doses are expressed in mg/Kg (taken from Crofton et al. 1995).

Figure 6. Influence of the selected endpoint on potency estimates for bifenthrin neurotoxicity. Dose-response patterns observed in rats at ~4 hours after oral exposure to bifenthrin in corn oil using FOB neurobehavioral assays (Wolansky et al. 2007a). In all assays (save internal temperature changes), authors used a scoring scale from 1 (control-like performance) to 4 (severe impairment) (see Panel A) for the effects of 1, 6, 12, and 20 mg/Kg bifenthrin (ascending doses denoted as increasingly darker figure bars). Note the variability of lowest-effective doses across neurobehavioral domains. Handling and tail pinch response were mostly unaffected, though a low-effective dose for tremor, pawing (Panel A), and body temperature (Panel B) was observed at ~6 mg/kg, consistent with a low-effective, ED_{30} dose of 3.2 mg/Kg (95% confidence interval: 2.6-3.8 mg/Kg) for alteration of motor activity as estimated in a prior bifenthrin study where similar dosing and testing conditions were used (Wolansky et al. 2006).

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Note: For factor "Age", the alluded maximal effect would be only possible at oral exposure levels equivalent to ≥1/20 LD_{50} (see oral LD_{50} for permethrin in rat pups and adults, in: http://www.epa.gov/teach/chem_summ/pyrethroids_summary.pdf).

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Structure. Rat oral LD50s observed across pyrethroid insecticides, from the least toxic compound (LD_{50} > 10 g/Kg) to the most potent compound (LD_{50} = 22 mg/Kg) (WHO 2005; Wolansky and Harrill 2008).

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Formulation. Three studies were considered. A comparison of the lethality of two formulations of deltamethrin (Lepeshkin et al. 1992), a comparison of the neurotoxicity of two formulations of permethrin and fenvalerate in mice (Williamson et al. 1989), and a study of the comparative effects of two permethrin test materials (a technical grade preparation and a 40%-pure, commercial formulation) on motor activity in time-course and dose-response assays conducted in rats (Wolansky, unpublished data).

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Vehicle. Study of the influence of four vehicles used to dissolve the test compound on the neurobehavioral toxicity of deltamethrin in rats, using motor activity as an endpoint (Crofton et al. 1995).

Species. A mild trend for a higher vulnerability in animals of smaller body size is apparent (Narahashi 2000). According to a few studies of deltamethrin and cypermethrin, mice appear to be 2-4-fold more susceptible than rats (taken from: INCHEM 1990b; INCHEM 1990c).

Gender - Strain. Limited evidence suggests no relevant influence on pyrethroid neurotoxicity.

Age. Based on the lethal toxicity and the acoustic-evoked startle response assays conducted in infant, weanling and adult rats after a single, oral dose of DLM in corn oil (Sheets et al. 1994; Sheets 2000).

Metabolites. Limited information is available suggesting no or very low neurotoxicity potential of pyrethroid metabolites in small rodents (Soderlund et al. 2002; see also difference in LD_{50} for deltamethrin and tralomethrin in section "Pyrethroid metabolites").

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Room Temperature. Study of the differential oral lethality of resmethrin in adult rats tested at three ambient temperatures, 4°C, 20°C and 30°C (White et al. 1976).

Realistic vs. Laboratory-Controlled Exposures: Available data (Eriksson and Talts 2000; Tsuji et al. 2002) is still insufficient to draw conclusions on possible pyrethroid sensitization manifesting from early life exposures to low doses of pyrethroids.

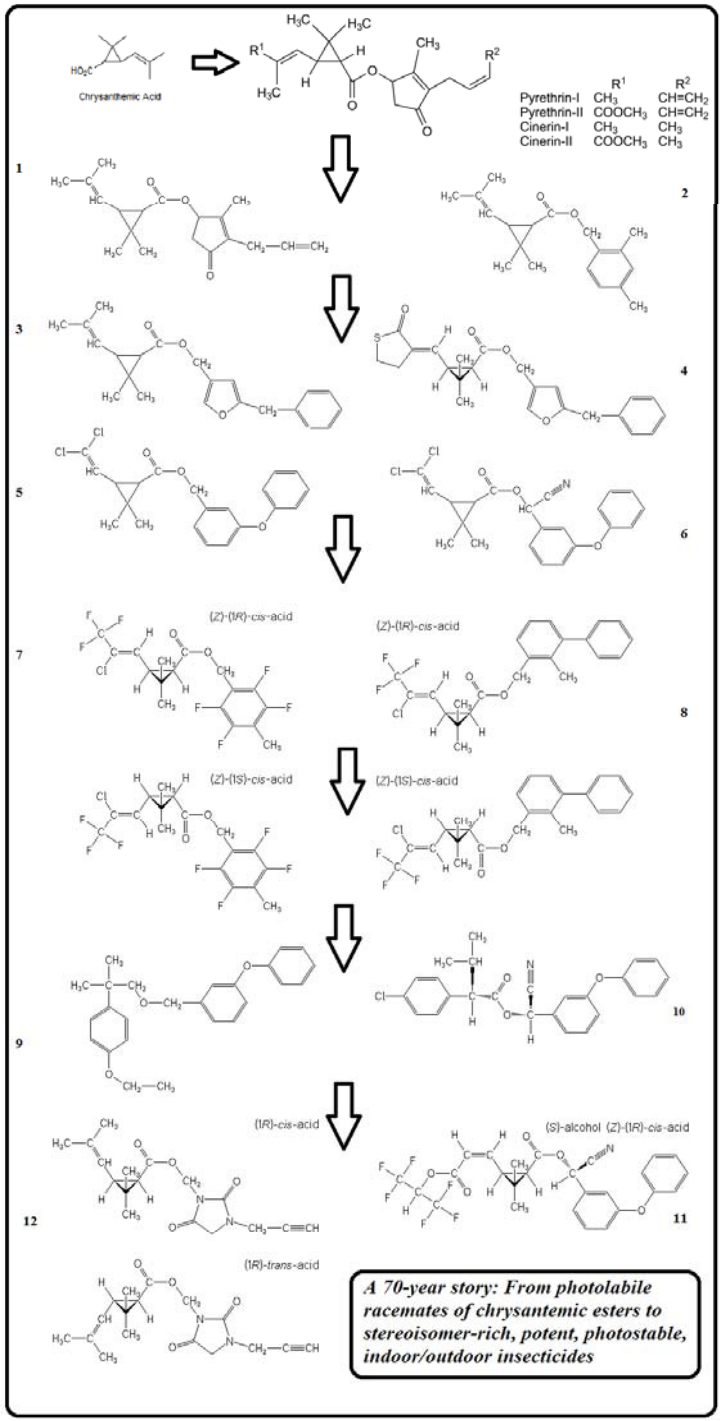
Table 1. Impact of experimental and organismic factors on pyrethroid neurotoxicity. The table classifies each determinant of toxicity with respect to pyrethroid toxicokinetics (TK) or toxicodynamics (TD) in laboratory animals. A relative score for the impact of each factor on potency estimation is also provided (maximum factor-effect between brackets in third column). Lack of information on the potential impact of these determinants on single-chemical risk assessments is marked in the fourth column when applicable.

Note: data on cumulative risk of neurotoxicity of pesticides has been recently started to be generated. For a part of the listed TK and TD factors, the influence of the experimental and organismic determinants on pyrethoid potency has not been incorporated to animal-human extrapolation procedures yet.

*Little evidence suggest no evident toxicodynamics-related, age-effect for acute oral exposures to low-effective doses of individual pyrethroids in small rodents. Moreover, no information is available for the influence of aging on pyrethroid vulnerability.

**The PoD used in risk assessment is regularly derived from the most sensitive endpoint assay; there is no analysis available of endpoint sensitivity for a representative number of Type I, Type II, and Mixed Type I/II pyrethroids using a full dose range scheme of administered doses.

Figure 1. Structural diversification of pyrethroid insecticides.



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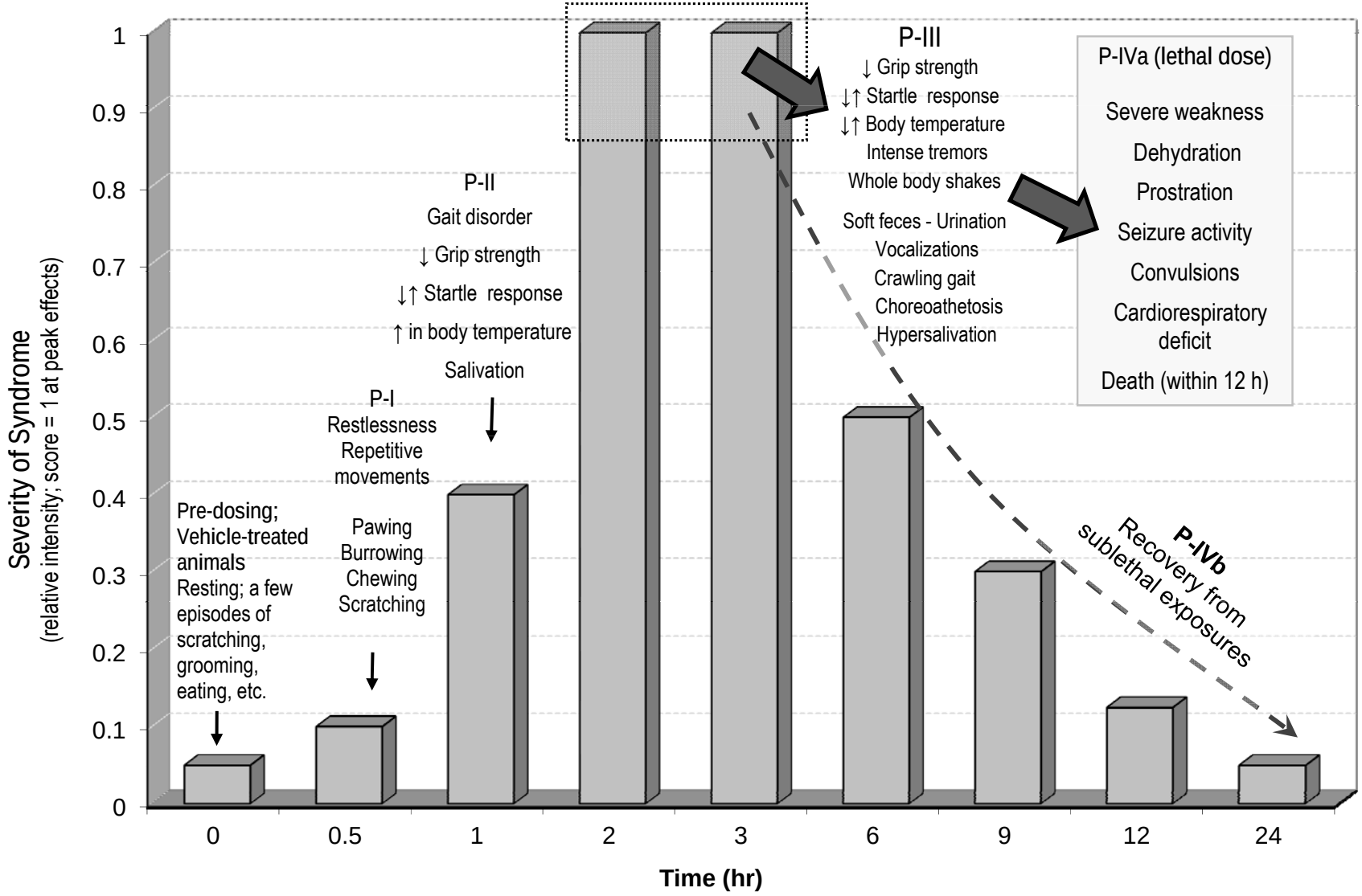

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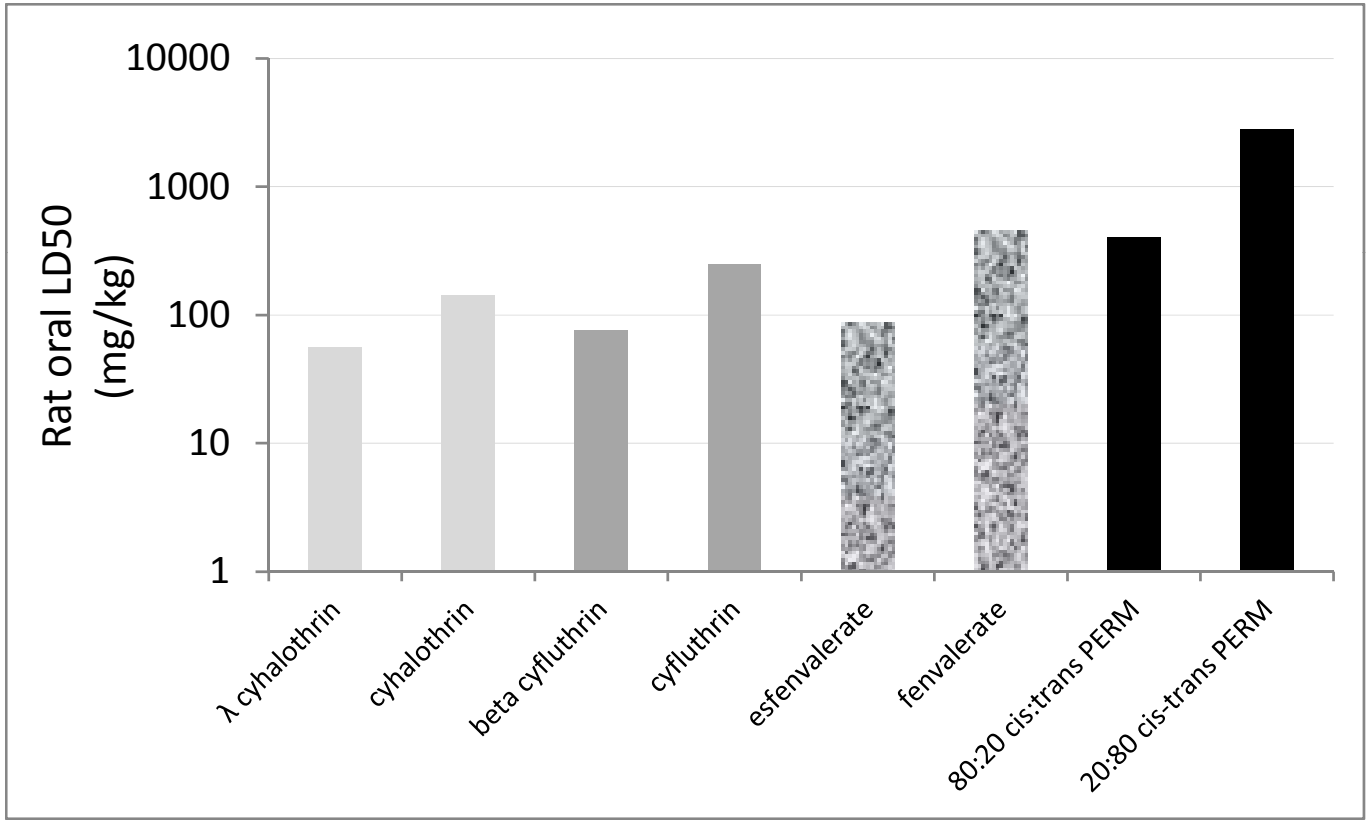

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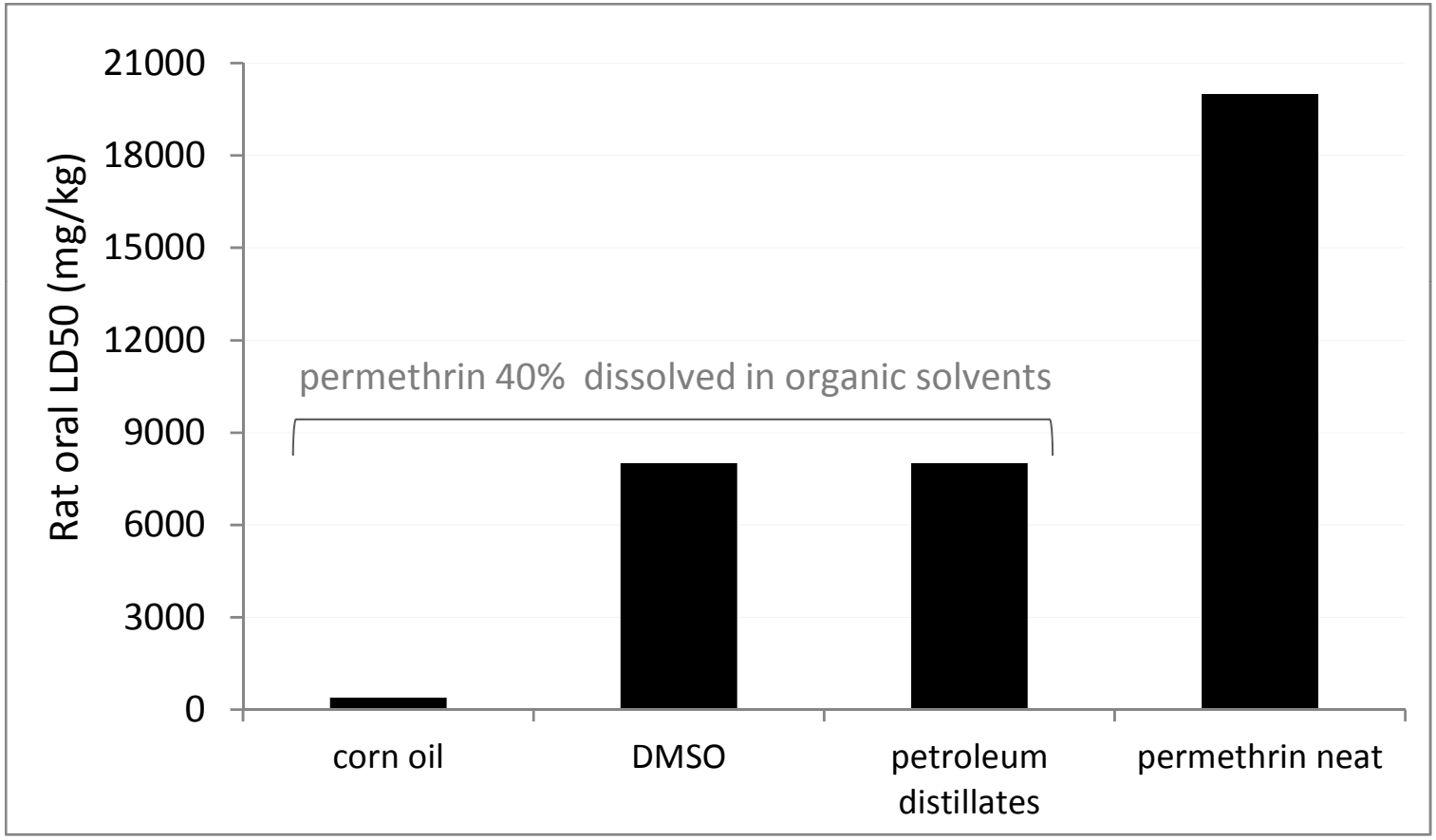

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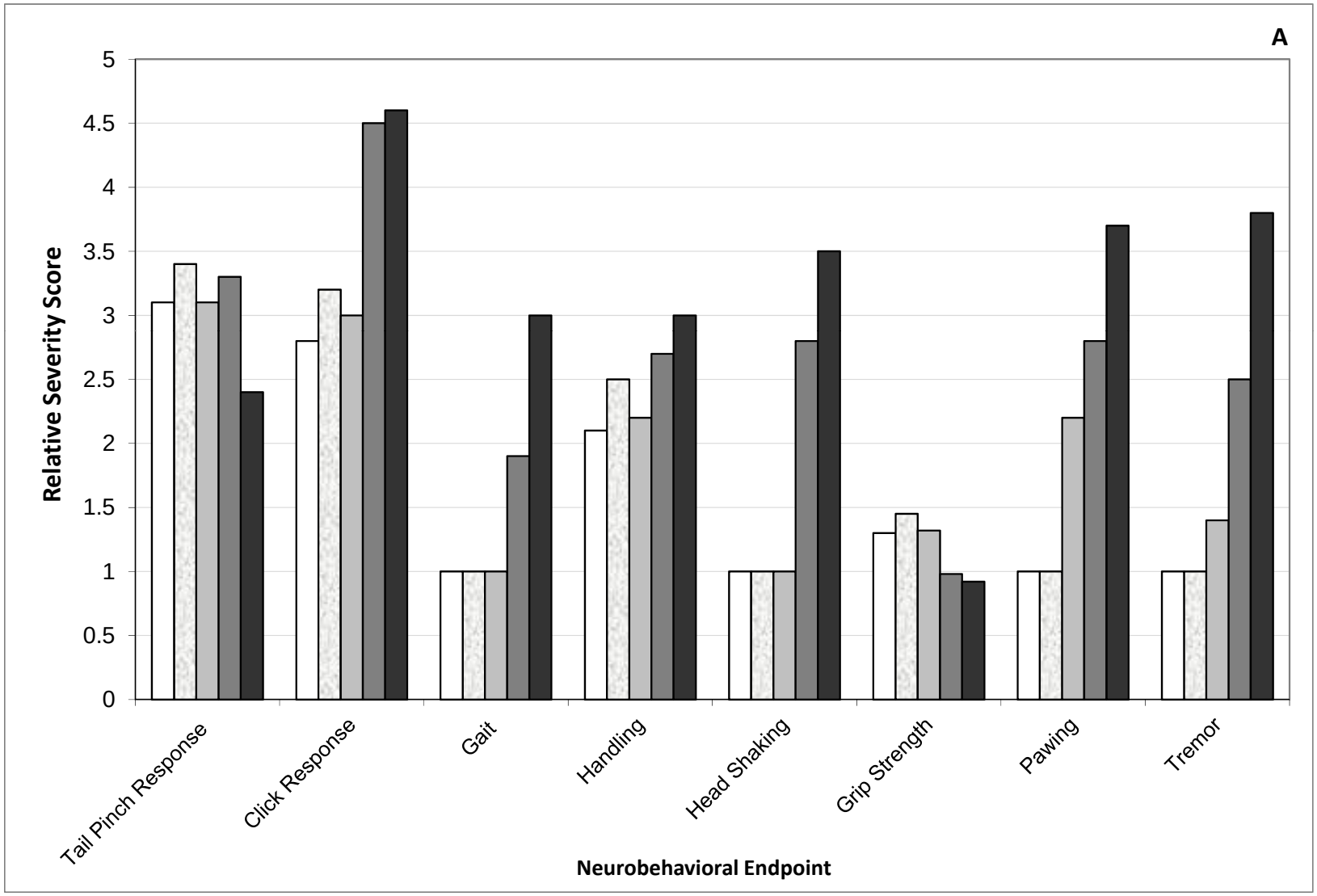

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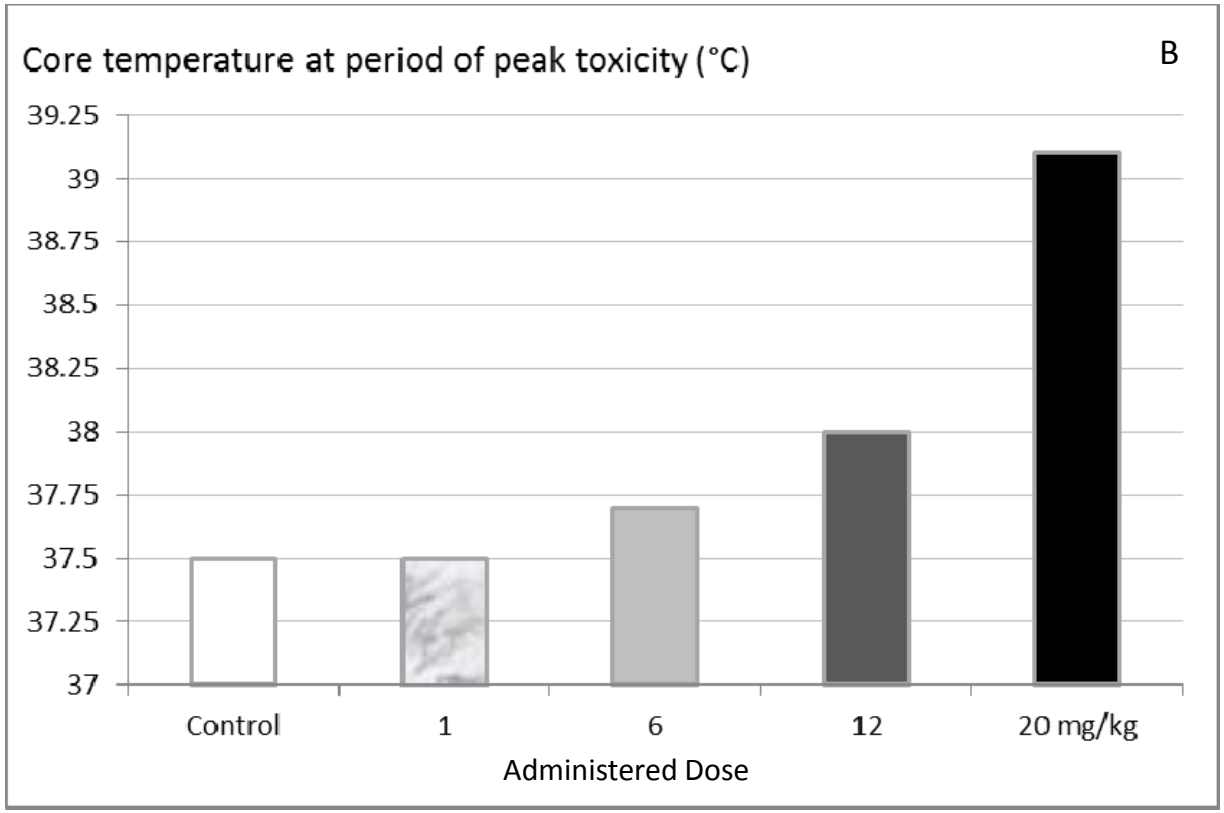

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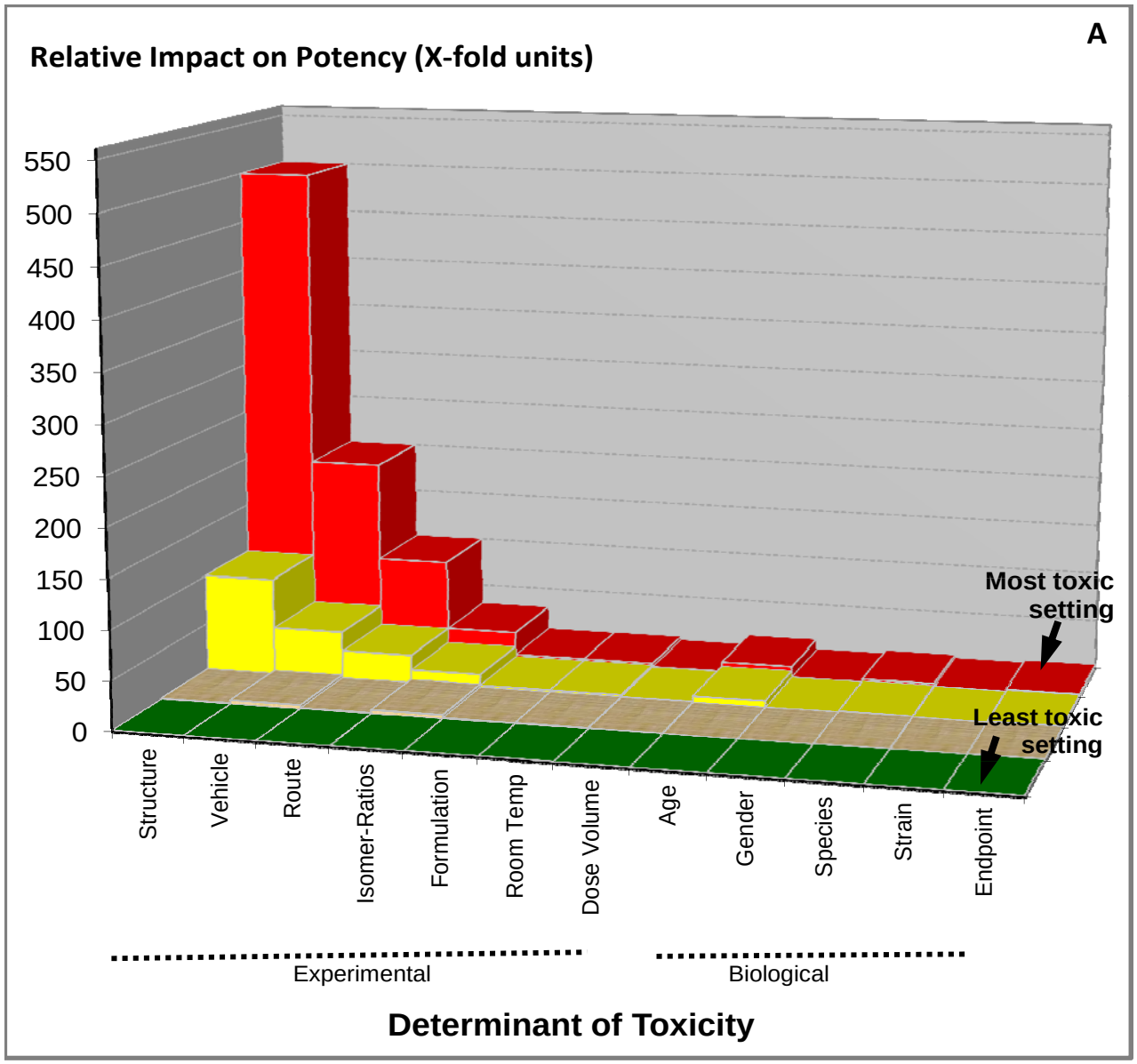

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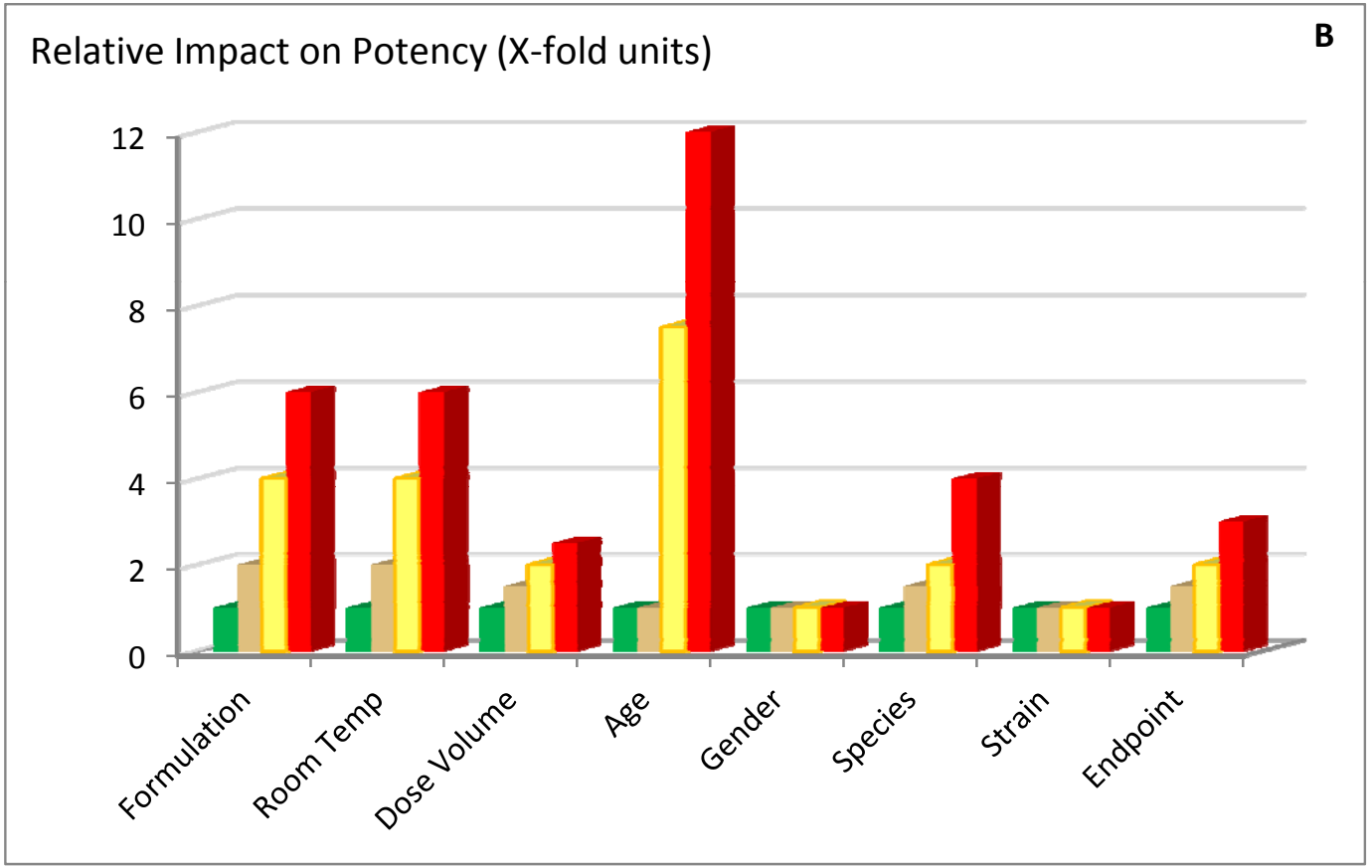

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Impact of experimental and organismic factors on pyrethroid neurotoxicity.

Toxicological Aspect	Toxicity Determinant	Maximum factor-effect in single-compound assays (pyrethroids' case)	Is consideration of the impact of these study design aspects a standard procedure in risk assessment for pesticides?
Toxicokinetics	Chemical Structure	++++++ (500-fold)	**Yes**
	Isomer Composition	+++ (25-fold)	**Yes**
	Formulation/Purity	+++ (50-fold)	**NO**
	Vehicle	+++++ (200-fold)	**NO**
	Route of Exposure	+++ (28-fold)	**Yes**
	Dose Volume	+ (3-fold)	**NO**
	Dosing Solution	+ (≤ 2-fold)	**NO**
	Metabolic Activation	+ (≤ 1.5-fold)	**NO**
	Age (Detoxification System Maturation)	++ (10-fold)*	**YES**
Toxicodynamics	Species (Rodent)	++ (4-fold)	**YES**
	Age (Nervous System Development)	No effect? *	**YES***
	Endpoint	+ (3-fold)	**NO****
	Physiological Status	+ (2-fold)	**NO**
	Morbidity	No data available	**NO**
Testing Room	Ambient Temperature	++ (6-fold)	**NO**
History of pesticide exposure episodes (from gestation to adulthood)	Realistic Sequential Exposures vs. Laboratory Controlled Acute Exposure	Little data available	**NO**

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