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Patricia L. Bishop, Vicki L. Dellarco & Douglas C. Wolf

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REVIEW ARTICLE



Is the 90-day dog study necessary for pesticide toxicity testing?

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ABSTRACT

When registering a new pesticide, 90-day oral toxicity studies performed with both rodent and non-rodent species, typically rats and dogs, are part of a standard battery of animal tests required in most countries for human health risk assessment (RA). This analysis set out to determine the need for the 90-day dog study in RA by reviewing data from 195 pesticides evaluated by the US Environmental Protection Agency (USEPA) from 1998 through 2021. The dog study was used in RA for only 42 pesticides, mostly to set the point of departure (POD) for shorter-term non-dietary pesticide exposures. Dog no-observed-adverse-effect-levels (NOAELs) were lower than rat NOAELs in 90-day studies for 36 of the above 42 pesticides, suggesting that the dog was the more sensitive species. However, lower NOAELs may not necessarily correspond to greater sensitivity as factors such as dose spacing and/or allometric scaling need to be considered. Normalizing doses between rats and dogs explained the lower NOAELs in 22/36 pesticides, indicating that in those cases the dog was not more sensitive, and the comparable rat study could have been used instead for RA. For five of the remaining pesticides, other studies of appropriate duration besides the 90-day rat study were available that would have offered a similar level of protection if used to set PODs. In only nine cases could no alternative be found in the pesticide's database to use in place of the 90-day dog study for setting safe exposure levels or to identify unique hazards. The present analysis demonstrates that for most pesticide risk determinations the 90-day dog study provided no benefit beyond the rat or other available data.

Abbreviations: AI: active ingredient; ALS: acetolactate synthase; BW: body weight; HED: human equivalent dose; LOAEL: lowest observed adverse effect level; LOC: level of concern; MOE: margin of exposure; NLN: next lowest NOAEL; NOAEL: no observed adverse effect level; PAD: population adjusted dose; PBPK: physiologically-based pharmacokinetic; POD: point of departure; RA: risk assessment; RfD: reference dose

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Introduction

The use of the dog in pesticide testing

Pesticides are one of the most stringently regulated substances in commerce and must undergo substantial toxicological and exposure testing before being brought to market. The United States Environmental Protection Agency (USEPA) performs a scientific, legal, and administrative registration process (USEPA 2023) that considers how the chemical will be used and associated potential health risks to humans under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §301 et seq. 1938), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. §136 et seq. 1996), and the Food Quality Protection Act (H.R.1627 1996), as well as the benefits under FIFRA. When registering a new pesticide active ingredient (AI), companies are required to provide a toxicological data package on a wide range of potential adverse health outcomes, routes of exposure, exposure durations, species, and life stages. These studies are designed to identify potential hazards and provide a basis for determining potential risks to humans. In the US the standard data requirements are codified in 40 Code of Federal Regulations (CFR) Part 158 (<https://www.ecfr.gov/current/title-40/chapter-I/subchapter-E/part-158>) and in comparable legislation for most other countries that authorize and register pesticides. FIFRA provides the USEPA with flexibility to require, or not require, data and information for the purposes of making regulatory decisions for pesticides (USEPA 2013a). This flexibility is important to reflect evolving program needs and advances in science. Additionally, the USEPA can waive animal study requirements for pesticide risk assessments if it determines that there are sufficient data from alternate sources to adequately inform a regulatory decision under the applicable statutory standard. In fact, the USEPA reported granting nearly 1,000 waivers for pesticide toxicity testing between 2012 and 2018, saving over 200,000 animals, \$300 million in study costs, and \$600 million in study review costs (Craig et al. 2019).

Pesticide toxicity testing is typically carried out on rodents (rats and mice) and non-rodents (dogs and rabbits). Repeat-dose testing in species additional to the rat is done to cover the possibility that the rat may not be the most sensitive species to systemic chemical effects (Doe et al. 2006). Similarly, developmental toxicity testing is often performed with both the rat and rabbit to compare effects in the rodent and non-rodent species. Thus, a second species phylogenetically removed from the rat is traditionally thought to increase the likelihood that at least one species will be as or more sensitive or susceptible as humans.

This concept of testing on multiple species and the use of dogs as a standard laboratory animal was first introduced in the 1940s with a publication describing procedures for evaluating the toxicity of chemicals in food (Lehman et al. 1949). Based on further work by Lehman et al. (1955), a multi-species testing paradigm (rats, mice, dogs and rabbits) was adopted in 1965 by the United States Food and Drug Administration (FDA) to ensure the identification of any drug-induced effects not observed in rodents. By 1982, the USEPA had formalized health effects guidelines for testing chemical

substances that called for subchronic and chronic testing in rodent and non-rodent species, usually rats and dogs (USEPA 1982). These principles are still applied today, for example, in the toxicity test guidance issued by the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Organization for Economic Cooperation and Development (OECD), respectively, for pharmaceuticals and chemicals, including pesticides.

Subchronic 90-day oral toxicity studies performed on both rats and a non-rodent species, usually dogs, are standard data requirements for pesticide registration in the US (40 CFR Part 158), and other countries such as the European Union (EU) (European Commission 2013), Japan (MAFF 2019), and Australia (APVMA 2014). The guideline study in non-rodents, OPPTS 870.3150 (USEPA 1998a) and OECD No. 409 (OECD 1998), is designed to permit the determination of a no-observed-adverse-effect-level (NOAEL) and a lowest-observed-adverse-effect-level (LOAEL) and describe the toxic effects associated with repeated oral exposure to a test substance. The study requires a minimum of 32 dogs consisting of four/-sex/dose with a control and usually three treatment doses at a low, mid-, and high-level. Often, additional dogs are used prior to performing the final study that is submitted to the regulatory agency as part of the pesticide data package: for example, two dogs, one/sex, to determine the high dose, and another 24 dogs, three/sex/dose to confirm appropriate dose setting and identify specific effects and target organs in a separate 28-day study, information from which is used to improve the design of the final guideline study. Thus, for a typical investigational new pesticide AI, 58 or more dogs are used by the completion of the testing program.

The design of using four dogs of each sex per exposure group in the subchronic study has not changed since it was first described more than 70 years ago. At that time, there was no discussion regarding how this number of dogs was determined to be adequate other than to state that “For a second species, four dogs usually suffice...” (Lehman et al. 1949). The current OECD and USEPA test guidelines still require four dogs/sex/dose group without any further explanation on the source of the number of animals used or the associated statistical power to determine the effects of treatment.

Historically, most pesticide regulatory authorities required both subchronic 90-day and chronic 1-year oral studies in dogs. The 1-year study (USEPA 1998b; OECD 2018a) is no longer a core test for new pesticide AI approval in most major markets. Multiple retrospective analyses comparing the results of the two studies found that additional exposure time did not materially change any risk-based conclusions that could have been determined from the 90-day study and, thus, there was no added benefit to human health protection by performing the 1-year study (Spielmann and Gerbracht 2001; Box and Spielmann 2005; Doe et al. 2006; Dellarco et al. 2010; Kobel et al. 2010; Kobel et al. 2014; Linke et al. 2017; Ono et al. 2018).

Pesticide safety evaluation process

Using the toxicological data from various animal tests and estimated exposures based on pesticide use patterns, the

USEPA conducts dietary, occupational, residential, and aggregate exposure assessments, as needed, to determine potential risks to human health (USEPA 2023b). Target organ effects and doses at which these occur form the basis of the hazard assessment. The lowest doses that correspond to a NOAEL in the repeat-dose studies are typically used to set the point of departure (POD) on the dose-response curve. Doses below the POD would be considered to carry little appreciable risk for adverse effects based on use patterns for the pesticide. The USEPA assesses non-dietary incidental and occupational exposure risks to humans by comparing the margin of exposure (MOE), defined as the ratio of a substance's NOAEL to its estimated human exposure dose (USEPA 2012a), to a level of concern (LOC), usually equal to 100. The LOC is typically calculated by multiplying two uncertainty factors (UFs) of 10X, to account for experimental animal-to-human differences (i.e. the interspecies UF) and interhuman variation (i.e. the intraspecies UF). The LOC may be higher if more UFs are employed to address database issues such as lack of a critical study, use of a LOAEL instead of a NOAEL, residual concerns for the susceptibility of children, and study design/conduct issues. The use of UFs is intended to account for the potential for underestimating risk and to allow for a sufficient margin of safety. While the USEPA generally considers MOEs greater than the LOC to indicate a safe human exposure level, the closer the MOE is to the LOC, the greater the concern for potential risk. For dietary RA, the reference dose (RfD) is usually calculated by dividing the NOAELs selected as the respective PODs for chronic and acute exposures by the product of the UFs (usually 100X). Estimated dietary exposures of various population subgroups are then compared to the RfD to determine the level of risk and are expressed as a %PAD, which is the population-adjusted dose (PAD) divided by the RfD times 100. A %PAD below 100 is usually considered safe.

The animal study NOAEL selected as the POD in various exposure scenarios is usually the lowest one from the available rodent and non-rodent studies of appropriate duration, i.e. acute, subchronic, and chronic, and is typically considered to identify the most sensitive species under those exposure conditions. However, when comparing NOAELs from a dog and a rat 90-day study, for example, differences in the dosing regimens of the two studies are generally not taken into account. Nor are allometric principles generally applied when regulatory agencies select PODs. Both the USEPA (2006) and Health Canada's Pest Management Regulatory Agency (Linke et al. 2017) have noted that observed lower NOAELs in dogs do not necessarily indicate greater sensitivity because differences in physiological processes have not been accounted for by dose normalization (i.e. allometric scaling). Larger species tend to show effects at lower doses of the same substance than smaller species, indicating that an isometrically-scaled, external dose does not sufficiently correct for body size when comparing doses in different species (Boxenbaum, 1982; Dourson and Stara 1983; Davidson et al. 1986; Bokkers and Slob, 2007). However, when allometrically scaling the dose to metabolic rate, which adjusts for the internal dose, assuming that internal dose is proportional to metabolic rate, species of different sizes tend to be equally sensitive, on

average, for a large number of substances (Bokkers and Slob, 2007). Once the "equipotent doses" have been established, quantitative changes in the endpoint can be compared to determine if there are true differences in sensitivity among species.

Body weight scaling in mammals based on metabolic rate or caloric demand has been accepted to follow the general allometric relationships between body weight and physiological and biological processes, as related to kinetics, described by Kleiber (1932, 1947, 1961). This is expressed as body weight to the $3/4$ power, i.e. $BW^{3/4}$ based on absolute intake; dose rates may be scaled using the inverse of $BW^{3/4}$ or $BW^{-1/4}$. The USEPA recommends the use of $BW^{3/4}$ as a general default procedure, in the absence of measured toxicokinetic data, to extrapolate toxicologically equivalent doses of orally administered substances among animals of differing sizes and from animals to humans when deriving human equivalent (HE) doses based on animal studies (USEPA, 2011).

Are standard batteries of animal tests needed?

The dog has been used as a model in studies on human diseases, in preclinical drug testing, and in radiation research (e.g. Tsai et al. 2007, Switonski 2014, Parkinson and Grasso 1993, Bailey et al. 2013, Bolman in press, McClellan 2023). The current trend in chemical testing, however, is to reduce the unnecessary use of animals in research and regulatory testing whenever possible. Various groups have continued to assess the usefulness and variability of whole animal studies in chemical safety evaluation (e.g. Karmaus et al. 2022; NAS 2022), including for pesticide AIs. A recent retrospective examination of pesticide toxicological data submitted to the USEPA for the avian acute oral test (USEPA 2012b) versus the subacute avian dietary test (USEPA 2012c) showed that the dietary test, despite being a standard required study for pesticide ecological RA, was not used 99% of the time (Hilton et al. 2019), and, subsequently, the USEPA issued guidance for waiving it (USEPA 2020a). The USEPA determined that the acute dermal toxicity test in rats (USEPA 1998c), another standard test requirement in pesticide safety assessment, was rarely used for classification and labeling, and followed with guidance to waive the dermal test for both formulations (USEPA 2016a) and AIs (USEPA 2020b). Even the requirement to routinely perform the traditional rat and mouse chronic and cancer bioassays for pesticide assessment is being questioned with the recent publication of a weight-of-evidence approach that would enable the waiving of this study (Hilton et al. 2022). In the pharmaceutical arena, the necessity for conducting standard tests was examined recently by Prior et al. (2020) to determine if opportunities exist for reducing from a two (rodent and non-rodent) to a one-species paradigm during drug development. Their retrospective analysis of 172 drug candidates found that, in hindsight, there were a number of cases where, after shorter-term studies with two species, longer-term studies could have used only one species with little impact on human safety, although there were several caveats to this finding. Thus, as more critical review takes place and more information

becomes available, there appears to be an opportunity to move away from a standard battery of animal tests in multiple species and still be protective using fewer animals.

Considering these past findings, ascertaining whether the 90-day dog study is being performed for pesticide evaluation when it may not always be needed to adequately address hazard identification and human safety and risk, would be consistent with past retrospective analyses as well as the USEPA's goals to reduce animal use in the future (USEPA 2021a). Thus, the present analysis seeks to assess the dog study in the context of the USEPA pesticide toxicological evaluation program used to set regulatory exposure standards. This was approached by conducting a comparative analysis of dog and rodent pesticide toxicological data and identifying those cases where the dog study was an essential driver for RA.

Methods

Pesticide dataset

The most recent versions of human health RAs were obtained from public sources (<https://www.regulations.gov/>) for 195 pesticides registered in the US or evaluated for import tolerances by the USEPA Office of Pesticide Programs between 1998 and 2021 as listed in Appendix A alphabetically with Chemical Abstract Service (CAS) numbers. Of the initial 195, 38 pesticides were removed from the comparative analysis because either there was an incomplete toxicological dataset for species comparison (e.g. dog study missing, dosing regimens not given) or the test substance was not toxic to any species. This left 157 pesticides for which both 90-day dog and rat studies were available and there were measurable toxicological effects for comparison (Table 1). Many were new AI registrations, but several were re-registrations of older pesticides. All major categories of pesticides regulated by the USEPA under FIFRA, i.e. fungicides, herbicides, insecticides/acaricides, nematocides, and plant and insect growth regulators, were represented. Pesticide chemical class was determined using the information in the RAs and the online Compendium of Pesticide Common Names (BCPC 2022). Chemical structures of pesticides included in this analysis may be viewed at the USEPA CompTox Chemicals Dashboard (<https://comptox.epa.gov/dashboard/>). Modes of action are listed for fungicides at the Fungicide Resistance Action Committee website (<https://www.frac.info/fungicide-resistance-management/by-frac-mode-of-action-group>), for herbicides at the Herbicide Resistance Action Committee website (<https://hracglobal.com/tools/hrac-mode-of-action-classification-2022-map>), and for insecticides at the Insecticide Resistance Action Committee website (<https://irac-online.org/mode-of-action/classification-online/>).

The scenarios for which risks were assessed and the dog study was relevant to include non-dietary pesticide exposures through oral, dermal and inhalation routes, such as *via* spray drift, residential application, incidental hand-to-mouth contact, and occupational handling and application, of a length approximating the subchronic study duration, i.e. 1–30 days (short-term) and 1–6 months (intermediate-term). Depending on how the pesticide is used and the observed toxicities *via*

different exposure routes, not all exposure routes may be assessed for that particular pesticide. For example, if there was no observed dermal toxicity, then only oral/inhalation exposures would be evaluated in the RA. Chronic and acute dietary exposures *via* the oral route were also included in the assessment of dog study use.

Information was collected from the RAs and placed in a spreadsheet including: 1) chemical class and pesticidal mode of action; 2) dosing regimens, NOAELs/LOAELs, and toxicological effects summaries for the 90-day dog and rat studies; 3) the animal test(s) used in RA; and 4) in cases where the dog was used in RA, other available NOAELs/LOAELs and effects from tests of similar duration to the dog study. The pesticides for which the 90-day dog NOAEL was lower than the 90-day rat NOAEL and the pesticides for which the dog study was used in RA were also identified.

Analysis approach

In order to determine whether observed lower NOAELs in dogs to some pesticides were representative of greater species sensitivity, two approaches were used. First, dosing regimens for the 90-day dog and rat studies were compared to see if dose spacing influenced the selection of lower NOAELs in dogs rather than rats. An example of dose spacing that could account for an observed lower NOAEL in dogs is shown below for the fungicide isofetamid (USEPA 2014) – NOAELs for each study are bolded, while LOAELs are italicized. Due to large gaps between doses, the true NOAEL of either species may not be confidently captured and could be considerably higher, with the dog not necessarily being the lower of the two.

Dog doses (mg/kg) : 0, 3.0, **29**, 301

Rat doses (mg/kg) : 0, 6.7, **69**, 637

The second approach employed allometric scaling to assess observed lower dog NOAELs. In the absence of any substance- or species-specific mechanistic or ADME data, allometric scaling in mammals based on metabolic rate or caloric demand is considered an appropriate default method for estimating interspecies differences in internal exposures of treatment substances. Extrapolation using allometric scaling generally assumes that the parent compound is the toxic agent and that detoxification is related to the metabolic rate and, thus, controls the tissue level (ECETOC 2003).

Allometric scaling was used to predict equivalent 90-day dog NOAELs from 90-day rat NOAELs using the formula below based on USEPA (2011):

$$\begin{aligned} \text{Predicted NOAEL}_{\text{dog}}(\text{mg/kg}) \\ = (\text{BW}_{\text{rat}} \times \text{NOAEL}_{\text{rat}}[\text{mg/kg}]) \times \text{BW}_{\text{SF}}/\text{BW}_{\text{dog}} \end{aligned} \quad (1)$$

where $\text{BW}_{\text{rat}} = 0.25 \text{ kg}$, $\text{BW}_{\text{dog}} = 12 \text{ kg}$, and

$$\begin{aligned} \text{Body weight scaling factor } (\text{BW}_{\text{SF}}) &= (\text{BW}_{\text{dog}}/\text{BW}_{\text{rat}})^{3/4} \\ &= 18.2 \end{aligned} \quad (2)$$

A ratio of predicted/reported dog NOAELs of 1.0 would indicate equal sensitivity of the dog and rat to the treatment

Table 1. Pesticides included in the analysis and their chemical classes based on BCPC (2022).

FUNGICIDES		
<ul style="list-style-type: none">Amides<ul style="list-style-type: none"><i>Benalaxyl-M</i>Anilides<ul style="list-style-type: none"><i>Fenhexamid</i>Benzamides<ul style="list-style-type: none">FluopicolideFluopyramCinnamamide oximes<ul style="list-style-type: none"><i>Dimethomorph</i>Cyanoacetamide oximes<ul style="list-style-type: none"><i>Cymoxanil</i>Mandelamides<ul style="list-style-type: none">MandipropamidPhenylacetamide oximes<ul style="list-style-type: none"><i>Cyflufenamid</i>Phenylxoethy thiophenacetamides<ul style="list-style-type: none"><i>Isofetamid</i>Pyrazole carboxamides<ul style="list-style-type: none">BenzovindiflupyrBixafenFluindapyrFluxapyroxadInpyrfluxam<i>Isopirazam</i><i>Penflufen</i>PenthiopyradPydiflumetofenSedaxanePyridinecarboxamides<ul style="list-style-type: none"><i>Boscalid</i>FenpicoxamidSulfamides<ul style="list-style-type: none">TolyfluanidThiadiazolecarboxamides<ul style="list-style-type: none"><i>Isotianil</i>Thiazolecarboxamides<ul style="list-style-type: none"><i>Ethaboxam</i>Valinamidedecarbamates<ul style="list-style-type: none">Benthiavalicarb<i>Iprovalicarb</i><i>Valifenalate</i>Aminopyrazolinones<ul style="list-style-type: none"><i>Fenpyrazamine</i>Antibiotics<ul style="list-style-type: none"><i>Kasugamycin</i>Aryl phenyl ketones<ul style="list-style-type: none">MetrafenonePyriofenoneAzoles<ul style="list-style-type: none">Triazoles<ul style="list-style-type: none"><i>Bromuconazole</i>Epoxiconazole<i>Flutriafol</i><i>Ipconazole</i><i>Mefentrifluconazole</i><i>Metconazole</i>Triazolinthiones<ul style="list-style-type: none"><i>Prothioconazole</i>Carbamates<ul style="list-style-type: none">DiethofencarbCyanoimidazoles<ul style="list-style-type: none">CyazofamidDinitroanilines<ul style="list-style-type: none">FluazinamDinitrophenols<ul style="list-style-type: none"><i>Meptyldinocap</i>	<ul style="list-style-type: none">Imidazolines<ul style="list-style-type: none">FenamidonMorpholines<ul style="list-style-type: none">FenpropimorphOxazolidinediones<ul style="list-style-type: none"><i>Famoxadone</i>Pyrimidines<ul style="list-style-type: none">Anilinoypyrimidines<ul style="list-style-type: none">Cyprodinil<i>Mepanipyrim</i>PyrimethanilQuinazolines<ul style="list-style-type: none">ProquinazidQuinolines<ul style="list-style-type: none">QuinoxifenQuinones<ul style="list-style-type: none"><i>Dithianon</i>Spiroketalamines<ul style="list-style-type: none">SpiroxamineStrobilurins<ul style="list-style-type: none">Azoxystrobin<i>Fluoxastrobin</i><i>Mandestrobin</i><i>Picoxystrobin</i><i>Pyraclostrobin</i>TrifloxystrobinSulfamoyltriazoles<ul style="list-style-type: none">AmisulbromTetrazolines<ul style="list-style-type: none"><i>Picarbutrazox</i>Triazolopyrimidines<ul style="list-style-type: none">Ametoctradin	
HERBICIDES		
<ul style="list-style-type: none">Amides<ul style="list-style-type: none">Chloroacetamides<ul style="list-style-type: none"><i>Dimethenamid-P</i>PethoxamidSulfonanilides<ul style="list-style-type: none"><i>Pyrimisulfan</i>Aromatic acids<ul style="list-style-type: none">Arylcarboxylic acids<ul style="list-style-type: none"><i>Diflufenzopyr</i>Benzoic acids<ul style="list-style-type: none"><i>Bispyribac-sodium</i>Benzyl ether acids<ul style="list-style-type: none">MethiozolinPyridinecarboxylic acids<ul style="list-style-type: none"><i>Aminopyralid</i><i>Halaxifen-methyl</i>Pyrimidinecarboxylic acids<ul style="list-style-type: none">AminocyclopyrachlorCyclohexene oximes<ul style="list-style-type: none"><i>Tepraloxydim</i><i>Tralkoxydim</i>Isoxazolines<ul style="list-style-type: none"><i>Pyroxasulfone</i>N-phenylimides<ul style="list-style-type: none">Butafenacil<i>Flufenpyr-ethyl</i><i>Flumioxazin</i>FluthiacetSaflufenacilTiafenacil<i>Trifludimoxazin</i>N-phenyltriazolinones<ul style="list-style-type: none"><i>Azafenidin</i><i>Carfentrazone-ethyl</i>Sulfentrazone	<ul style="list-style-type: none">Oxyacetamides<ul style="list-style-type: none">FlufenacetPhenoxys<ul style="list-style-type: none">Aryloxyphenoxypropionics<ul style="list-style-type: none"><i>Clodinafop-propargyl</i><i>Cyhalofop-butyl</i>Pyrazoles<ul style="list-style-type: none">Benzoylpyrazoles<ul style="list-style-type: none">PyrasulfatoleTolpyralateTopramezonePhenylpyrazoles<ul style="list-style-type: none">Pyraflufen-ethylPhenylpryrazolines<ul style="list-style-type: none"><i>Pinoxaden</i>Pyridazines<ul style="list-style-type: none"><i>Pyridate</i>Triazines<ul style="list-style-type: none"><i>Indaziflam</i>Triazolones<ul style="list-style-type: none"><i>Amicarbazone</i>Triazolopyrimidines<ul style="list-style-type: none"><i>Diclosulam</i><i>Florasulam</i><i>Penoxsulam</i>PyroxsulamTriketones<ul style="list-style-type: none">BenzobicyclonBicyclopyroneMesotrione<i>Tembotrione</i>Ureas<ul style="list-style-type: none">Sulfonylureas<ul style="list-style-type: none"><i>Flazasulfuron</i><i>Flucarbazone-sodium</i>	<ul style="list-style-type: none"><i>Iodosulfuron-methyl sodium</i><i>Mesosulfuron-methyl</i><i>Orthosulfamuron</i>Propoxycarbazone<i>Sulfosulfuron</i><i>Thiencarbazone-methyl</i><i>Trifloxysulfuron-sodium</i>

(Continued)

Table 1. Continued.

INSECTICIDES/GROWTH REGULATORS and ACARICIDES		NEMATOCIDES
<ul style="list-style-type: none"> Amidines <ul style="list-style-type: none"> Demiditraz Benzoylureas <ul style="list-style-type: none"> Flufenoxuron Teflubenzuron Dicyclhydrazines <ul style="list-style-type: none"> Methoxyfenozide Diamides <ul style="list-style-type: none"> Cyantranilprole Flubendiamide Tetranilprole Hydrazides <ul style="list-style-type: none"> Bifenazate Macrocyclic latones <ul style="list-style-type: none"> Avermectins Emamectin benzoate Spinosyns <ul style="list-style-type: none"> Spinetoram/Spinosad Meta-diamides <ul style="list-style-type: none"> Broflanilide Neonicotinoids <ul style="list-style-type: none"> Butenolides <ul style="list-style-type: none"> Flupyradifurone Cyano imidamides <ul style="list-style-type: none"> Acetamiprid Thiacloprid Mesoionics <ul style="list-style-type: none"> Triflumezopyrim Nitroguanidines <ul style="list-style-type: none"> Clothianidin Dinotefuran Thiamethoxam Sulfoximines <ul style="list-style-type: none"> Sulfoxaflor 	<ul style="list-style-type: none"> Oxadiazines <ul style="list-style-type: none"> Indoxacarb Pyrazoles <ul style="list-style-type: none"> Ethiprole Tebufenpyrad Tolfenpyrad Pyrethroids <ul style="list-style-type: none"> Alpha-cypermethrin Metofluthrin Momfluorothrin Pyridine azomethines <ul style="list-style-type: none"> Pymetrozine Pyrifluquinazon Pyropenes <ul style="list-style-type: none"> Afidopyropen Quinazolines <ul style="list-style-type: none"> Fenazaquin Quinones <ul style="list-style-type: none"> Acequinocyl Tetramic acids <ul style="list-style-type: none"> Spirotetramat Tetronic acids <ul style="list-style-type: none"> Spirodiclofen Spiromesifen Unclassified <ul style="list-style-type: none"> Buprofezin Etoxazole Fenpyroximate Flonicamid Pyridalyl 	<ul style="list-style-type: none"> Fluroalkenyls <ul style="list-style-type: none"> <i>Fluensulfone</i> Organophosphates <ul style="list-style-type: none"> Fosthiazate Unclassified <ul style="list-style-type: none"> Tioxazafen <hr/> <p>PLANT GROWTH ACTIVATORS/GROWTH REGULATORS</p> <hr/> <ul style="list-style-type: none"> Benzothiadiazoles <ul style="list-style-type: none"> <i>Acibenzolar-s-methyl</i> Unclassified <ul style="list-style-type: none"> Ecolyst (PT807-HCl) <i>Forchlorfenuron</i> Prohexadione calcium

Pesticides in italics are ones for which the 90-day dog study NOAEL was lower than the 90-day rat study NOAEL. Pesticides in bold were ones for which the 90-day dog study was used in risk assessment.

substance, while a ratio of <1.0 would indicate the rat had greater sensitivity. Applying the same criteria as Kobel et al. (2010, 2014), who compared NOAELs of the 90-day dog study to those of the 1-year dog study as part of analyses that provided evidence for eliminating the 1-year test, the NOAELs of predicted dog and reported dog were considered different if their ratios were greater than a factor of 2.0.

To evaluate the impact of a lack of a 90-day dog study on human health protection for those pesticides where it had been used in RA, the availability of other tests with NOAELs similar to the dog study NOAEL that could have been used instead to set the POD was established. Following a practice employed by the USEPA in several recent human health RAs reviewed in this analysis (e.g. USEPA 2019a, 2021b) to assess interspecies differences between the dog and other species, allometric scaling was performed to derive HEDs as a way to compare the dog NOAEL to the next lowest NOAEL (NLN) from these various available studies and identify which species was most sensitive. HEDs were calculated using the formula below based on USEPA (2011):

$$\text{NOAEL}_{\text{human}} (\text{mg/kg}) = (\text{BW}_{\text{sp}} \times \text{NOAEL}_{\text{sp}} [\text{mg/kg}]) \times \text{BW}_{\text{SF}} / \text{BW}_{\text{human}} \quad (3)$$

where $\text{BW}_{\text{mouse}} = 0.025 \text{ kg}$, $\text{BW}_{\text{rat}} = 0.25 \text{ kg}$, $\text{BW}_{\text{rabbit}} = 5 \text{ kg}$, $\text{BW}_{\text{dog}} = 12 \text{ kg}$, $\text{BW}_{\text{human}} = 70 \text{ kg}$, and

$$\text{BW}_{\text{SF}} = (\text{BW}_{\text{human}} / \text{BW}_{\text{mouse}})^{3/4} = 385 \quad (4)$$

$$\text{BW}_{\text{SF}} = (\text{BW}_{\text{human}} / \text{BW}_{\text{rat}})^{3/4} = 68.5 \quad (5)$$

$$\text{BW}_{\text{SF}} = (\text{BW}_{\text{human}} / \text{BW}_{\text{rabbit}})^{3/4} = 7.2 \quad (6)$$

$$\text{BW}_{\text{SF}} = (\text{BW}_{\text{human}} / \text{BW}_{\text{dog}})^{3/4} = 3.7 \quad (7)$$

In assessing impacts on the identification of potential risks without the dog study, the effects on the MOE in the context of the LOC for non-dietary incidental and occupational exposures, and on the RfD for chronic and acute dietary exposures, were determined by substituting the NLN from another available test for the dog study in those cases where it was used in RA.

Impacts on human health protection in the absence of a dog study were also assessed by determining if dogs displayed unique toxicological effects that would have been missed in tests on other species, or if effects on target organs were observed in dogs at much lower doses than in other species. Effects were defined as unique if they were observed only in dogs and the USEPA considered them potentially adverse in humans.

Results

Of the 195 pesticides registered in the US or evaluated for import tolerances by the USEPA between 1998 and 2021, 157 had sufficient data to facilitate the present comparative analysis for determining the value of the 90-day dog study in RA and management decisions. A dog study was performed for 14 of the 38 pesticides removed from the comparative analysis but not used in RA. The available information for the remaining 24 substances indicates that the dog study was not necessary because it was not part of the data package, or it was specifically waived, or the data requirement was satisfied by another test, most often the 1-year dog study.

Considering lower dog NOAELs in the context of dosing and allometric scaling

The 90-day dog NOAEL was lower than the 90-day rat NOAEL for 86/157 (55%) pesticides analyzed (Table 1). The preponderance of lower dog NOAELs were observed in six chemical classes including the triazole and strobilurin fungicides, the triazolopyrimidine and sulfonyleurea herbicides, and the diamide and neonicotinoid insecticides.

The test guidelines for the 90-day dog study and the 90-day rat study (USEPA 1998d, OECD 2018b) each call for at least three treatment dose levels, with doses spaced appropriately to produce test groups with a range of toxicological effects. While a few dog studies had four dose levels, most in this analysis had three dose levels, some with large gaps between doses. The rat studies had dose levels ranging from three to six, but most had four, with generally smaller gaps in spacing, thus, different doses were often used in the rat than in the dog. Rat and dog study NOAELs/LOAELs for the 86 pesticides where the dog NOAEL was lower than the rat are shown in Appendix B. For 28/86 pesticides, the lower NOAEL in the dog could be attributed to dose spacing and differences in the doses selected for each species making it unclear as to which species truly had the lower NOAEL; for 8/28 the dog was used in RA.

When allometric scaling using $BW^{3/4}$ was applied to 90-day rat study NOAELs to predict equipotent 90-day dog study NOAELs, 56/86 pesticides had ratios of predicted to reported dog NOAELs of 2.0 or less (Appendix C). Based on this criterion, the dog would not be considered more sensitive than the rat for these pesticides. In fact, 22 of the 56 pesticides had ratios of <1.0 , indicating that the rat was the more sensitive species, while 34 had ratios of 1.0–2.0 suggesting similar species sensitivity. For the remaining 30 pesticides, dog NOAELs were predicted by the rat NOAEL to be 2.1 or more times higher than reported dog NOAELs, potentially indicating a greater sensitivity in dogs than in rats, based on comparison of 90-day study results.

Allometric scaling alone accounted for observed lower NOAELs in dogs for 30 pesticides, either allometric scaling or dose spacing explained lower NOAELs in another 27 pesticides, and dose spacing alone accounted for lower dog NOAELs in two more pesticides. Thus, dose spacing and/or allometric body weight scaling accounted for observed lower

NOAELs in dogs in 59/86 (69%) pesticides for which the dog NOAEL was lower than the rat NOAEL in 90-day studies.

Use of the 90-day dog study and other animal tests in USEPA human health risk assessment

The 90-day dog study was used in human health RA for 42/157 (27%) pesticides examined that had a complete data-set for comparative analysis (Table 1), comprising 10 fungicides, 19 herbicides, 12 insecticides/acaricides, and one plant activator/growth regulator. In 36/42 the 90-day dog NOAEL was lower than the 90-day rat NOAEL (or the 90-day mouse NOAEL in one case when the rat study was not considered), and in 6/42 the dog NOAEL was greater than the rat NOAEL. Dose spacing and/or allometric scaling accounted for observed lower NOAELs in dogs for 22/36.

For 40/42 pesticides, the dog NOAEL was used to set PODs for non-dietary exposures through various routes in addition to chronic dietary exposures for 3/40, acute dietary exposure for 1/40, and for both chronic and acute exposures for 1/40 (Table 2). For the two remaining pesticides where a non-dietary exposure RA was not performed, the dog study was used to set the chronic dietary POD once and the acute dietary POD once. Thus, the predominant use of the dog study when it was used in RA was to set PODs for non-dietary exposures. In some cases, it was used as the only study in RA, while other times it was used co-critically with another study, or as one of multiple studies that were used for different exposure routes and durations. As an example, the dog study may have been used for short-term oral exposure, while a rat inhalation test was used for short- and intermediate-term inhalation exposures for the same pesticide.

Non-dietary RAs were performed on 135/157 pesticides evaluated in this analysis; the remaining 22 were either assessed for dietary residues on imported produce only with no residential and/or occupational exposures or, in a few cases, had minimal observed toxic effects and, thus, no quantitative RA was performed (i.e. no MOEs calculated). A total of 201 subchronic and chronic animal tests were used in assessing oral, dermal, and inhalation risks from non-dietary exposures for the 135 pesticides, with different tests used for different exposure routes for some pesticides. While the 90-day dog study accounted for 40/201, the 1-year dog study was used 9/201, and range-finding dog studies were used 4/201. Oral, dermal, and inhalation rodent studies made up 132/201, while rabbit studies accounted for 16/201. The most frequently used oral rodent studies used to set the PODs for non-dietary exposure routes were the 2-generation rat reproductive, the 90-day rat, the chronic/carcinogenicity, developmental toxicity, and developmental neurotoxicity studies.

Availability of other tests to replace the dog study in risk assessment

For the 42 pesticides where the 90-day dog study was used in RA, NOAELs from other studies of appropriate duration were also available (Table 3). In many cases, NOAELs from these other studies were comparable to or lower than the

dog NOAEL. When applying allometric scaling to the dog study NOAEL and the NLN from respective rat, mouse, or rabbit studies to convert to HEDs, the NLN was at least as health-protective or more so than the dog study for 33/42 pesticides. For the remaining 9/42, the dog continued to be the most sensitive species based on a ratio of NLN HED/Dog NOAEL HED >2.0 . Three of the nine had HEDs of the NLN study that were approximately a magnitude greater than HEDs of the dog study, i.e. fluoxastrobin, florasulam, and pyrimisulfan, while six had HEDs based on the NLN that ranged from 2.1 – 6.5 times higher.

To evaluate the impact on human health protection without the 90-day dog study in the data package, MOEs and cases of potential risk (MOEs below the LOC) were examined for the 40 pesticides where the dog study was used in non-dietary RA. For the majority of human exposure scenarios, estimated doses were very low, corresponding MOEs were very high, and there were no cases of risk concern identified. The LOCs for nearly all were 100, although two had an additional uncertainty factor of 10. When the lowest MOEs based on the dog NOAEL and NLN were compared (Table 4), there were six pesticides for which the NLN produced a much less protective MOE: fluoxastrobin, valifenalate, flucarbazone-sodium, iodosulfuron-methyl sodium, pyrimisulfan, and sulfosulfuron although of these only fluoxastrobin had cases of potential risk identified in the RA. Without the dog study, MOEs based on the NLN would have remained above the LOC and missed potential non-dietary risks identified by the dog study for fluoxastrobin in nine exposure scenarios under baseline conditions, i.e. personal protective equipment (PPE) of a long-sleeve shirt, long pants, shoes, and socks without gloves or respirator. An additional pesticide, emamectin benzoate, had one case of risk missed without the dog study, also under baseline conditions, but HEDs of the dog NOAEL and NLN were comparable (Table 3), indicating that the dog was not more sensitive than the rat. For the other five pesticides with identified risk concerns (dimethomorph, dimethenamid-P, thienicarbazone-methyl, flupyradifurone, and spinetoram/spinosad) using the NLN from another study in place of the dog study would have addressed some or all the risks.

RfDs based on the dog study were compared to RfDs based on the NLN from other available studies of appropriate exposure route/duration to assess the impact of a lack of a dog study where it was used in acute and chronic dietary risk assessment (Table 5). Fold differences in RfDs ranged from 1.8 to 12 using an alternate study in place of the dog.

However, if RfDs were compared using HEDs of respective dog and NLN study NOAELs, fold differences were reduced and for only three pesticides, pyrimisulfan, meptyldinocap, and flucarbazone-sodium, did fold differences remain >2.0 . The dog study was used in acute dietary RA for isopyrazam based on transient neurotoxic effects in one dog that were not seen in a second 90-day dog study, the 1-year dog study, or the acute or subchronic neurotoxicity rat studies. The USEPA noted the uncertainty in the neurotoxic effects of isopyrazam and considered the endpoint to be conservative and acute dietary risks were not of concern as the aPAD for all populations was $<5\%$ (USEPA 2013b).

When the 90-day dog study was most relevant for RA

There were no cases of insecticides/acaricides where the dog appeared necessary for RA. Lack of reports of unique or more severe effects in the dog than in other species, effects of dose spacing (Appendix B), and HEDs of dog NOAELs that were all comparable to or greater than HEDs of NLNs (Table 3) suggest that use of rodent data provided an equal or more protective POD for these types of agrochemicals and data from the dog study did not benefit the RA.

For four fungicides and five herbicides (Table 6), however, the 90-day dog study was used in RA and neither dose spacing nor allometric scaling could account for lower NOAELs in the dog compared to NOAELs from the 90-day rat, nor were there other available studies with comparable NOAELs after converting to HEDs. Dog NOAELs for 8/9 pesticides were $<10\text{ mg/kg}$ suggesting that dogs were particularly sensitive to these substances. The ratio of HEDs based on the dog NOAEL and the NLN ranged from just over 2-fold to almost 10-fold greater, illustrating the greater sensitivity of the dog compared to the rodent or rabbit. The results for these nine pesticides are presented in detail as follows.

Famoxadone

Many of the effects of this oxazolidinedione fungicide were seen across species, including reduced body weight, body weight gains, and food consumption, anemia, spleen effects, and hepatotoxicity (USEPA 2020c). Myotonic twitches were seen only in the 90-day dog study at the highest dose of 23 mg/kg beginning on day 21, and the mid-dose of 10 mg/kg was used as the POD for short-term non-dietary oral and dermal exposures (these effects were not seen in the 1-year dog study). The NLN of 11 mg/kg from the rat reproductive study

Table 2. Exposure scenarios for which the 90-day dog study was used to set the POD in risk assessment, either alone, co-critically with another study, or in situations where different studies were used for different exposure routes (oral, dermal, inhalation) and/or durations (short-term, intermediate-term).

Studies Used	Exposure Scenarios for which 90-day Dog Study Used to Set the POD					
	Non-dietary only	Non-dietary + chronic dietary	Non-dietary + acute dietary	Non-dietary + chronic and acute dietary	Chronic dietary only	Acute dietary only
90-day dog study alone	19	1	2	1	1	1
90-day dog study co-critical with another study	3	1				
90-day dog with other studies for different exposure routes/durations	12	1				
Total	34	3	2	1	1	1

Table 3. Availability of other studies in lieu of the 90-day dog study for the 42 pesticides where the dog study was used in risk assessment.

Pesticide	Dog NOAEL	NLN	HED of Dog NOAEL	HED of NLN	HED NLN /HED Dog NOAEL
Fungicides					
Cyflufenamid ^a	23	20	15	4.9	0.3
		90-day rat			
Dimethomorph	15	21	9.5	5.1	0.5
		Rat repro (P)			
Famoxadone ^b	1.4 (IT)	11	0.90	2.8	3.1
	10 (ST)	Rat Repro (P)	6.3	2.8	0.4
Fluoxastrobin	3.0	70	1.9	17	9.0
		90-day rat			
Isopyrazam	30	8.9	19	2.2	0.1
		Rat repro (P)			
Kasugamycin	11	10	6.7	5.1	0.8
(co-critical with rabbit dev tox)		Rabbit dev tox (M)			
Meptyldinocap ^c	1.5	12	1.0	6.2	6.5
		Rabbit dev tox (M)			
Penflufen	56	64	35	16	0.4
		Rat repro (P)			
Pyraclostrobin	5.8	5.0	3.7	1.3	0.3
		Rabbit dev tox (M)			
Valifenalate	50	277	32	68	2.1
		Rat repro (P)			
Herbicides					
Amicarbazone	6.3	5.0	4.0	2.6	0.6
		Rabbit dev tox (M)			
Bispyribac-sodium	100	72	63	9.4	0.1
		90-day rat			
Carfentrazone-ethyl	50	75	32	18	0.6
		28-day rat			
Diclosulam	25	10	16	5.1	0.3
		Rabbit dev tox (M)			
Diflufenzopyr	58	100	37	51	1.4
		Rabbit dev tox (M)			
Dimethenamid-P ^d	10	34	6.3	8.3	1.3
		90-day rat			
Flazasulfuron	2.0	12	1.3	2.9	2.3
		90-day rat			
Florasulam	5.0	100	3.2	25	7.7
		90-day rat			
Flucarbazone-sodium ^e	7.4	74	4.7	18	3.9
		90-day rat			
Indaziflam	7.5	14	4.8	7.2	1.5
		90-day rat			
Iodosulfuron-methyl sodium	8.1	67	5.1	16	3.2
		90-day rat			
Penoxsulam	18	25	11	13	1.1
		Rabbit dev tox (M)			
Pyridate ^f	20	63	13	15	1.2
		90-day rat			
Pyrimisulfan	10	120	6.3	62	9.7
		Rabbit dev tox (M)			
Pyroxasulfone	2.0	7.2	1.3	1.8	1.4
		Rat repro (P)			
Sulfosulfuron	100	313	63	77	1.2
		Rat repro (P)			
Tembotrione	27	64	17	8.8	0.5
		90-day mouse			
Thiencarbazone-methyl	159	123	101	30	0.3
		90-day rat			
Trifludimoxazin ^e	15	6.4	9.5	1.6	0.2
		EOGRTS (P)			
Insecticides/Acaricides					
Bifenazate	0.90	1.6	0.57	0.39	0.7
		Rat repro (P)			
Cytraniliprole	3.0	1.4	1.9	0.34	0.2
		Rat repro (P)			
Emamectin benzoate	0.25	0.60	0.16	0.15	0.9
		Rat repro (P)			
Fenazaquin	5.0	9.6	3.2	2.3	0.7
		90-day rat			
Fenpyroximate	2.0	1.5	1.3	0.37	0.3
		90-day rat			
Flubendiamide	2.6	3.3	1.6	0.81	0.5
		Rat repro (P)			

(continued)

Table 3. Continued.

Pesticide	Dog NOAEL	NLN	HED of Dog NOAEL	HED of NLN	HED NLN /HED Dog NOAEL
Flupyradifurone (co-critical with rat repro)	12	7.7 Rat repro (O)	7.6	1.9	0.2
Spinetoram/spinosad	4.9	7.5 90-day mouse	3.1	1.0	0.3
Spirodiclofen	7.7	15 90-day mouse	4.9	2.1	0.4
Spirotetramat	32	40 Rabbit dev tox (M)	20	21	1.0
Tebufenpyrad	2.0	6.8 90-day rat	1.3	1.7	1.3
Triflumezopyrim ⁹	56	64 90-day rat	17	16	0.9
Plant Growth Regulators/Activators					
Prohexadione calcium	80	40 Rabbit dev tox (M)	51	21	0.4

Allometric scaling was applied to estimate the human equivalent doses (HEDs) derived from the dog NOAEL and the next lowest NOAEL (NLN) and when ratios were ≤ 2 the dog was not considered more sensitive. Pesticides in bold were ones for which the dog continued to be the most sensitive species after allometric scaling. All NOAELs in mg/kg.

^aA second dog study was listed in the toxicological data package with a NOAEL of 45 mg/kg (USEPA 2022), suggesting the value of 23 mg/kg used in risk assessment was an artifact of dose spacing.

^bShort-term (ST) oral and dermal risk assessments (1 – 30 days) used the NOAEL of 10 from the 90-day dog study based on myotonic twitches that occurred within 21 days of dosing. Intermediate-term oral and dermal assessments (1 – 6 months) used the NOAEL of 1.4 based on lens cataracts occurring with 2–3 months of dosing (USEPA 2020c). There was no comparable NOAEL for the IT NOAEL used.

^cThe subchronic 90-day dog study was used for chronic dietary exposure RA, however, there were no long duration studies more appropriate included in the data package for comparison as meptyldinocap was assessed for import tolerances only (USEPA 2009).

^dThe NOAEL used in the RA for dimethenamid-P of 10 mg/kg was from the 1-year dog study, while the NOAEL from the 90-day dog study was 4.7, a difference attributed by USEPA to dose spacing (USEPA 2020d).

^eNOAEL from 1-year dog study, not established in 90-day dog study.

^fWhile the NLN for pyridate was 11 mg/kg from the rat reproductive toxicity study (parental), there were no neurotoxic effects in this study as seen in 90-day studies in dogs and rats, and upon which the RA was based (USEPA 2019b). Therefore, the 90-day rat study with a NOAEL of 63 mg/kg was used as the NLN.

⁹The NOAEL of 56 mg/kg from 1-year dog study was used in the risk assessment because the NOAEL of 27 mg/kg reported for the 90-day dog study was considered by USEPA to be an artifact of dose spacing (USEPA 2017b).

Key

Dev tox (P): Parental effects in the rat developmental toxicity test

Dev tox (M): Maternal effects in the rabbit developmental toxicity test

Repro (P): Parental effects in the rat 2-generation reproductive toxicity test

Repro (O): Offspring effects in the rat 2-generation reproductive toxicity test

EOGRS (P): Parental effects in the extended 1-generation reproductive toxicity test

would have been protective of this effect. Microscopic lens cataracts were observed after 2 – 3 months of treatment in both subchronic and chronic dog studies at doses of 9 – 10 mg/kg, and the NOAEL of 1.4 mg/kg was used as the POD for intermediate-term non-dietary dermal exposure. Cataract formation was not observed in any other species, including cynomolgus monkeys. If cataracts are a potential hazard of famoxadone to humans, then the dog NOAEL of 1.4 mg/kg was needed to provide human health protection, although, due to the lack of this effect in other test species, this remains unclear. However, there were no MOEs below the LOC identified in the most recent RA (USEPA 2020c) for occupational handler intermediate-term dermal exposures using this dog NOAEL, thus no potential risks would have been missed without the dog study. Risk estimates were based on the use of single-layer clothing, with chemical-resistant gloves and no respirator according to current label requirements, which would likely have remained unchanged in the absence of a dog study.

Fluoxastrobin

The USEPA considered the most sensitive toxicological effect in the database for the strobilurin fungicide fluoxastrobin to be liver cholestasis, which occurred in dogs at a 35-fold lower dose than what elicited adverse effects in other species (USEPA 2017a). There were no comparable NOAELs, even when

allometrically scaled to HEDs. Potential risks were identified under baseline PPE dermal exposure conditions with MOEs below the LOC of 100 using the dog NOAEL of 3.0 mg/kg (USEPA 2010, USEPA 2017a) that would have been missed using the NLN of 70 mg/kg from the 90-day rat study. Without the dog data, label directions may have been less conservative, i.e. not requiring gloves as is currently the case. The factors presented here would indicate that the dog was more sensitive to fluoxastrobin than other species and was needed for the RA. The dog was also used in RA for pyraclostrobin, one of five other strobilurins that were examined in this analysis, but the NOAEL/LOAEL of other species were comparable to the dog in this case and the dog HED was actually higher after allometric scaling. For the remaining strobilurins, the dog study was not used in RA because other studies provided more protective endpoints. Further investigation into what makes fluoxastrobin unique in comparison to other strobilurins regarding toxicity in dogs may provide insight on when the dog study may or may not be needed in future registrations of strobilurin AIs.

Meptyldinocap

This dinitrophenol fungicide is one of six isomers found in the pesticide dinocap, with meptyldinocap making up 22% of dinocap. The USEPA noted that the two are somewhat toxicologically different with meptyldinocap being less toxic (USEPA

Table 4. Impact on determination of potential risks from non-dietary exposure if the 90-day dog study were not available for the 40 pesticides where it was used in risk assessment and the next lowest NOAEL (NLN) were used instead.

Pesticide	LOC	Lowest MOE Using:		Cases of Risk Missed
		Dog NOAEL	NLN	
Fungicides				
Cyflufenamid	100	12,000	10,000	0 out of 4
Dimethomorph	1,000 ^a	400	553	
Famoxadone	100 (ST)	840 ^b	924	
	100 (IT)	120 ^c	943	9 out of 9
Fluoxastrobin	100	21	490	
Kasugamycin	100	58,000	53,000	
Penflufen	100	23,000	26,000	
Pyraclostrobin	100	400	340	
Valifenalate	100	2,800	15,000	
Herbicides				
Amicarbazone	100	350	358	0 out of 1 3 out of 4
Bispyribac-sodium	100	4,700	3,300	
Carfentrazone-ethyl	100	1,800	4,500	
Diclosulam	100	41,000	17,000	
Diflufenzopyr	100	5,700	10,000	
Dimethenamid-P	100	5	35	
	1000 ^a	40	132	
Flazasulfuron	100	810	3,500	
Florasulam	100	20,000	400,000	
Flucarbazone-sodium	100	700	68,000	
Indaziflam	100	100	188	
Iodosulfuron-methyl sodium	100	510	4,200	
Penoxsulam	100	1,500	2,100	
Pyridate	100	2,900	9,300	
Pyrimisulfan	100	130	1,500	
Pyroxasulfone	100	110	390	
Sulfosulfuron	100	6,300	20,000	
Tembotrione	100	30,000	70,000	
Thiencarbazone-methyl	100	97	75	0 out of 1
Trifludimoxazin ^d	—	—	—	
Insecticides				
Bifenazate	100	200	378	1 out of 1
Cytraniliprole	100	190	89	
Emamectin benzoate	100	83	205	
Fenazaquin	100	160	310	
Fenpyroximate	100	2,400	1,800	
Flubendiamide	100	1,300	1,700	
Flupyradifurone	100	58	37	0 out of 1 1 out of 2
Spinetoram/spinosad	100	23	36	
Spirodiclofen	100	3,700	7,100	
Spirotetramat	100	1,900	2,400	
Tebufenpyrad ^e	—	—	—	
Triflumezopyrim ^f	—	—	—	
Plant activators/growth regulators				
Prohexadione calcium	100	1,160	580	

The lowest MOE derived from the dog NOAEL and NLN are compared, and cases of potential risk missed using the NLN are identified. Potential risks are defined by MOE < LOC.

^aInhalation LOC has additional 10x uncertainty factor (USEPA 2016b [dimethomorph]; USEPA 2020d [dimethenamid-P]).

^bBased on NOAEL of 10 from 90-day dog study for short-term (ST, 1 – 30 days) effects.

^cBased on LOAEL of 1.4 from 90-day dog study for intermediate-term (IT, 1 – 6 months) effects.

^d90-day dog study was selected as the POD for ST incidental oral exposure in children 1–2 years old. However, no RA was conducted for this scenario as only occupational exposure was expected. Therefore, there are no MOEs to compare.

^eDog NOAEL used for IT inhalation only. No tables available showing various exposures and corresponding MOEs; therefore, unable to compare to other study NOAELs.

^fNot registered for use in U.S., so no exposures and MOEs calculated. Dog study was selected for POD should RAs be performed in the future.

Key

MOE (Margin of exposure) = NOAEL/exposure dose

LOC (Level of concern) = 10x interspecies factor X 10x intraspecies factor = 100 usually. LOCs can have additional uncertainty factors added to them as in the cases of dimethomorph and dimethenamid-P.

ST: Short-term; IT: intermediate-term

2009). One male dog out of four treated with meptyldinocap exhibited increased serum levels of liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST) at two points during the 90-day study at a LOAEL of 3.6 mg/kg (NOAEL of 1.5 mg/kg); no LOAEL was observed in females. No other effects of treatment were observed. A satellite group of dogs continued receiving treatment for a year to evaluate effects on the retina because previous studies with dinocap had shown effects on the eye. No measurements of liver effects were taken from this group, so it is unknown whether the elevated liver enzymes seen in one dog was truly an adverse effect. Rats in the 90-day study experienced body weight and food consumption decreases at the highest dose of 113 mg/kg and slight liver, kidney and thyroid effects that were considered toxicologically insignificant. The rabbit dams in the developmental toxicity study experienced body weight and food consumption decreases at 48 mg/kg (NOAEL of 12 mg/kg). The subchronic 90-day dog study was used to set the POD for chronic dietary exposures of this pesticide evaluated for import tolerances only, as no chronic studies were included in the data package. Estimates of %PAD using the dog study RfD of 0.005 (Table 5) were 35% or less at the assumed tolerance residue levels, while using the RfD of 0.040 based on the NLN would have produced the highest %PAD of 4%, suggesting a larger margin of safety than was actually the case using the dog study. Yet, due to the observation of transitory liver effects in a single male dog only and the lack of confirmatory liver effect measurements in the satellite study, the need for the dog study, in this case, remains uncertain.

Valifenalate

Liver effects were observed after subchronic exposure to this valinamidocarbamate fungicide in both the 90-day dog study at 250 mg/kg (NOAEL of 50 mg/kg) and the 2-generation reproductive rat study (parental/systemic) at 986 mg/kg (NOAEL of 277 mg/kg) (USEPA 2019c). The thyroid was also a target in the 90-day dog study. Chronic liver effects, as well as thyroid effects, were seen in the mouse carcinogenicity study at 97 mg/kg, the 1-year dog study at 250 mg/kg, and the combined chronic/carcinogenicity rat study at 1,000 mg/kg. While overall effects in the dog were not unique, they occurred at lower doses in the shorter-duration studies. However, MOEs with baseline attire (no respirator) were all quite high (range of 2,800 – 17,000,000 with an LOC = 100), indicating very low exposure rates. While MOEs using the rat NOAEL of 277 mg/kg would have produced even higher MOEs (indicating less chance of risk) the use of the pesticide would have remained safe under the evaluated label PPE requirements, which were already at the baseline level.

Flazasulfuron

Subchronic oral exposure to this sulfonylurea herbicide resulted in liver abnormalities in dogs and decreased body weight gain, slight anemia, and kidney effects in rats (USEPA 2015a). The HED of the 90-day rat NOAEL (12 mg/kg) was

Table 5. Impact on chronic and acute dietary reference doses (RfDs) if the 90-day dog study were absent from the data package and the next lowest NOEL (NLN) were used instead.

Pesticide	90-day Dog NOAEL	RfD	NLN	Alternate RfD	RfD fold difference	HED RfD fold difference
Chronic Dietary						
Pyrimisulfan	10	0.10	120	1.2	12	9.7
Flucarbazone-sodium ^a	7.4	0.07	74	0.74	10	3.9
Meptyldinocap ^b	1.5	0.005	12	0.040	8.0	6.5
Emamectin benzoate	0.25	0.0025	0.6	0.0060	2.4	0.9
Fenazaquin ^c	5.0	0.05	9.2	0.092	1.8	0.7
Acute Dietary						
Pyridate ^d	20	0.20	63	0.63	3.0	1.2
Emamectin benzoate	0.25	0.0025	0.6 ^d	0.006	2.4	0.9
Indaziflam	7.5	0.075	14	0.14	1.9	1.5
Isopropylazam ^e	30	0.30	–			

NOAELs and RfDs in mg/kg. Dog NOAELs and NLNs were converted to HEDs, with ratios ≤ 2.0 suggesting minimal impact on dietary health protection.

^aCo-critical with 1-year dog study; NOAEL from 1-year dog study used.

^bFood Quality Protection Act (1996) safety factor of 3x added to the standard 100x due to use of a short-term study for a long-term assessment. No long-term guideline studies were submitted for this pesticide as it was registered for import tolerances only (USEPA 2009).

^cCo-critical with 1-year dog study which had the same NOAEL.

^dRats exhibited signs of acute toxicity at doses about three times higher than in dogs, which the USEPA notes in the RA were approximately equivalent when allometrically scaled (USEPA 2019b).

^eNo acute test for comparison; uncertainty in neurotoxic effects seen in one dog (USEPA 2013b).

Table 6. Nine pesticides and their chemical classes for which the 90-day dog study was used in RA and neither dose spacing nor allometric scaling could account for lower NOAELs in the dog compared to NOAELs from the 90-day rat study and ratios of NLN HED to the dog HED were greater than a factor of two.

Name	Chemical class	Dog NOAEL (mg/kg)	NLN HED / Dog HED
Fungicides			
Famoxadone	Oxazolidinedione	1.4	3.1
Fluoxastrobin	Strobilurin	3.0	9.0
Meptyldinocap	Dinitrophenol	1.5	6.2
Valifenalate	Valinamidedecarboxylate	50	2.1
Herbicides			
Flazasulfuron	Sulfonylurea	2.0	2.3
Florasulam	Triazolopyrimidine	5.0	7.8
Flucarbazone-sodium	Sulfonylurea	7.4	3.8
Iodosulfuron-methyl-sodium	Sulfonylurea	8.1	3.1
Pyrimisulfan	Sulfonanilide	10	9.8

2.9 mg/kg compared to the HED of the dog NOAEL (2 mg/kg) of 1.3 mg/kg, a fold difference of 2.3. There were no MOEs of concern (LOC = 100) based on the dog NOAEL with baseline PPE, the lowest MOE being 4,800. While the use of the NLN instead would have produced even higher (less riskier) MOEs, it would not have impacted the RA by calling for less protective PPE, which was already at baseline.

Florasulam

Dog studies with the triazolopyrimidine herbicide florasulam showed liver toxicity and decreases in body weight, body weight gains, and food consumption, while rat studies showed decreases in body weight, body weight gains, and food consumption, and slight nephrotoxicity (USEPA 2021c). Effects on dogs occurred at a magnitude lower dose with a LOAEL of 50 mg/kg (NOAEL of 5 mg/kg) than that in rats with a LOAEL of 500 mg/kg (NOAEL of 100 mg/kg). The clear hazard of liver effects at the lower LOAEL would have been missed in the absence of the dog study. Estimated human exposures based on label directions were so low (highest daily dose of 0.000245 mg/kg/day, MOE of 20,000), however, that the current RA would not have been impacted without the dog study, since exposures would have to be 200 times higher for the lack of the dog study to compromise human health protection.

Flucarbazone-sodium

This sulfonylurea herbicide caused decreases in thyroid hormone T4 levels and adaptive liver effects in both the 90-day and 1-year dog studies at a LOAEL of 34 – 36 mg/kg, while rats experienced immunological effects at a LOAEL of 287 mg/kg that were subsequently determined to represent slight or moderate nonspecific toxicity rather than immunotoxicity (USEPA 2018a). Other species were largely unaffected. The dog NOAEL used was 7.4 mg/kg, while the NLN was a magnitude higher at 74 mg/kg. Lack of a dog study would have impacted the chronic dietary RA for flucarbazone-sodium (Table 5) if estimated dietary exposures were 25 – 50 times higher. For non-dietary dermal exposures, MOEs based on the dog study were all well above the LOC of 100 with baseline PPE and there were no cases of risk identified (Table 4). Using the NLN would produce much higher MOEs, but would not have impacted the required PPE, which was already at baseline.

Iodosulfuron-methyl-sodium

In dogs the target organs were the liver and the hematopoietic system, there was hepatotoxicity in the mouse, and the rat exhibited decreases in body weight/weight gain and food consumption only (USEPA 2015b) when exposed to this sulfonylurea herbicide. Effects in both the 90-day and 1-year dog studies occurred at about 50 mg/kg, while in rats, effects

were observed at about 350 mg/kg. There were no major differences between the dog and rat in ADME studies that could account for the observed greater sensitivity in dogs. Using the dog NOAEL of 8.1 mg/kg, occupational handler exposure estimates resulted in MOEs ranging from 9,500 to 1,400,000 with no risk concerns. Aggregate risk MOEs (dietary and incidental non-dietary exposures) of adults and children ranged from 510 to 1,100, the lowest still well above the LOC of 100, but the corresponding lowest MOE using the NLN from the 90-day rat study of 67 mg/kg would be 4,200, clearly less protective. The comparative HEDs from these study NOAELs differ by a factor of about three suggesting that lack of the dog study could have compromised the safety assessment of this pesticide, but only if human exposures were five or more times higher than those estimated in the RA.

Pyrimisulfan

Pyrimisulfan is a sulfonanilide registered for use as an herbicide for the control of weeds on turf grasses, with no proposed food uses, although a dietary RA was performed by the USEPA (USEPA 2018b). Observed effects on the thyroid were limited to oral studies in the dog and the dermal study in the rat. Toxicity occurred in the dog at lower doses than other species: the dog NOAEL/LOAEL was 10/50 mg/kg, compared to NOAELs ranging from 120 to about 500 mg/kg and LOAELs ranging from 500 to 1,000 mg/kg in rat and rabbit studies. The HEDs of the dog NOAEL and the NLN were 6.3 and 62 mg/kg, respectively. Residential handler exposure MOEs ranged from 1,300 to 47,000,000, while residential post-application MOEs ranged from 1,000 to 4,900,000. Occupational handler and post-application MOEs ranged from 1,300 to 270,000 under baseline PPE conditions except for applying granules by hand around foundations, which had an MOE of 130, a value close to the LOC of 100. Only a slightly higher occupational exposure rate under this scenario than what is currently estimated based on label directions could result in potential risks that would not be identified using the NLN. The dog study was also used in the chronic dietary RA, but since there were no food uses, only drinking water exposures were evaluated. Use of the NLN of 120 mg/kg resulted in an RfD an order of magnitude higher than the RfD based on the dog (Table 5), clearly less human health protective and risks could have been missed if estimated exposures were ten times higher.

Unique or lower dose effects in dogs

In addition to any described in the results of the nine pesticides presented above, there were unique effects or effects at lower doses observed in another seven pesticides where the dog was used for RA but in all cases, there were either comparable NOAELs available from other studies of appropriate duration that would have been protective or conversion to HEDs of dog NOAELs and NLNs from a rodent or rabbit study showed equal sensitivity in the species.

Other considerations regarding use of the dog

The dog study appears to have played a role in RA for a diverse group of herbicides of different chemistries known as acetolactate synthase (ALS) inhibitors, which block key enzymes responsible for normal plant growth and development. Of the 16 ALS inhibitors included in this analysis, the dog study was used to set the POD in RA for 11 substances. The five herbicides listed in Table 6 for which the dog NOAEL remained the lowest after consideration of dose spacing, allometric scaling, and comparison of dog NOAEL and NLN HEDs, were all ALS inhibitors. Target organs were commonly the liver, urinary tract, and thyroid. Further analysis to ascertain why chemicals with this mode of action elicit toxicities in the dog and whether these toxicities are relevant to humans would be useful in determining if a dog study is needed when registering a new ALS-inhibiting herbicide.

Number of dogs used in assessing 195 pesticides

A 90-day dog study was submitted to the USEPA for each of the 157 pesticides included in the comparative analysis as well as for 11/38 pesticides that were not included for a total of 168 pesticides having dog studies. Applying the conservative estimate of approximately 58 dogs per pesticide used for various preliminary studies and in the formal submitted guideline study results in a potential of 9,744 dogs used for evaluating 168 pesticides. The 42/168 cases for which the USEPA selected the dog study to set PODs used 2,436 dogs for human health risk decisions. However, based on the analysis presented here, information from dog studies appeared to drive the RAs of only nine pesticides, equating to 522 dogs. Thus, the challenge is to be able to prospectively identify those few cases when the dog study may benefit the RA.

Discussion

Testing in multiple species including rodents, rabbits, and dogs is traditionally performed to identify the most sensitive species to assess a substance's potential effects on humans. Tibbitts (2003) noted that distinct differences in toxicity are sometimes observed between the dog and rat and concluded that physiological characteristics unique to the dog could affect pharmacokinetics, making comparisons between dogs and other species, including humans, uncertain. While mammals share similar physiology, biochemical and cellular structures and functions, making it logical to use rodents and dogs as animal models to assess human health risk, cross-species comparison of pharmacokinetic parameters requires appropriate scaling in order to be meaningful (Timchalk 2004).

In the case of pesticides, testing on the dog has long been regarded as necessary for uncovering toxic effects that could be missed or occur at lower doses than in rodent species and impact human safety determinations. Some evaluations have concluded that the dog is the more sensitive species in enough cases that it should not be eliminated from the test battery for pesticides (e.g. Gerbracht and Spielmann 1998), particularly now that the 1-year dog study

is no longer required. Using the lowest NOAEL as the key indicator of species sensitivity would result in the dog being the most sensitive when isometrically comparing subchronic studies for 86/157 of the pesticides evaluated in this analysis. However, spacing of and differences in doses between rat and dog studies and allometric scaling as the default method for extrapolating doses between species, were shown to account for the majority of these lower NOAELs in dogs, suggesting that the dose at which the dog exhibited no toxic effects was likely the same or greater than the dose at which the rat showed no effects, and thus the rat alone could be used in the majority of pesticide RAs without compromising human health protection.

The long-term goal for chemical testing is to move away from animal models and predict human outcomes using innovative human-relevant new approach methods (NAMs), e.g. *in silico* and *in vitro* models, “omics,” chemistry-based approaches, and dosimetry/pharmacokinetic models, that are based on identifying and understanding mechanisms of toxicity. The transition has been gradual as new advanced technologies develop and confidence in them grows. Thus, use of animal models and associated standardized test guidelines is likely to continue for some time, however, there is no reason to perform studies in multiple species that are redundant and unnecessary. The traditional multi-species testing paradigm used to search for the most sensitive species is outdated when better techniques are available to select appropriate test species. Short-term, non-lethal *in vivo* tests, *in vitro* assays, and well-established techniques such as physiologically-based pharmacokinetic (PBPK) models could be implemented prior to performing a battery of animal tests. Timchalk (2004) recommended a comparative species (rat versus dog) PBPK analysis early in the toxicology evaluation process of new organic acid herbicides, a class of pesticides to which he showed dogs are particularly sensitive and not representative of humans, that would provide insight into the relevance of using dog toxicity data for the extrapolation of human health risk. Extending this type of analysis prior to conducting full guideline dog studies for registration of other new agrochemicals could help select appropriate test species and result in a reduction of dog use. As shown in this analysis, insecticides/acaricides appear to be likely candidates for which dog studies could be avoided in the future without compromising the setting of protective human exposure levels. Further investigation through the methods described above could help confirm such findings and develop criteria for when a dog study is or is not appropriate, thus providing confidence when not using the dog.

Comparative *in vitro* metabolism studies of humans and animals could better inform dose and species extrapolation as well and are already a requirement in the EU when evaluating pesticides to determine the relevance of the animal data and guide the interpretation of findings (European Commission 2013). In a 2021 scientific opinion on testing and interpretation of comparative *in vitro* metabolism studies submitted to the European Food Safety Authority (EFSA), the Panel on Plant Protection Products and their Residues confirmed that these studies provide useful information to select the most relevant species in toxicological

studies for newly developed substances and should be conducted before other toxicity studies are performed in order to reduce animal use (Hernandez-Jerez et al. 2021). NAMs, such as micro-physiological systems, also could be used to assist in identifying target organ toxicity relevant to humans.

In addition to applying more modern approaches, there are decades worth of toxicological dog data for all chemical classes of pesticides that can be further mined and analyzed to determine when the dog may be an appropriate model for humans, with particular attention paid to substances like ALS inhibitors that appear to have a mode of action to which the dog is susceptible. Retrospective analyses such as the present one, and a similar one performed by the EFSA (Panzarea et al. 2022), demonstrate how, in most cases, the dog does not impact the RA and that the “risk” of eliminating the dog study is low in terms of human health protection. Development of criteria for waiving the dog study will depend not only on these retrospective studies, but on prospective case examples using NAMs and weight of evidence approaches when developing new pesticide AIs that demonstrate the utility of proposed waiver criteria as well. The use of analogues and read-across methods, as well as mode-of-action and adverse outcome pathway knowledge, may help support and provide confidence when waiving dog studies.

Conclusions

An initial dataset of 195 pesticide human health RAs was examined; 157 had information sufficient to do a comparative analysis of 90-day dog and rat study NOAELs and toxicological effects. In the majority of cases, the dog was found to be no more sensitive than the rat after consideration of dosing and application of allometric scaling as a default method to extrapolate doses between species. Lack of the dog study in nearly all of the 42 cases where it was used in RA would not have impacted human health protection because there was another study available with a comparable NOAEL and/or exposures was low and there were no risks identified. Furthermore, the dog study was determined to benefit risk decisions made by the USEPA since 1998 for only 9/195 pesticides (4.6%) examined in this analysis and only 522 out of the nearly 9,800 dogs used were needed for making these decisions. To avoid future unnecessary use of dogs, we must challenge the traditional approach of a standard battery of tests and work toward more scientifically justifiable methods that incorporate NAMs and can prospectively inform when a 90-day dog study can be waived and when it may have an impact on pesticide RA.

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Author contributions

PB – Conceptualization, data collection and curation, methodology, analysis, writing – original draft, writing – review and editing. DW and VD – Conceptualization, writing – review and editing.

Declaration of interest

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Appendix A.

The 195 pesticides registered or evaluated for import tolerances by the US environmental protection agency (USEPA) from 1998–2021 listed alphabetically with chemical abstract service (CAS) numbers. Pesticides in italics were removed from the comparative analysis of 90-day dog and rat studies due to lack of toxic effects in all species or incomplete toxicological data, including missing/waived dog studies, dosing regimens, or other.

Name	CAS Number	Continued.	CAS Number
Acequinocyl	57960-19-7	Florasulam	145701-23-1
Acetamiprid	135410-20-7	<i>Florpyrauxifen-benzyl</i>	1390661-72-9
Acibenzolar-s-methyl	135158-54-2	Fluazinam	79622-59-6
Afidopyropen	915972-17-7	Flubendiamide	272451-65-7
<i>Alpha-chloralose</i>	15879-93-3	Flucarbazono-sodium	181274-17-9
Alpha-cypermethrin	67375-30-8	Fluensulfone	318290-98-1
<i>Ametoctradin</i>	865318-97-4	Flufenacet	142459-58-3
Amicarbazone	129909-90-6	Flufenoxuron	101463-69-8
Aminocyclopyrachlor	858956-08-8	Flufenpyr-ethyl	188489-07-8
Aminopyralid	150114-71-9	Fluindapyr	1383809-87-7
Amisulbrom	348635-87-0	<i>Flumethrin</i>	69770-45-2
Azafenidin	68049-83-2	Flumioxazin	103361-09-7
Azoxystrobin	131860-33-8	Fluopicolide	239110-15-7
Benalaxyl-M	98243-83-5	Fluopyram	658066-35-4
Benthiavalicarb-isopropyl	177406-68-7	Fluoxastrobin	361377-29-9
Benzobicyclon	156963-66-5	Flupyradifurone	951659-40-8
Benzovindiflupyr	1072957-71-1	<i>Fluroxypyr</i>	69377-81-7
Bicyclopyrone	352010-68-5	Fluthiacet-methyl	117337-19-6
Bifenazate	149877-41-8	<i>Flutianil</i>	958647-10-4
Bispyribac-sodium	125401-92-5	Flutriafol	76674-21-0
Bixafen	581809-46-3	Fluxapyroxad	907204-31-3
Boscalid	188425-85-6	<i>Foramsulfuron</i>	173159-57-4
Broflanilide	1207727-04-5	Forchlorfenuron	68157-60-8
Bromuconazole	116255-48-2	Fosthiazate	98886-44-3
Buprofezin	69327-76-0	<i>Furfural</i>	98-01-1
Butafenacil	134605-64-4	Halauuxifen-methyl	943831-98-9
Carfentrazone-ethyl	128639-02-1	<i>Imazosulfuron</i>	122548-33-8
<i>Chlorantraniliprole</i>	500008-45-7	<i>Imiprothrin</i>	72963-72-5
<i>Chlorothalonil</i>	1897-45-6	Indaziflam	950782-86-2
Clodinafop-propargyl	105512-06-9	Indoxacarb	173584-44-6
<i>Cloransulam-methyl</i>	147150-35-4	Inpyrfluxam	1352994-67-2
Clothianidin	210880-92-5	<i>Iodomethane</i>	74-88-4
Cyantraniliprole	736994-63-1	Iodosulfuron-methyl-sodium	144550-36-7
Cyazofamid	120116-88-3	Ipconazole	125225-28-7
<i>Cyclaniliprole</i>	736994-63-1	lprovalicarb	140923-17-7
Cyflufenamid	180409-60-3	Isofetamid	875915-78-9
Cyflumetofen	400882-07-7	Isoprazam	881685-58-1
Cyhalofop-butyl	122008-85-9	Isotianil	224049-04-1
Cymoxanil	57966-95-7	<i>Isoxaflutole</i>	141112-29-0
Cyprodinil	121552-61-2	Kasugamycin	6980-18-3
Demiditraz	944263-65-4	<i>Kresoxim-methyl</i>	143390-89-0
Diclosulam	145701-21-9	<i>Lufenuron</i>	103055-07-8
Diethofencarb	87130-20-9	Mandestrobin	173662-97-0
<i>Difenacoum</i>	56073-07-5	Mandipropamid	374726-62-2
Diiflufenzopyr	109293-97-2	Mefentrifluconazole	1417782-03-6
Dimethenamid-P	163515-14-8	Mepanipyrin	110235-47-7
Dimethomorph	110488-70-5	Meptyldinocap	131-72-6
<i>Dimethyl disulfide</i>	624-92-0	Mesosulfuron-methyl	208465-21-8
Dinotefuran	165252-70-0	Mesotrione	104206-82-8
Dithianon	3347-22-6	<i>Metaflumizone</i>	139968-49-3
Ecolyst (PT807-HCl)	274671-61-3	Metconazole	125116-23-6
Emamectin benzoate	155569-91-8	Methiozolin	403640-27-7
Epoxiconazole	133855-98-8	Methoxyfenozide	161050-58-4
Ethaboxam	162650-77-3	Metofluthrin	240494-70-6
<i>Ethamsulfuron-methyl</i>	97780-06-8	Metrafenone	220899-03-6
Ethiprole	181587-01-9	<i>Milbemectin</i>	1799297-76-9
<i>Etofenprox</i>	80844-07-1	Momfluorothrin	609346-29-4
Etoxazole	153233-91-1	<i>Nicarbazin</i>	330-95-0
Famoxadone	131807-57-3	<i>N-methylneodecanamide</i>	105726-67-8
Fenamidone	161326-34-7	<i>Nootkatone</i>	4674-50-4
Fenazaquin	120928-09-8	<i>Novaluron</i>	116714-46-6
Fenhexamid	126833-17-8	<i>Noviflumuron</i>	121451-02-3
Fenpicoxamid	517875-34-2	Orthosulfamuron	213464-77-8
<i>Fenpropiidin</i>	67306-00-7	<i>Oxalic acid</i>	144-62-7
Fenpropimorph	67564-91-4	<i>Oxathiapiiprolin</i>	1003318-67-9
Fenpyrazamine	473798-59-3	Penflufen	494793-67-8
Fenpyroximate	134098-61-6	Penoxsulam	219714-96-2
Flazasulfuron	104040-78-0	Penthiopyrad	183675-82-3
Flonicamid	158062-67-0		

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Name	CAS Number	Name	CAS Number
Pethoxamid	106700-29-2	Spirotetramat	203313-25-1
Picarbutrazox	500207-04-5	Spiroxamine	118134-30-8
Picaridin	119515-38-7	Sulfentrazone	122836-35-5
Picoxystrobin	117428-22-5	Sulfosulfuron	141776-32-1
Pinoxaden	243973-20-8	Sulfoxaflor	946578-00-3
Prohexadione-calcium	127277-53-6	Tebufenpyrad	119168-77-3
Propazine	139-40-2	Teflubenzuron	83121-18-0
Propoxycarbazone-sodium	145026-81-9	Tembotrione	335104-84-2
Proquinazid	189278-12-4	Tepraloxydim	149979-41-9
Prothioconazole	178928-70-6	<i>Tetraconazole</i>	112281-77-3
Pydiflumetofen	1228284-64-7	Tetraniliprole	1229654-66-3
Pymetrozine	123312-89-0	Thiacloprid	111988-49-9
Pyraclostrobin	175013-18-0	Thiamethoxam	153719-23-4
Pyraflufen-ethyl	129630-19-9	Thiencarbazone-methyl	936331-72-5
Pyrasulfatole	365400-11-9	Tiafenacil	1220411-29-9
Pyridalyl	179101-81-6	Tioxazafen	330459-31-9
Pyridate	55512-33-9	Tolfenpyrad	129558-76-5
Pyrifluquinazon	337458-27-2	Tolpyralate	1101132-67-5
Pyrimethanil	53112-28-0	Tolyfluanid	731-27-1
Pyrimisulfan	221205-90-9	Topramezone	210631-68-8
Pyriofenone	688046-61-9	Tralkoxydim	87820-88-0
Pyroxasulfone	447399-55-5	<i>Transfluthrin</i>	118712-89-3
Pyroxulam	422556-08-9	Trifloxystrobin	141517-21-7
Quinoxifen	124495-18-7	Trifloxysulfuron-sodium	145099-21-4
Saflufenacil	372137-35-4	Trifludimoxazin	1258836-72-4
Sedaxane	874967-67-6	Triflumezopyrim	1263133-33-0
Spinosad/Spinetoram	168316-95-8/ 187166-40-1 and 187166-15-0	<i>Triticonazole</i>	131983-72-7
Spirodiclofen	148477-71-8	Valifenalate	283159-90-0
Spiromesifen	283594-90-1	<i>Zoxamide</i>	156052-68-5

(continued)

Appendix B.

Doses for 90-day rat and dog studies and the likelihood that dose spacing was a factor in the dog appearing to be the more sensitive species for pesticides where the 90-day dog study NOAEL was lower than the 90-day rat study NOAEL

	NOAEL/LOAEL (mg/kg/d)				
Pesticide	90-day Dog	90-day Rat	Dog Doses mg/kg/d	Rat Doses mg/kg/d	Dose Spacing a Factor
Fungicides					
Amisulbrom	NE/100	171/525	0, 100, 300, 1000	0, 171, 525, 1700	
Benalaxyl-M	32/112	154/861	0, 5.6, 16, 32, 112	0, 6.2, 30, 154, 861	
Boscalid	7.6/78	34/137	0, 7.6, 78, 730	0, 7.0, 34, 137, 347, 1060	*
Bromuconazole	2.5/25	14/68	0, 2.5, 25, 250/125 ^a	0, 2.7, 14, 68, 342	
Cymoxanil	4.9/9.7	48/102	0, 4.9, 9.7, 14	0, 6.5, 48, 102, 224	
Dimethomorph	15/43	>73/NE	0, 5, 15, 43	0, 2.9, 14.2, 73	
Dithianon	3.0/13	15/87	0, 0.63, 3.0, 13	0, 2.5, 15, 87	
Ethaboxam	15/40	16/50	0, 15, 40, 100	0, 16, 50, 154	*
Famoxadone	1.4/10	13/52	0, 1.4, 10, 23	0, 3.3, 13, 52, 106	
Fenhexamid	34/239	415/904	0, 34, 239, 1750	0, 202, 415, 904, 1900	
Fenpyrazamine	25/50	64/196	0, 25, 50, 150	0, 19, 38, 64, 196	
Fluindapyr	40/200	330/NE	0, 10, 40, 200	0, 6, 24, 110/330	
Fluoxastrobin	3.0/25	70/580	0, 0.7, 1.4, 3.0, 25, 76	0, 8.7, 70, 580	
Flutriafol	5/15	14/158	0, 1, 5, 15	0, 1.5, 14, 158	
Iaconazole	10/40	26/52	0, 2, 10, 40	0, 2.5, 5.8, 13, 26, 52	*
Iprovalicarb	9.1/63	372/1520	0, 9.1, 63, 1250	0, 87, 372, 1520	
Isofetamid	29/301	69/637	0, 3.0, 29, 301	0, 6.7, 69, 637	*
Isotianil	51/200	1441/NE	0, 12, 51, 200	0, 7, 34, 166, 1441	
Kasugamycin	11/106	177/355	0, 11, 106, 182	0, 18, 58, 177, 355	
Mandestrobin	91/268	238/743	0, 91, 268, 933	0, 54, 283, 743, 1550	
Mefentrifluconazole	15/90	76/256	0, 15, 90, 180	0, 27, 76, 256	
Mepanipyrim	7.5/15	14/109	NA	NA	
Meptyldinocap	1.5/3.6	37/113	0, 0.49, 1.5, 3.6	0, 11, 37, 113	
Metconazole	2.5/24	6.4/19	0, 2.5, 24, 225	0, 1.9, 6.4, 19, 64, 193	*
Penflufen	56/532	949/NE	0, 5.6, 56, 532	0, 9.5, 457, 949	
Picoxystrobin	8.9/17	42/105	0, 4.3, 8.9, 17	0, 8.5, 42, 105	
Prothioconazole	25/100	100/500	0, 25, 100, 300	0, 20, 100, 500	

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Pesticide	NOAEL/LOAEL (mg/kg/d)		Dog Doses mg/kg/d	Rat Doses mg/kg/d	Dose Spacing a Factor
	90-day Dog	90-day Rat			
Pyraclostrobin	5.8/13	11/35	0, 2.8, 5.8, 13	0, 3.5, 11, 35, 69, 106	
Valifenalate	50/250	1000/NE	0, 50, 250, 750	0, 7, 150, 1000	
Herbicides					
Amicarbazone	6.3/25	33/67	0, 6.3, 25, 62	0, 6.9, 18, 33, 67, 182, 354	
Aminopyralid	232/929	500/1000	0, 53, 232, 929	0, 10, 100, 500, 1000	*
Azafenidin	0.34/2.0	24/72	0, 0.34, 2.0, 4.0, 8.2	0, 4.0, 24, 72, 122	
Carfentrazone-ethyl	50/150	226/470	0, 50, 150, 500, 1000	0, 56, 226, 470, 831, 1200	
Clodinafop-propargyl	0.35/1.7	8.2/70	0, 0.35, 1.7, 7.9	0, 0.13, 0.92, 8.2, 70	
Cyhalofop-butyl	15/75	61/190	0, 2.9, 15, 75	0, 1.7, 17, 61, 190	
Diclosulam	25/50	50/100	0, 5, 25, 100/50 ^a	0, 50, 100, 500, 1000	
Diflufenzopyr	58/403	352/725	0, 58, 403, 1131	0, 61, 352, 725, 1513	*
Dimethenamid-P	4.7/34	34/98	0, 4.7, 34, 90	0, 3.5, 10, 34, 98, 204	
Flazasulfuron	2/10	12/57	0, 2, 10, 50, 250	0, 2.3, 12, 57, 287	
Florasulam	5/50	100/500	0, 5, 50, 100	0, 20, 100, 500, 1000	
Flucarbazone-sodium	7.4 ^c /34	74/287	0, 34, 162, 1674	0, 18, 74, 287, 1670	
Flufenpyr-ethyl	300/1000	>1200/NE	0, 100, 300, 1000	0, 55, 595, 1200	
Flumioxazin	10/100	65/197	1, 10, 100, 1000	0, 1.9, 19, 65, 197	*
Halauxifen-methyl	80/415	252/758	0, 19, 80, 415	0, 10, 50, 252, 758	
Indaziflam	7.5/15	14/338	0, 7.5, 15, 30	0, 14, 338, 689	
Iodosulfuron-methyl sodium	8.1/49	67/347	0, 8.1, 49, 301	0, 13.8, 67, 347, 686	
Mesosulfuron-methyl	648/NE	908/NE	0, 63, 348, 648	0, 18, 89, 435, 908	*
Orthosulfamuron	450/1000	706/NE	0, 150, 450, 1000	0, 19, 113, 706	*
Penoxulam	18/49	50/250	0, 5.9, 18, 49	0, 5, 50, 250, 500	
Pinoxaden	100/250	466/900	0, 25, 100, 250, 500	0, 15, 98, 466, 900	
Pyridate	20/60	63/177	0, 20, 60, 200	0, 63, 177, 500	
Pyrimisulfan	10/50	381/748	0, 10, 50, 250	0, 7.6, 38, 381, 748	
Pyroxasulfone	2.0/10	16/171	0, 0.2, 2.0, 10	0, 1.7, 16, 171	
Sulfosulfuron	100/300	370/1280	0, 30, 100, 300, 1000	0, 1.2, 12.1, 123, 370, 1280	
Tepraloxymid	13/63	22/223	0, 13, 63, 325	0, 22, 223, 383	*
Tralkoxydim	0.5/5	21/205	0, 0.5, 5, 50	0, 4.2, 21, 205	
Trifloxysulfuron-sodium	20/164	507/1050	NA	NA	
Trifludimoxazin	15 ^c /50	33/94	0, 50, 250, 750/500 ^a	0, 6, 33, 94, 193	*
Insecticides/acaricides					
Afidopyropen	15/30	18/61	0, 15, 30, 90/60 ^a	0, 8.9, 18, 61, 182	*
Alpha-cypermethrin	2.3/6.8	9.3/30	0, 0.75, 2.3, 6.8	0, 1.0, 3.1, 9.3, 30	
Bifenazate	0.9/10	3.2/16	0, 0.9, 10, 25	0, 3.2, 16, 33	*
Buprofezin	10/50	13/69	0, 2, 10, 50, 300	NA	*
Clothianidin	19/41	28/202	0, 9.2, 19, 41, 58	0, 9.0, 28, 202	*
Cyantraniliprole	3/32	7/27	0, 1, 3, 32, 281	0, 7, 27, 202, 1346	*
Dinotefuran	307/862	336/1620	0, 58, 307, 862	0, 34, 336, 1620, 3160	*
Emamectin benzoate	0.25/0.50	2.5/5.0	0, 1.0, 1.5 (1 st 2 wks) 0, 0.25, 0.50, 1.0	0, 0.5, 2.5, 13/8/5 ^a	
Etoazoxole	5.3/54	62/184	0, 5.3, 54, 268	0, 6.1, 18., 62, 184	
Fenazaquin	5/15	9.6/29	0, 1, 5, 15	0, 1.0, 3.0, 9.6, 29	*
Flonicamid	8/20	12/60	0, 3, 8, 20	0, 3.1, 12, 60, 119	*
Flubendiamide	2.6/53	13/128	0, 2.6, 53, 1080	0, 1.3, 3.3, 13, 128, 1320	*
Flufenoxuron	7.5 ^b /38	25/250	0, 38, 375, 3750	0, 2.5, 25, 250, 500, 2500	
Flupyradifurone	12/33	30/156	0, 12, 33, 102/85 ^a	0, 6.0, 30, 156	
Pymetrozine	3.1/14	33/360	0, 3.1, 14, 54	0, 3.4, 33, 360	
Pyriproxyfen	5/30	29/155	0, 2, 5, 30	0, 2.9, 5.7, 29, 155	
Spinetoram/spinosad^c	4.9/9.7	9.5/40	0, 4.9, 9.7, 33	0, 9.5, 40, 79, 159, 311	
Spirodiclofen	7.7/27	32/167	0, 7.7, 27, 85	0, 6.6, 32, 167, 851	
Spirotetramat	32/72	148/616	0, 6, 10, 32, 72	0, 9, 26, 148, 616	
Tebufenpyrad	2/10	6.8/29	0, 2, 10, 20	0, 0.7, 6.8, 29	*
Teflubenzuron	29/252	809/NE	0, 2.7, 29, 252	0, 8, 82, 809	
Tetraniliprole	126/440	138/485	0, 26, 126, 440	0, 30, 138, 485	*
Thiacloprid	8.5/35	29/123	0, 8.5, 35, 68	0, 1.9, 7.3, 29, 123	
Thiamethoxam	8.2/32	18/85	0, 1.6, 8.2, 32, 55	0, 1.7, 18, 85, 168, 329	*
Triflumezopyrim	27/115	64/257	0, 3.1, 12, 27, 115	0, 4.2, 17, 64, 257	*
Nematicides					
Fluensulfone	1.6/17	8.3/35	0, 0.2, 1.6, 17	0, 4.3, 8.3, 35, 139	*
Plant activators/growth regulators					
Acibenzolar-s-methyl	50/200	126/516	0, 10, 50, 200	0, 2.4, 25, 126, 516	*
Forchlorfenuron	17/162	84/428	0, 1.8, 17, 162	0, 17, 84, 428	*
Total number of pesticides where dose spacing could be considered a factor in dogs appearing more sensitive					28

The dog study was used in risk assessment for pesticides in bold.

NE: Not established; NA: Not available.

^aHigh dose reduced during study.^bNOAEL from 1-year dog study used.^cDog data from spinosad test; rat data from spinetoram test (USEPA considers these chemicals toxicologically equivalent).

Appendix C.

Allometric scaling ($BW^{3/4}$) of 90-day rat study NOAELs to predict equipotent 90-day dog study NOAELs for those 86 pesticides where the 90-day dog study had a lower NOAEL

Pesticide	90-day Rat NOAEL (mg/kg)	90-day Dog NOAEL (mg/kg)		Predicted Dog/Reported Dog	Not Different
		Predicted	Reported		
Fungicides					
Amisulbrom	171	65	<100	1.3	*
Benalaxyl-M	154	58	32	1.8	*
Boscalid	34	13	7.6	1.7	*
Bromuconazole	14	5.3	2.5	2.1	
Cymoxanil	48	18	4.9	3.7	
Dimethomorph	73	28	15	1.8	*
Dithianon	15	5.7	3.0	1.9	*
Ethaboxam	16	6.1	15	0.4	*
Famoxadone	13	4.9	1.4	3.5	
Fenhexamid	415	157	34	4.6	
Fenpyrazamine	64	24	25	1.0	*
Fluindapyr	330	125	40	3.1	
Fluoxastrobin	70	27	3.0	8.8	
Flutriafol	14	5.3	5	1.1	*
Ipconazole	26	9.9	10	1.0	*
Iprovalicarb	372	141	9.1	16	
Isofetamid	69	26	29	0.9	*
Isotianil	1441	546	51	11	
Kasugamycin	177	67	11	6.1	
Mandestrobin	238	90	91	1.0	*
Mefentrifluconazole	76	29	15	1.9	*
Mepanipyrim	14	5.3	7.5	0.7	*
Meptyldinocap	37	14	1.5	9.4	
Metconazole	6.4	2.4	2.5	1.0	*
Penflufen	949	360	56	6.4	
Picoxystrobin	42	16	8.9	1.8	*
Prothioconazole	100	38	25	1.5	*
Pyraclostrobin	11	4.2	5.8	0.7	*
Valifenalate	1000	380	50	7.6	
Herbicides					
Amicarbazone	33	13	6.3	2.0	*
Aminopyralid	500	190	232	0.8	*
Azafenidin	24	9.1	0.34	27	
Carfentrazone-ethyl	226	86	50	1.7	*
Clodinafop-propargyl	8.2	3.1	0.35	8.9	
Cyhalofop-butyl	61	23	15	1.5	*
Diclosulam	50	19	25	0.8	*
Diffluenzopyr	352	133	58	2.3	
Dimethenamid-P	34	13	4.7	2.7	
Flazasulfuron	12	4.6	2.0	2.3	
Florasulam	100	38	5.0	7.6	
Flucarbazone-sodium	74	28	7.4 ^a	3.8	
Flufenpyr-ethyl	1200	455	300	1.5	*
Flumioxazin	65	25	10	2.5	
Halauxifen-methyl	252	96	80	1.2	*
Indaziflam	14	5.3	7.5	0.7	*
Iodosulfuron-methyl sodium	67	25	8.1	3.1	
Mesosulfuron-methyl	908	344	648	0.5	*
Orthosulfamuron	706	268	450	0.6	*
Penoxsulam	50	19	18	1.1	*
Pinoxaden	466	177	100	1.8	*
Pyridate	62	24	20	1.2	*
Pyrimisulfan	381	144	10	14	
Pyroxasulfone	16	6.1	2.0	3.0	
Sulfosulfuron	370	140	100	1.4	*
Tepraloxydim	22	8.3	13	0.6	*
Tralkoxydim	21	8.0	0.5	16	
Trifloxysulfuron-sodium	507	192	20	9.6	
Trifludimoxazin	33	13	15 ^a	0.8	*
Insecticides/acaricides					
Afidopyropen	18	6.8	15	0.5	*
Alpha-cypermethrin	9.3	3.5	2.3	1.5	*
Bifenazate	3.2	1.2	0.9	1.3	*
Buprofezin	13	4.9	10	0.5	*

(continued)

Continued.

Pesticide	90-day Rat NOAEL (mg/kg)	90-day Dog NOAEL (mg/kg)		Predicted Dog/Reported Dog	Not Different
		Predicted	Reported		
Clothianidin	28	11	19	0.6	*
Cyantraniliprole	7	2.7	3	0.9	*
Dinotefuran	336	127	307	0.4	*
Emamectin benzoate	2.5	0.9	0.25	3.8	
Etoxazole	62	24	5.3	4.4	
Fenazaquin	9.6	3.6	5	0.7	*
Flonicamid	12	4.6	8	0.6	*
Flubendiamide	13	4.9	2.6	1.9	*
Flufenoxuron	25	9.5	7.5 ^a	1.3	*
Flupyradifurone	30	11	12	0.9	*
Pymetrozine	33	13	3.1	4.0	
Pyriproxyfen	29	11	5	2.2	
Spinetoram/spinosad	9.5	3.6	4.9	0.7	*
Spirodiclofen	32	12.2	7.7	1.6	*
Spirotetramat	148	56	32	1.8	*
Tebufenpyrad	6.8	2.6	2.0	1.3	*
Teflubenzuron	809	307	29	11	
Tetraniliprole	608	231	126	1.8	*
Thiacloprid	29	11	8.5	1.3	*
Thiamethoxam	18	6.8	8.2	0.8	*
Triflumezopyrim	64	24	27	0.9	*
Nematicides					
Fluensulfone	8.3	3.1	3.1 ^b	1.0	*
Plant activators/growth regulators					
Acibenzolar-s-methyl	126	48	50	1.0	*
Forchlorfenuron	84	32	17	1.9	*
Total Number of Ratios ≤ 2.0					56

The dog study was used in RA for pesticides in bold. Pesticides with predicted/reported NOAEL ratios of ≤ 2 were considered not different.

^aNOAEL from 1-year dog study, not established in 90-day dog study.

^bThe NOAEL of 3.1 mg/kg from 1-year dog study was used in the risk assessment because the NOAEL of 1.6 reported for the 90-day dog study was considered an artifact of dose spacing.