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Comparative mammalian hazards of neonicotinoid insecticides among exposure durations

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ABSTRACT

Neonicotinoid insecticides have become one of the most widely used insecticides over the past two decades. Recent studies have shown considerable risk of neonicotinoids to beneficial insects, however, their health risks to mammals are still under debate. Limited empirical mammalian toxicity information for neonicotinoids inherently presents challenges to environmental health practitioners performing health hazard and risk assessment. Therefore, we first compiled and examined publicly available hazard data for neonicotinoids, and knowledge gaps on mammals were identified. Probabilistic hazard assessment using chemical toxicity distributions (CTDs) was subsequently conducted, and initial thresholds of toxicological concern were derived for rat, dog, mouse, and rabbit under comparative experimental scenarios. Using the rat model, for example, oral 5% threshold concentrations (TC5s) of 0.11 (0.02, 0.36) and 0.23 (0.001, 3.2) mg/kg bw/day were estimated using chronic developmental and reproductive no observed adverse effect levels (NOAELs), respectively, while acute TC5 of 0.71 (0.25, 1.6) mg/kg bw/day was identified using neurological NOAELs. Comparatively, dermal and inhalational TC5s were estimated as 1583 (1172, 1777) and 451 (294, 615) mg/kg bw/day (equivalent to 486 (322, 622) mg/m^3), respectively, using acute median lethal doses. Uncertainty factors (UFs) were also estimated using both CTD comparisons and individual UF probability distribution approaches to test whether rodent oral toxicity information or default 10-fold UF approach can provide sufficient protection for mammals. These initially identified UFs were generally smaller than default values (e.g., 10) employed by regulatory stakeholders, yet larger UFs were occasionally noted. Our findings appear particularly useful for environmental health practitioners when conducting screening-level risk assessment for neonicotinoids, and provide an example for health hazard assessment of pesticides with limited toxicity information.

1. Introduction

Neonicotinoid insecticides have been extensively used for agricultural, veterinary, and residential practices globally since their introduction in the 1990s because of their systemic characteristics and high efficacy for insect control (Simon-Delso et al., 2015). Recent studies demonstrate that neonicotinoids are ubiquitous in the environment, resulting from their ever-growing use, high mobility, and relatively long environmental half-lives in water and soil. Their broad occurrence has presented urgent risks to biodiversity and integrity of beneficial organisms and populations (Goulson, 2013; Hladik et al., 2018). In addition to environmental media, including source waters for potable uses, neonicotinoids have also been frequently detected in food products, and hence directly or indirectly increase the probability for mammalian species or human exposures to neonicotinoids. For instance, the U.S. Department of Agriculture (USDA, 2014, 2016) found neonicotinoids in 12 of 19 fruits and vegetables sampled, with 11 of them containing multiple neonicotinoids, and the levels of thiamethoxam exceeded the maximum residue limit in summer squash. Other evidence of contamination of neonicotinoids and their metabolites was also demonstrated in drinking water (Seccia et al., 2005; Klarich et al., 2017), vegetables, fruits (Xie et al., 2011), bovine milk (Seccia et al., 2008), and honey (Mitchell et al., 2017).

Neonicotinoids are considered to be less potent to mammalian species in comparison with legacy insecticide classes (e.g., organochlorines, organophosphates, and carbamates) (Tomizawa and Casida, 2005; Jeschke et al., 2013); however, studies showed that exposure to neonicotinoids pose potential risks to mammalian species or humans (Han et al., 2018; Zhang et al., 2018). Neonicotinoids can adversely affect mammalian nicotinic acetylcholine receptors, leading to

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Table 1
Summary of current global established human limit values (HLVs) for neonicotinoid insecticides.

Chemical	CAS	Country/ agency	Acceptable daily intake (ADI; mg/kg bw/day)			Acute reference dose (ARfD; mg/kg bw/day)			Chronic reference dose (CRfD; mg/kg bw/day)			Acceptable operator exposure level - systemic (AOEL; mg/kg bw/day)			Source (reference)
			ADI	Dose	UF	ARfD	Dose	UF	CRfD	Dose	UF	AOEL	Dose	UF	
Acetamiprid	135410-20-7	US EPA	NA			0.1	10	100	0.07	7.1	100	NA			(US EPA, 2002)
		EU	0.025	2.5	100	0.025	2.5	100	NA			0.025	2.5	100	(EFSA, 2013; EC, 2017)
		FAO/WHO	0.07			0.1			NA			NA			(JMPR, 2017)
		Australia	0.1	9	100	NA			NA			NA			(Commonwealth of Australia, 2017)
		Health Canada	0.008	2.5	300	0.008	2.5	300	NA			NA			(Health Canada, 2010)
Clothianidin	210880-92-5	US EPA	NA			0.025	25	1000	0.0098	9.8	1000	NA			(US EPA, 2003b)
		EU	0.097		100	0.1	10	100	NA			0.1	10	100	(EC, 2005)
		FAO/WHO	0.1			0.6			NA			NA			(JMPR, 2012, 2014, 2017)
		Australia	0.05	9.7	100	NA			NA			NA			(Commonwealth of Australia, 2017)
		Health Canada	NR			NR			NR			NR			(Health Canada, 2017a)
Dinotefuran	165252-70-0	US EPA	NA			1.25	125	100	0.02	20 (LOAEL)	1000	NA			(US EPA, 2004)
		EU	0.22	22	100	1.75	175	100	NA			0.22		100	(EC, 2014)
		FAO/WHO	0.2			1			NA			NA			(JMPR, 2012)
		Australia	0.2	22	100	NA			NA			NA			(Commonwealth of Australia, 2017)
Imidacloprid	138261-41-3	US EPA	NA			0.14	42 (LOAEL)	300	0.057	5.7	100	NA			(US EPA, 2005)
		EU	0.06			0.08			NA			0.08			(EC, 2015)
		FAO/WHO	0.06			0.4			NA			NA			(JMPR, 2017)
		Australia	0.06	6	100	NA			NA			NA			(Commonwealth of Australia, 2017)
		Health Canada	0.06	5.7	100	0.08	8	100	NA			NA			(Health Canada, 2016)
Thiacloprid	111988-49-9	US EPA	NA			0.01	3.1	300	0.004	1.2	300	NA			(US EPA, 2003a)
		EU	0.01			0.03			NA			0.02			(EC, 2004)
		Australia	0.01	1.2	100	NA			NA			NA			(Commonwealth of Australia, 2017)
		Health Canada	0.004	1.2	300	0.01	3.1	300	NA			NA			(Health Canada, 2007)
Thiamethoxam	153719-23-4	US EPA	NA			1	100	100	0.006	0.6	100	NA			(US EPA, 2001)
		EU	0.026	2.6	100	0.5	50	100	NA			0.08	8	100	(EC, 2006)
		FAO/WHO	0.08			1			NA			NA			(JMPR, 2014)
		Australia	0.02	2	100	NA			NA			NA			(Commonwealth of Australia, 2017)
		Health Canada	NR			NR			NR			NR			(Health Canada, 2017b)
Imidaclothiz	105843-36-5		NA			NA			NA			NA			
Nitenpyram	150824-47-8		NA			NA			NA			NA			
Nithiazine	58842-20-9		NA			NA			NA			NA			
Paichongding	948994-16-9		NA			NA			NA			NA			

Notes: US EPA: the United States Environmental Protection Agency; EU: the European Union; FAO/WHO: the Food and Agriculture Organization of the United Nations/World Health Organization; NA indicates data was not available; NR indicates no human risks identified for clothianidin and thiamethoxam by Health Canada (2017a, b); Dose refers to NOAEL used for a given HLV, unless stated otherwise (LOAEL); Default uncertainty factor (UF) of 100 was used accounting for 10-fold of inter-and 10-fold of intra-species variances; Composite UF (one > 100) was used accounting for 100-fold inter- and intra-species variances, and additional uncertainties. The corresponding mammalian toxicity studies of NOAELs/LOAELs are summarized in Table S1. NA indicates that data is not available, and NR indicates that data is not reported.

neurobehavioral deficits and increased expression of glial fibrillary acidic protein in the motor cortex and hippocampus (Abou-Donia et al., 2008; Li et al., 2011; Kimura-Kuroda et al., 2012). These receptors are important for nervous system functions, including memory, cognition and behavior development (Kimura-Kuroda et al., 2012; Chen et al., 2014). Detrimental effects of neonicotinoids to mammalian species included developmental (e.g., decreased body weight and reduced food consumption and water intake), reproductive (e.g., decreased sperm production and function (motility), and delayed sexual maturation), and neurological responses (e.g., decreased motor and locomotor activities), and skin and eye irritation, and even tumor (thiacloprid) (US EPA, 2002, 2003a, b, 2004).

Recognizing potential risks of neonicotinoids to mammals or humans, a number of regulatory human limit values (HLVs), such as acceptable daily intakes (ADIs), acute/chronic reference dose (ARfD/CRfD), and acceptable operator exposure level (AOEL; systemic) have been established for neonicotinoid around the world (Table 1). Due to paucity of human epidemiological data, most of current HLVs for neonicotinoids were derived from the existing mammalian toxicity information (Table S1) and adjusted by appropriate uncertainty factors (UFs) for conservatism. Mammal chronic no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) values commonly served as point of departure (PoD), and a default 100-fold UF approach was used accounting for inter- (10-fold) and intra-species (10-fold) variances when establishing HLVs (US EPA, 2002; EFSA, 2013; Commonwealth of Australia, 2017). Additional composition UF accounting for extrapolations of LOAEL-to-NOAEL ($UF_{L\text{-}N}$) or subchronic-to-chronic ($UF_{S\text{-}C}$), adequacy of database, or modifying factor was also adopted upon less than ideal data for a chemical (US EPA, 2003a, 2005; Health Canada, 2010). Take acetamiprid as an example, ARfD and CRfD of 0.1 and 0.07 mg/kg bw/day were recommended by the U. S. Environmental Protection Agency (US EPA, 2002) based on rodent acute neurotoxicity (male LOAEL: 30 mg/kg/day) and chronic/oncogenicity studies (male and female LOAEL: 17.5 mg/kg/day), respectively. More stringently, the European Union (EFSA, 2013; EC, 2017) refined HLVs (ADI, ARfD, AOEL, and acute AOEL (AAOEL)) for acetamiprid to a value of 0.025 mg/kg bw/day when they applied a smaller NOAEL of 2.5 mg/kg bw/day (developmental neurotoxicity) as a PoD. Health Canada (2010) dropped the ADI and ARfD for acetamiprid to 0.008 mg/kg bw/day by dividing the NOAEL of 2.5 mg/kg bw/day by a composite UF of 300 (additional 3-fold was refined as *Pest Control Products Act* factor).

Though commonly used in regulatory settings, whether default UF approach (e.g., 100-fold) can provide sufficient (or over- or under-) protection for humans when mammalian toxicity data of neonicotinoids are used as surrogates remains understudied. Whether rodent oral toxicity information can provide adequate protection for other mammal species under comparative experimental scenarios has not been robustly evaluated. A critical review is also warranted to examine all publicly available hazard data for mammalian species under comparative exposure scenarios, and to identify data gaps for future toxicity testing. Therefore, three primary objectives were targeted in the current study. First, we collated and examined publicly available acute median lethal dose (LD50) and developmental, reproductive and neurological NOAEL and LOAEL values of neonicotinoids under comparative experimental scenarios for different model species from previous sources for knowledge gaps identifications. Probabilistic hazard assessment (PHA) using chemical toxicity distribution (CTD) were subsequently conducted for particular endpoints (e.g., rat oral developmental chronic NOAEL), and threshold concentrations and corresponding 95% confidence intervals (95% CIs) were derived for identifying initial thresholds of toxicological concern (TTCs), based on existing information. Finally, both CTD comparisons and individual UF probability distribution approaches were used to identify UFs for neonicotinoids, including 1) extrapolations of LD50-to-NOAEL (e.g., acute-to-chronic ratios (ACRs)), exposure durations (e.g., subchronic-to-chronic), and LOAEL-to-NOAEL within a model species, 2) species-to-species extrapolation (e.g., rat-to-mouse/rabbit), and 3) route-to-route extrapolation (e.g., oral-to-dermal/inhalation).

2. Methods

2.1. Data mining

In this review, ten currently used neonicotinoids were considered (see Table S2 for their physicochemical properties), and hazard data of nine neonicotinoids (except for paichongding) for common mammalian toxicology model species (rat, dog, mouse, and rabbit) under oral, dermal, and inhalation exposures were collected from publicly available databases and peer-reviewed publications. The databases include US EPA Office of Pesticide Programs (US EPA OPP), Pesticide Properties Database (PPDB), Toxicology Data Network (TOXNET), and California EPA Department of Pesticide Regulation (California EPA DPR). Toxicity endpoints included LD50s for lethality, and acute/subacute/subchronic/chronic NOAELs and LOAELs for developmental, reproductive, and neurological responses.

2.2. Chemical toxicity distributions (CTDs)

Probabilistic hazard assessments (PHA) using CTDs approach were conducted for each neonicotinoid using datasets we reviewed and compiled. Briefly, any outlier(s) detected by Grubbs' (Grubbs, 1969) or Tietjen-Moore (Tietjen and Moore, 1972) tests were excluded for each dataset. A geometric mean was used when there were multiple data for a chemical under a particular exposure scenario for a species. Only datasets contained a minimum of five data points (i.e., at least five neonicotinoids) were used for CTDs constructions. Normality of residuals for each dataset (log-transformed) was checked by the Shapiro-Francia test (Shapiro and Francia, 1972), and goodness of fit at the lower tail of each distribution was assessed by Anderson-Darling test (Anderson and Darling, 1954). Hazard data were then ranked in ascending order, and percentiles were assigned from the Weibull formula (Eq. (1)).

$$\text{Percentile} = i/(n + 1) \times 100\% \quad (1)$$

where i is the rank of the datum in ascending order and n is the total number of data points. The CTDs were constructed and fitted by the log-normal regression model (SigmaPlot, version 13.0, San Jose, CA, USA).

Threshold concentration (TC) values and corresponding 95% CIs at 1^{st}, 5^{th}, 10^{th}, 50^{th}, 90^{th}, 95^{th}, and 99^{th} percentiles for each CTD were determined from the log-normal model by incorporating Monte Carlo simulation approach (resampled 5000 times) in the Statistical Analysis System package (SAS, version 9.4, Cary, NC, USA). For unit consistency (mg/kg bw/day), rat inhalation acute LD50 data expressed in mg/L were first transformed to mg/m^3, and subsequently converted to mg/kg bw/day based on an allometric approach (Bide et al., 2000) (see Appendix A for data-transformation methodology). Rat inhalation acute LD50 CTDs using data with units of mg/m^3 and mg/kg bw/day, respectively, were constructed for TCs and 95% CIs estimates.

2.3. Uncertainty factors (UFs)

In the present study, both CTD comparisons and individual UF probability distributions approaches were used to identify UFs for neonicotinoids within a model species (e.g., ACRs, $UF_{S\text{-}C}$, and $UF_{L\text{-}N}$), species-to-species, and route-to-route extrapolations under a particular experimental scenario following our previously reported methods (Wang et al., 2018). In brief, the UFs were first derived from pairwise TC ratios and 95% CIs from corresponding pairwise CTDs using all available data (in SAS as mentioned above). Concurrent meta-analyses were conducted using two corresponding datasets containing common (similar) chemicals to rectify potential influences caused by different

chemical compositions for both CTDs. The slope and/or intercept parameters of the pairwise log-normal fitted CTDs were also compared by one-way analysis of covariance (ANCOVA; SPSS, version 23, Chicago, IL, USA). To further compare differences between the two distributions quantitatively, TC5 ratio (95% CI) was applied for each comparison; if the 95% CI overlapped with unity, then the ratio was equal to 1 (i.e., both CTDs shared similar sensitivity) (Sokal and Rohlf, 1995). Second, UFs were calculated separately for all chemicals from the pairwise datasets containing common chemicals, and corresponding hazard data available to a similar species for a given endpoint. All calculated UFs were then ranked and assigned percentiles following the Weibull formula (Eq. 1) to construct a probability distribution, which was then fitted by the log-normal regression model. Afterwards, overall UFs and 95% CIs covering 90%, 95%, and 99% of concerned chemicals were determined for each distribution with an inverse prediction method. Whether a factor of 10 or 100 would be protective for various distributions of neonicotinoids was examined.

3. Results and discussion

3.1. Data availability and knowledge gaps

Availability of data varied significantly across the neonicotinoids of concern (Table S3). Hazard data for acetamiprid, clothianidin, dinotefuran, imidacloprid, thiacloprid, and thiamethoxam had high representativeness of various concerned toxicity endpoints, which accounted for > 50% of time for the endpoints of concern. They also dominated 20 generated CTDs (datasets with ≥5 neonicotinoids) with 80%–95% of frequency. On the contrary, a few acute data were available for imidaclothiz (two acute LD50s), nitenpyram (five acute LD50s), and nithiazine (three acute LD50s, one rat oral developmental acute NOAEL, and one rat oral neurological acute NOAEL), and no hazard data were found for paichongding. In addition, hazard data for rats under oral exposure dominated the datasets among species and exposure routes of concern, respectively. This represented an important observation because oral exposure through pesticide residues in food represents an important exposure route for humans. The application of CTDs (as demonstrated below) was also largely dependent on the quantity of data. In this study, and consistent with previous practices (Dobbins et al., 2008, 2009; Berninger and Brooks, 2010; Williams et al., 2011; Berninger et al., 2011; Dreier et al., 2015; Wang et al., 2018), a dataset containing a minimum of five data points was considered to be suitable for CTD development, particularly considering data availability for neonicotinoids. Scarce and even no toxicity data for imidaclothiz, nitenpyram, nithiazine, and paichongding calls for additional data generation (toxicity testing) or read across from other neonicotinoids to fill data gaps during future hazard and risk assessments.

3.2. Chemical toxicity distributions (CTDs) and thresholds of toxicological concern (TTCs)

Among all datasets used to construct CTDs, no outlier(s) were detected by Grubbs' and Tietjer-Moore tests, thus all available data were used in our meta-analyses (Table S4). Acute, developmental, reproductive, and neurological CTDs were subsequently generated for rat (oral, dermal, and inhalation; Fig. 1; see Fig. S1 for rat inhalation acute LD50 CTD using data expressed in mg/m^3), dog, mouse, and rabbit (oral only; Fig. 2). All datasets passed the Shapiro-Francia (normality of residuals; $p > 0.05$) and Anderson-Darling tests ($p > 0.05$; Table S5). Derived TCs and 95% CIs at 1st, 5th, 10th, 50th, 90th, 95th, and 99th percentiles were listed in Table 2.

Using TC5s as examples, neonicotinoids tended to be acutely lethal to rats at or below 56 (95% CI: 22, 99), 1583 (1172, 1777), and 451 (294, 615) mg/kg bw/day for 5% of chemicals under oral, dermal, and inhalation exposures, respectively. Comparatively, there were 5% probability of neonicotinoids to elicit chronic developmental and reproductive responses (LOAELs) to rat (oral) at or below 1.7 (0.76, 3.2) and 4.2 (0.01, 20) mg/kg bw/day, respectively, and corresponding TC5s using NOAELs were estimated at 0.11 (0.02, 0.36) and 0.23 (0.001, 3.2) mg/kg bw/day. Although rodent neurological hazard data are limited, acute TC5s can still be estimated at 2.7 (0.94, 5.6) and 0.71 (0.25, 1.6) mg/kg bw/day using LOAELs and NOAELs, respectively.

Since dermal and inhalation data were scarce for other species, only oral CTDs were generated for dog (developmental subchronic and chronic NOAELs), mouse (acute LD50s, developmental subchronic and chronic NOAELs/LOAELs), and rabbit (developmental subacute NOAELs/LOAELs; Fig. 2). Accordingly, when considering developmental responses, chronic TC5s were estimated at 2.4 (1.4, 3.2) for dog (using NOAELs only) and 0.75 (0.01, 3.3) and 0.66 (0.24, 1.2) mg/kg bw/day for mouse (using LOAELs and NOAELs), respectively, and subacute TC5s of 17 (9.4, 24) and 5.9 (0.20, 14) mg/kg bw/day were estimated for rabbit using LOAELs and NOAELs, respectively (Table 2).

The use of CTD in PHA can support screening level risk assessment for risk practitioners or assessors with a criterion threshold value to protect a given level (e.g., 5%) of effects for chemicals within a particular chemical class (e.g., neonicotinoids) (Wang et al., 2018). These derived TC values (e.g., TC5) and 95% CIs may serve directly as initial TTCs or adjusted by a factor (e.g., 10-fold) for a species exposed to neonicotinoids under a given exposure scenario (e.g., rat oral developmental/reproductive chronic NOAEL). The TCs (or TC ratios) and their 95% CIs derived from the pairwise CTDs can also be used to compare relative sensitivity between or among different distributions (Solomona et al., 2000; Wang et al., 2018). For example, TC5 ratios and 95% CIs (as demonstrated below) were used in this study to compare relative sensitivities between model species (rat to dog, mouse, or rabbit) or between exposure routes of interest (oral to dermal or inhalation). In addition, the exceedance profile that describes the probability of a class of chemicals such as neonicotinoids exceeding the concentration associated with a particular degree of effect can be estimated practically from the derived log-normal regression functions (e.g., $y = ax + b$; Table 2).

The TTC concept is an alternative approach in health risk assessment that can be used in the absence of chemical-specific toxicity data. This approach is based on establishing the levels of mammal/human doses for a chemical (a TTC) that would not present a safety concern using toxicity data from other chemicals sharing similar structures (Kroes et al., 2005; Munro et al., 2008; EFSA, 2016). After its initial application by US FD&C Act (1958) with a TTC-like approach for chemicals in food additives in the U.S., it has been adopted to evaluate chemical classes, such as food additives and food contact articles by US FDA (1995) and ILSI Europe (Kroes et al., 2004; Barlow, 2005), flavoring substances by EFSA (EC, 2000; EFSA, 2010) and JECFA (1995), industrial chemicals by ECETOC (2004), and genotoxic impurity by EMA (2006). The TTC and other TTC-like approaches (e.g., dermal sensitization threshold (DST) for dermal and concentration of no toxicological concern (CoNTC) for inhalation) were also applied for assessing chemicals introducing dermal and inhalation toxicity, such as skin sensitizing substances (Api et al., 2008; Keller et al., 2009; Safford et al., 2011) and air pollutants (Drew and Frangos, 2007; Escher et al., 2010).

Our study also incorporated the TTC concept in hazard assessment of neonicotinoids to multiple mammalian species and exposure routes, and a number of TCs and 95% CIs for mammalian species under comparative exposure scenarios against neonicotinoids were derived (oral, dermal, and inhalation; Table 2). Those TC values (e.g., TC1 or TC5) or their lower-bound of 95% CIs may be useful as initial TTCs for neonicotinoids during regulatory applications. For example, if TC1 of 0.11 mg/kg bw/day derived from developmental chronic NOAEL CTD was borrowed as an overall PoD and adopted by a 100-fold UF (accounting inter- and intra-species variances), an interim HLV of 0.001 mg/kg bw/day was derived. Until more robust toxicology

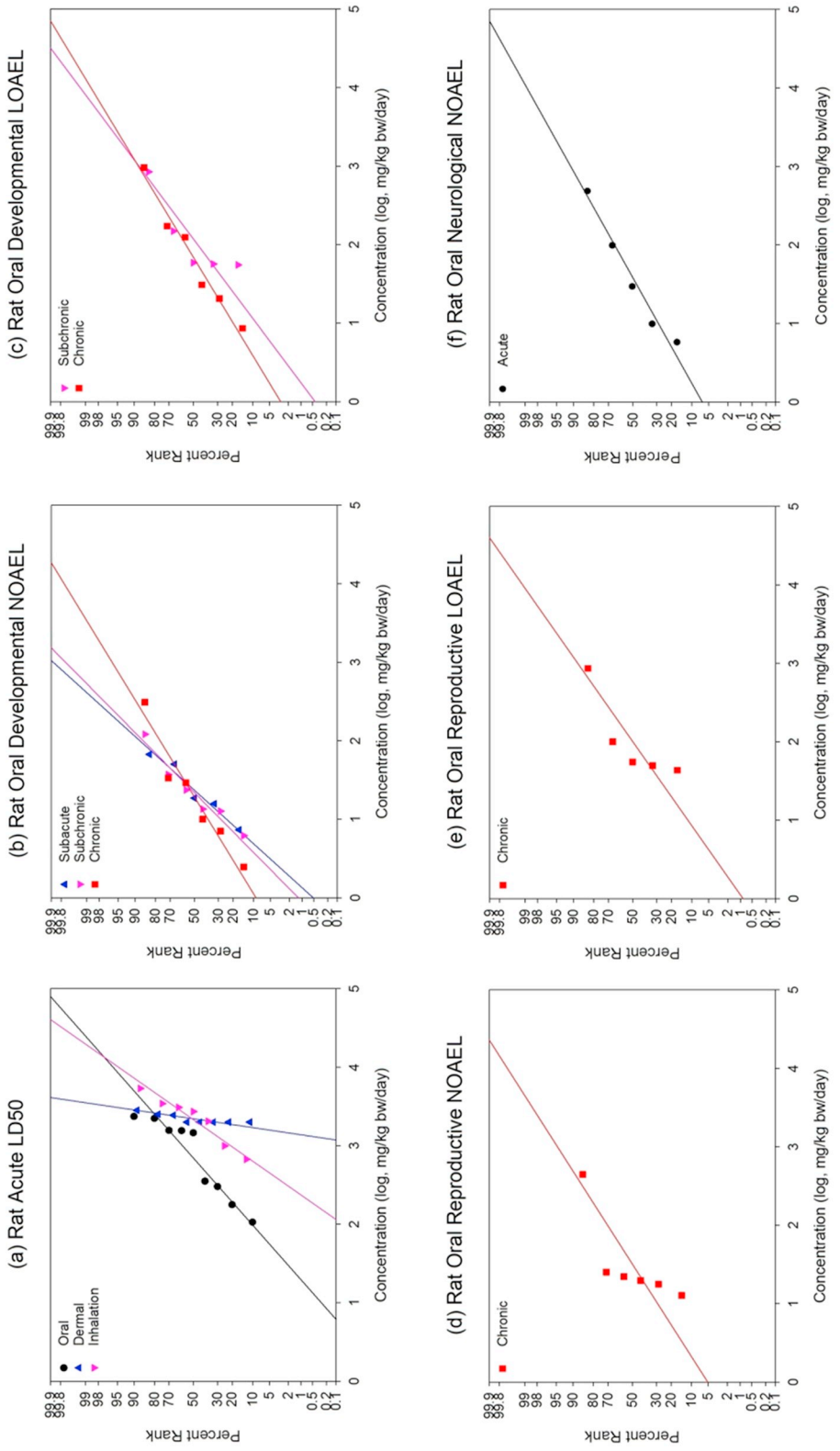

Fig. 1. Rodent acute (a: LD50), developmental (b: NOAEL and c: LOAEL), reproductive (d: NOAEL and e: LOAEL), and neurological (f: NOAEL and g: LOAEL) chemical toxicity distributions (CTDs) using all available data for neonicotinoid insecticides.

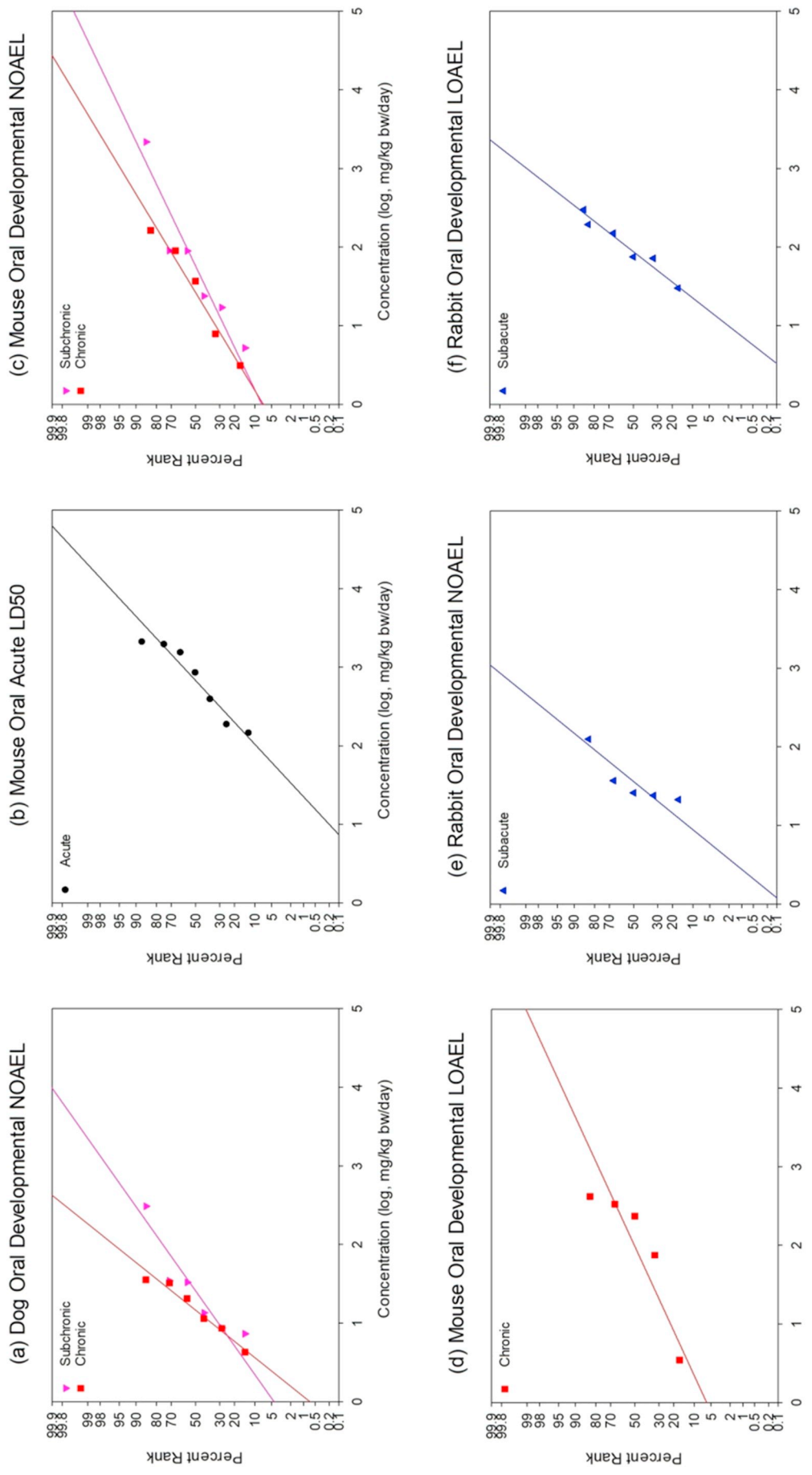

Fig. 2. Chemical toxicity distributions (CTDs) for dog (a: developmental NOAEL), mouse (b: acute LD50, c: developmental NOAEL, and d: developmental LOAEL), and rabbit (e: developmental NOAEL and f: developmental LOAEL).

Table 2
Threshold concentrations (TCs) and their 95% confidence intervals (95% CIs) at 1st, 5th, 10th, 50th, 90th, 95th, and 99th percentiles for each chemical toxicity distribution (CTD) considering all chemicals.

CTDs	Exposure duration	Specie	Exposure route	Unit	n	$y = a\,x + b$			TC1 (95% CI)	TC5 (95% CI)	TC10 (95% CI)	TC50 (95% CI)	TC90 (95% CI)	TC95 (95% CI)	TC99 (95% CI)
						a	b	R^2							
Acute LD50	Acute	Rat	Oral	mg/kg bw/day	9	50.6	−94.0	0.908	20 (5.5, 43)	56 (22, 99) a	98 (46, 157)	697 (512, 935)	4981 (3064, 10,321)	8698 (4855, 21,439)	24,746 (11,385, 85,968)
		Rat	Dermal	mg/kg bw/day	8	387	−124	0.754	1379 (908, 1611)	1583 (1172, 1777) b	1703 (1344, 1875)	2205 (2071, 2363)	2856 (2607, 3691)	3073 (2753, 4225)	3526 (3041, 5476)
		Rat	Inhalation	mg/kg bw/day	7	82.3	−224	0.932	236 (131, 362)	451 (294, 615) c	636 (453, 821)	2152 (1851, 2464)	7278 (5671, 10,443)	10,280 (7614, 16,039)	19,650 (13,028, 36,206)
				mg/m^3	7	82.3	−227	0.932	254 (143, 389)	486 (322, 662)	687 (495, 885)	2322 (1988, 2676)	7852 (6112, 11,296)	11,091 (8153, 17,366)	21,199 (13,967, 39,415)
		Mouse	Oral	mg/kg bw/day	7	54.3	−104	0.949	22 (6.4, 43)	61 (24, 98) a	104 (49, 153)	680 (507, 864)	4444 (2784, 8353)	7568 (4324, 16,711)	20,542 (9763, 62,080)
Developmental NOAEL	Subacute	Rat	Oral	mg/kg bw/day	5	66.0	−40.5	0.961	1.3 (0.6, 2.3)	3.1 (1.7, 4.6)	4.9 (3.0, 6.7)	24 (20, 28)	114 (82, 187)	178 (119, 331)	412 (236, 987)
		Rabbit	Oral	mg/kg bw/day	5	72.7	−63.2	0.754	2.8 (0.02, 8.7)	5.9 (0.20, 14)	8.8 (0.59, 18)	36 (24, 67)	149 (92, 1356)	222 (122, 4098)	471 (202, 32,457)
	Subchronic	Rat	Oral	mg/kg bw/day	6	54.6	−21.2	0.859	0.70 (0.11, 1.8)	1.9 (0.50, 3.8)	3.2 (1.1, 5.7)	20 (15, 30)	128 (73, 352)	217 (110, 760)	579 (232, 3309)
		Dog	Oral	mg/kg bw/day	6	41.2	−8.15	0.848	0.3 (0.01, 1.4)	1.1 (0.12, 3.5)	2.2 (0.4, 5.8)	26 (17, 52)	303 (143, 2012)	609 (245, 6420)	2256 (652, 55,917)
		Mouse	Oral	mg/kg bw/day	6	27.7	1.15	0.880	0.08 (0.003, 0.54)	0.54 (0.05, 2.3)	1.5 (0.23, 5.0)	58 (32, 131)	2191 (784, 15,612)	6142 (1749, 71,144)	42,494 (7352, 1,218,487)
	Chronic	Rat	Oral	mg/kg bw/day	6	35.5	4.32	0.922	0.11 (0.02, 0.36)	0.50 (0.13, 1.2) a	1.1 (0.38, 2.3)	19 (13, 31)	334 (170, 958)	750 (327, 2783)	3410 (1100, 20,260)
		Dog	Oral	mg/kg bw/day	6	73.5	−35.6	0.967	1.2 (0.6, 1.7)	2.4 (1.4, 3.2) b	3.6 (2.4, 4.6)	15 (12, 17)	59 (44, 85)	88 (61, 140)	184 (115, 356)
		Mouse	Oral	mg/kg bw/day	5	36.3	−1.63	0.978	0.14 (0.04, 0.33)	0.66 (0.24, 1.2) a	1.5 (0.65, 2.4)	27 (19, 35)	472 (265, 990)	1068 (533, 2726)	4936 (1941, 18,476)
Developmental LOAEL	Subacute	Rabbit	Oral	mg/kg bw/day	5	80.5	−106	0.936	8.3 (3.7, 14)	17 (9.4, 24)	24 (15, 32)	86 (71, 102)	311 (231, 532)	448 (310, 869)	888 (533, 2207)
	Subchronic	Rat	Oral	mg/kg bw/day	5	44.5	−42.1	0.746	1.7 (0.002, 10)	6.0 (0.05, 23)	12 (0.3, 36)	118 (58, 304)	1207 (530, 45,249)	2332 (838, 243,385)	8030 (1886, 5,057,791)
	Chronic	Rat	Oral	mg/kg bw/day	6	35.4	−15.1	0.964	0.37 (0.12, 0.88)	1.7 (0.76, 3.2)	3.9 (2.0, 6.5)	69 (53, 93)	1229 (751, 2326)	2778 (1529, 6167)	12,827 (5692, 38,212)
		Mouse	Oral	mg/kg bw/day	5	27.3	−4.1	0.787	0.10 (0.001, 0.87)	0.75 (0.01, 3.3)	2.2 (0.02, 7.1)	97 (22, 236)	4272 (697, 1,413,544)	12,501 (1386, 19,631,546)	93,692 (5215, 2,202,875,318)
Reproductive NOAEL	Chronic	Rat	Oral	mg/kg bw/day	6	36.5	−4.91	0.600	0.23 (0.001, 3.2)	0.97 (0.001, 7.3)	2.1 (0.001, 12)	32 (11, 248)	490 (149, 1627)	1063 (251, 5348)	4533 (605, 49,066)
Reproductive LOAEL	Chronic	Rat	Oral	mg/kg bw/day	5	41.5	−33.0	0.722	1.1 (0.001, 8.8)	4.2 (0.01, 20)	8.4 (0.07, 31)	101 (43, 316)	1201 (492, 9342)	2426 (800, 60,757)	9073 (1917, 216,156)
Neurological NOAEL	Acute	Rat	Oral	mg/kg bw/day	5	33.4	−2.96	0.972	0.13 (0.03, 0.4)	0.71 (0.25, 1.6)	1.7 (0.77, 3.4)	39 (29, 58)	874 (537, 2417)	2115 (1136, 7306)	11,102 (4555, 59,758)
Neurological LOAEL	Acute	Rat	Oral	mg/kg bw/day	6	36.2	−22.5	0.956	0.59 (0.14, 1.6)	2.7 (0.94, 5.6)	5.9 (2.6, 11)	101 (72, 145)	1711 (976, 4317)	3821 (1934, 12,048)	17,238 (6787, 81,753)

Table 3
Uncertainty factors (UFs) derived from chemical toxicity distribution (CTD) comparisons (i.e., threshold concentration 5% (TC5) ratios), whereas the both datasets consisting of all chemicals.

1) UFs within a species (oral)

TC5 ratio (95% CI)	Developmental subacute NOAEL	Developmental subchronic NOAEL	Developmental chronic NOAEL	Reproductive chronic NOAEL	Neurological acute NOAEL
Acute LD50	Rat: 18 (6.4, 42)	Rat: 24 (8.2, 62) Mouse: 113 (21, 1438)	Rat: 112 (32, 464) Mouse: 92 (30, 295)	Rat: 58 (5.8, 858)	Rat: 79 (23, 253)
Developmental subacute NOAEL		Rat: 1.7 (0.6, 6.4)	Rat: 6.2 (2.0, 24)		
Developmental subchronic NOAEL			Rat: 3.8 (0.7, 17) Dog: 0.4 (0.05, 1.6) Mouse: 0.8 (0.06, 4.9)		
Developmental subacute LOAEL	Rabbit: 2.8 (0.9, 57)				
Developmental subchronic LOAEL		Rat: 3.2 (0.1, 22)			
Developmental chronic LOAEL			Rat: 3.4 (1.0, 15)		
Reproductive chronic LOAEL				Rat: 4.3 (0.01, 143) Mouse: 1.1 (0.01, 8.6)	
Neurological acute LOAEL					Rat: 3.7 (1.0, 14)

2) UFs for species-to-species and route-to-route extrapolations

TC5 ratio (95% CI)		Acute LD50s	Developmental subacute NOAEL	Developmental subchronic NOAEL	Developmental chronic NOAEL
Species-to-species	Rat-to-dog (oral)			0.8 (0.2, 1.9)	0.5 (0.08, 5.1)
	Rat-to-mouse (oral)	0.9 (0.3, 2.7)		3.5 (0.5, 43)	0.8 (0.2, 3.0)
	Rat-to-rabbit (oral)		0.5 (0.2, 14)		
Route-to-route	Oral-to-dermal (rat)	0.04 (0.01, 0.07)			
	Oral-to-inhalation (rat)	0.1 (0.05, 0.3)			

Table 4
Uncertainty factors derived from chemical toxicity distribution (CTD) comparisons (i.e., threshold concentration 5% (TC5) ratios), whereas the both datasets consisting of similar ingredients. NA indicates that the both datasets has no sufficient data (i.e., $n < 5$) when considering similar chemicals for the pairwise CTDs' comparison.

1) UFs within a species (oral)

TC5 ratio (95% CI)	Developmental subacute NOAEL	Developmental subchronic NOAEL	Developmental chronic NOAEL	Reproductive chronic NOAEL	Neurological acute NOAEL
Acute LD50	Rat: 20 (4.0, 58)	Rat: 35 (5.2, 100) Mouse: 113 (21, 1438)	Rat: 159 (22, 707) Mouse: NA	Rat: 82 (4.8, 681)	Rat: 64 (13, 230)
Developmental subacute NOAEL		Rat: 1.0 (0.4, 2.9)	Rat: 3.0 (1.4, 9.0)		
Developmental subchronic NOAEL			Rat: 3.8 (0.7, 17)[a] Dog: 0.4 (0.05, 1.6)[a] Mouse: 0.4 (0.01, 3.6)		
Developmental subacute LOAEL	Rabbit: 2.8 (0.9, 57)[a]				
Developmental subchronic LOAEL		Rat: 2.9 (0.1, 12)			
Developmental chronic LOAEL			Rat: 3.4 (1.0, 15)[a]		
Reproductive chronic LOAEL				Rat: 5.0 (0.01, 825) Mouse: 1.1 (0.01, 8.6)[a]	
Neurological acute LOAEL					Rat: NA

2) UFs for species-to-species and route-to-route extrapolations

TC5 ratio (95% CI)		Acute LD50s	Developmental subacute NOAEL	Developmental subchronic NOAEL	Developmental chronic NOAEL
Species-to-species	Rat-to-dog (oral)			0.8 (0.2, 1.9)[a]	0.5 (0.08, 5.1)[a]
	Rat-to-mouse (oral)	1.5 (0.2, 5.2)		3.5 (0.5, 43)[a]	0.6 (0.1, 2.2)
	Rat-to-rabbit (oral)		NA		
Route-to-route	Oral-to-dermal (rat)	0.03 (0.008, 0.07)			
	Oral-to-inhalation (rat)	0.2 (0.04, 0.5)			

[a] The available data for pairwise CTDs contain similar chemicals (i.e., the value equals to that in Table 3).

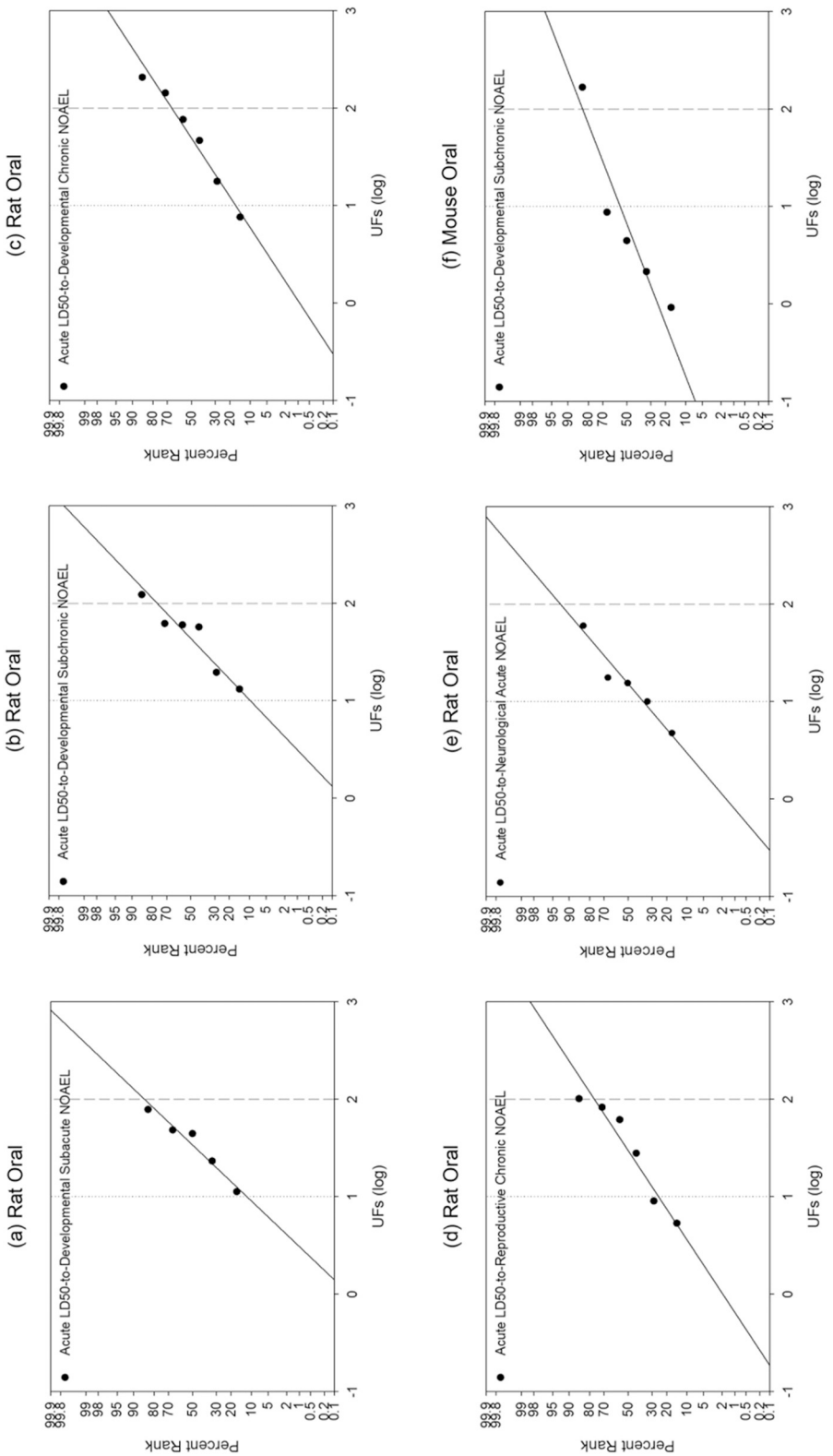

Fig. 3. Individual uncertainty factor (UFs) probability distributions for neonicotinoid insecticides to a species for (a–f) rodent/mouse LD50 - to - developmental/reproductive/neurological NOAEL, (g–k) rodent/mouse/rabbit oral developmental/reproductive LOAEL - to - NOAEL, and (l–p) rodent/dog/mouse developmental exposure duration extrapolations. Vertical reference lines are default UF values of 10 (dotted line) and 100 (dash line).

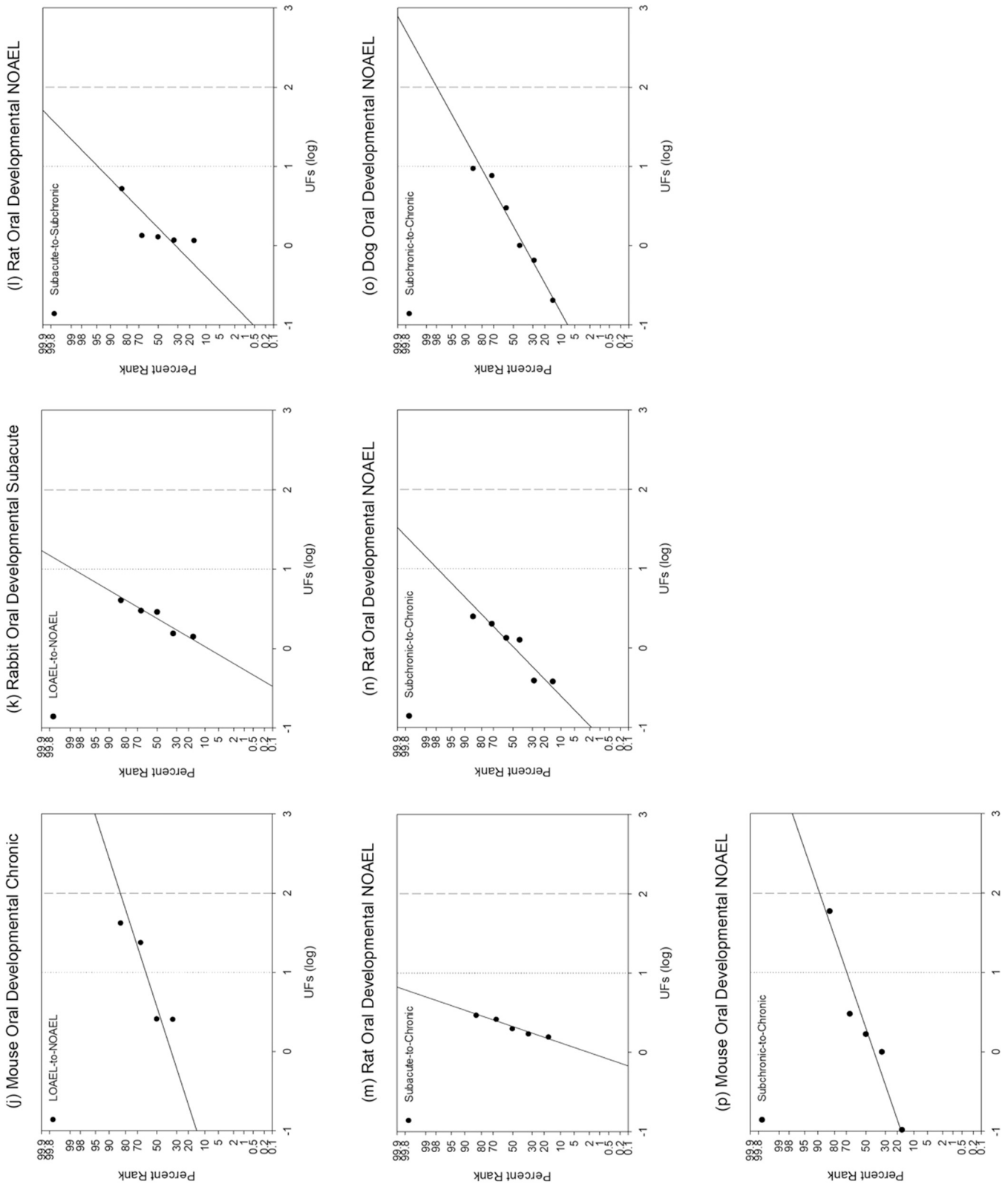

Fig. 3. (*continued*)

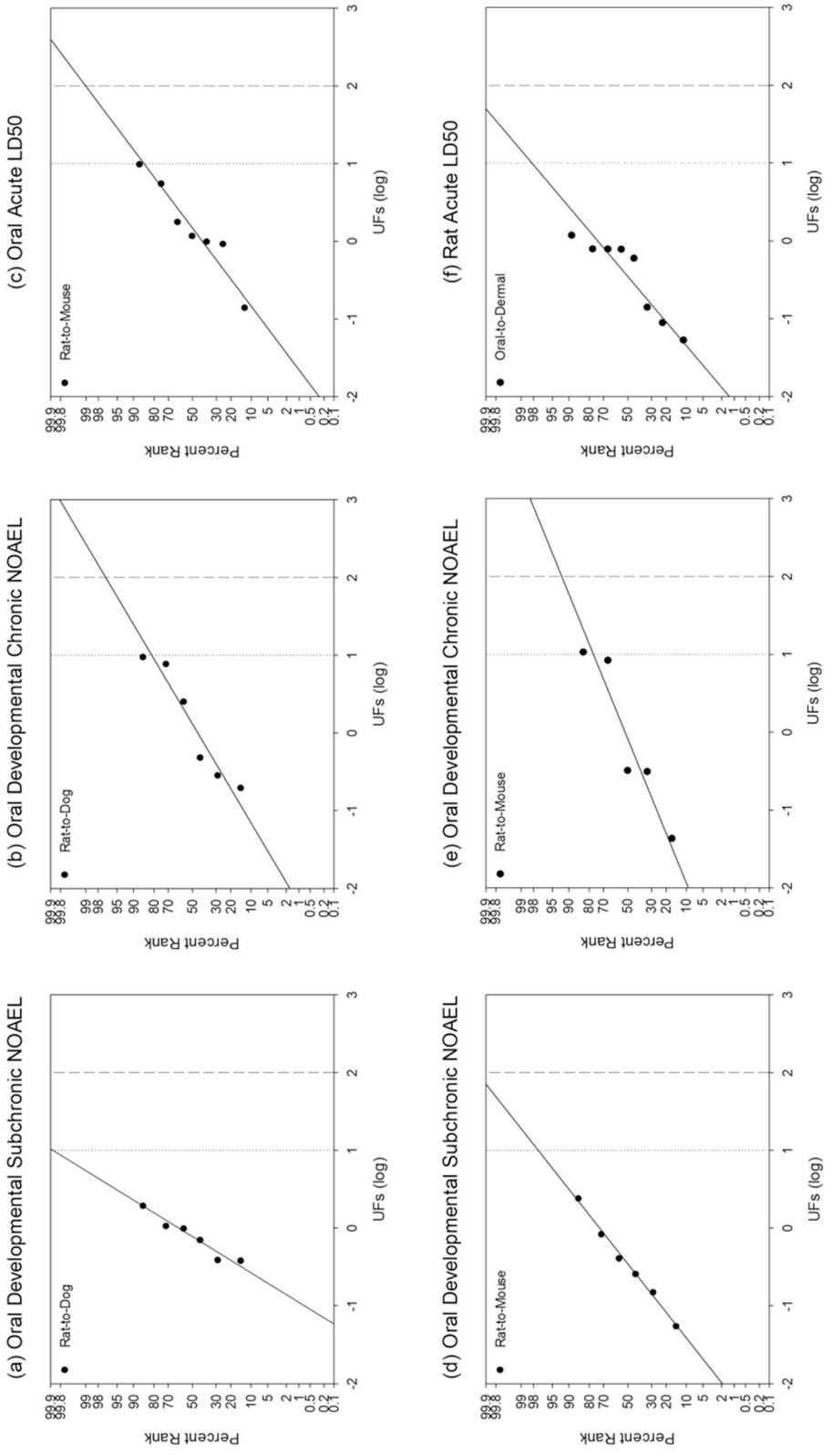

Fig. 4. Individual uncertainty factor (UFs) probability distributions for neonicotinoid insecticides for (a–e) species (rat) - to - species (dog/mouse) extrapolation using oral developmental NOAELs or acute LD50s under a particular exposure duration and (f–g) oral-to-dermal/inhalation extrapolation using rodent acute LD50 values. Vertical reference lines are default UF values of 10 (dotted line) and 100 (dash line).

Table 5
Uncertainty factors (UFs) derived from individual UF probability distributions at 90th, 95th, and 99th percentiles. The percentiles of NNIs being protected under default UF of 10 and 100 were also derived from each log-normal fitted distribution.

1) UFs within a species (oral)

UFs		Species	n	$y = a\,x + b$			90th (95% CI)	95th (95% CI)	99th (95% CI)	% of NNIs being protect under default UF of 10	% of NNIs being protect under default UF of 100
				a	b	R^2					
LD50-to-NOAEL	Acute LD50-to-developmental subacute NOAEL	Rat	5	78.3	−69.8	0.943	127 (93, 206)	185 (125, 335)	373 (220, 840)	11%	85%
	Acute LD50-to-developmental subchronic NOAEL	Rat	6	58.0	−64.8	0.892	186 (130, 380)	281 (179, 691)	608 (326, 2061)	9.0%	76%
		Mouse	5	28.6	26.5	0.881	242 (87, 3851)	673 (189, 20,806)	4563 (775, 573,455)	55%	83%
	Acute LD50-to-developmental chronic NOAEL	Rat	6	48.3	−31.8	0.977	411 (280, 623)	749 (475, 1277)	2311 (1265, 4921)	16%	66%
	Acute LD50-to-reproductive chronic NOAEL	Rat	6	48.8	−22.0	0.940	246 (141, 547)	447 (231, 1233)	1370 (571, 5618)	25%	76%
	Acute LD50-to-neurological acute NOAEL	Rat	5	62.9	−24.4	0.925	78 (52, 130)	124 (75, 243)	296 (150, 800)	37%	93%
Exposure duration	Developmental subacute-to-subchronic NOAEL	Rat	5	72.0	34.0	0.591	6.9 (3.6, 7801)	10 (4.7, 98,909)	22 (7.2, 11,307,051)	94%	> 99%
	Developmental subacute-to-chronic NOAEL	Rat	5	221	−21.9	0.970	3.4 (3.1, 4.0)	3.9 (3.5, 4.8)	5.0 (4.3, 6.7)	> 99%	> 99%
	Developmental subchronic-to-chronic NOAEL	Rat	6	71.9	48.7	0.901	4.4 (2.7, 10)	6.6 (3.7, 19)	14 (6.7, 59)	97%	> 99%
		Dog	6	40.6	40.0	0.975	22 (14, 41)	45 (25, 98)	174 (80, 508)	81%	97%
		Mouse	5	25.3	42.4	0.910	114 (40, 590)	359 (100, 2862)	3094 (549, 55,278)	69%	89%
LOAEL-to-NOAEL	Developmental subacute LOAEL-to-NOAEL	Rabbit	5	128	1.71	0.922	5.4 (4.3, 8.5)	6.8 (5.1, 12)	10 (7.1, 23)	98%	> 99%
	Developmental subchronic LOAEL-to-NOAEL	Rat	5	110	−24.9	0.961	12 (10, 16)	16 (13, 22)	27 (20, 40)	83%	> 99%
	Developmental chronic LOAEL-to-NOAEL	Rat	6	260	−93.6	0.887	5.3 (4.8, 6.7)	5.9 (5.2, 7.9)	7.3 (6.1, 11)	> 99%	> 99%
	Reproductive chronic LOAEL-to-NOAEL	Rat	5	153	−13.8	0.925	5.1 (4.3, 6.7)	6.2 (5., 8.6)	8.9 (6.7, 14)	> 99%	> 99%
		Mouse	5	23.9	36.6	0.901	274 (75, 3508)	934 (190, 21,417)	9296 (1090, 742,476)	61%	83%

2) UFs for species-to-species and route-to-route extrapolations

UFs		Endpoints	n	$y = a\,x + b$			90th (95% CI)	95th (95% CI)	99th (95% CI)	% of NNIs being protect under default UF of 10	% of NNIs being protect under default UF of 100
				a	b	R^2					
Species-to-species	Rat-to-dog (oral)	Developmental subchronic NOAEL	6	95.1	60.2	0.950	2.3 (1.8, 3.2)	3.1 (2.3, 4.8)	5.5 (3.7, 10)	> 99%	> 99%
		Developmental chronic NOAEL	6	35.3	45.7	0.948	25 (12, 91)	57 (23, 288)	272 (81, 2573)	81%	97%
	Rat-to-mouse (oral)	Acute LD50s	7	42.9	42.7	0.900	15 (9.0, 35)	29 (16, 80)	99 (43, 395)	85%	99%
		Developmental subchronic NOAEL	6	46.1	71.0	0.982	3.2 (2.7, 4.3)	5.9 (4.7, 8.3)	19 (14, 28)	97%	> 99%
		Developmental chronic NOAEL	5	24.4	52.0	0.912	59 (17, 589)	199 (42, 3889)	1925 (221, 134,456)	77%	92%
Route-to-route	Oral-to-dermal (rat)	Acute LD50s	8	48.7	72.2	0.863	2.7 (1.5, 7.3)	4.9 (2.4, 17)	15 (5.5, 78)	98%	> 99%
	Oral-to-inhalation (rat)	Acute LD50s	7	127	90.9	0.961	1.1 (0.9, 1.4)	1.3 (1.1, 1.9)	2.0 (1.6, 3.2)	97%	> 99%

information becomes available, this interim HLV could be adequately protective for the six commonly used neonicotinoids (acetamiprid, clothianidin, dinotefuran, imidacloprid, thiacloprid and thiamethoxam; Table 1) around the globe.

3.3. Uncertainty factors (UFs)

Most pairwise log-normal CTDs using all (Figs. S2 and S3) and common (Figs. S4 and S5) neonicotinoids visually diverged, indicating different sensitivity. This observation was further supported by significantly different slope and/or intercept parameters (Tables S6 and S7). Using the CTD comparisons approach, 18 UFs were identified for a single species (12, 4, 1 and, 1 for rat, mouse, dog, and rabbit, respectively) including LD50-to-NOAEL, exposure durations, and LOAEL-to-NOAEL extrapolations using all hazard data (Tables 3 and S8). Concurrently, additional UFs were identified using CTD comparisons for both datasets having similar neonicotinoids (except rat neurological acute LOAEL-to-NOAEL and mouse acute LD50-to-developmental chronic NOAEL TC ratios ($n < 5$) and five UFs for pairwise datasets having similar neonicotinoids; Tables 4 and S9). Corresponding TC values for the pairwise CTDs contained similar neonicotinoids were estimated (Table S10). Probability distributions were also constructed using all calculated UFs for individual neonicotinoids from the pairwise datasets (Figs. 3 and 4), and overall UFs covering 90%, 95%, and 99% of neonicotinoid chemicals of concern were estimated (Table 5). Meanwhile, probability of encountering each UF for neonicotinoids above or below common factors of 10 or 100 were determined (Table 5).

The UFs are not always applied to chronic NOAELs for toxicity endpoints of concern; rather, UFs represent alternative choices when ideal hazard information is not available. It is also crucial to evaluate uncertainties during hazard and risk assessment, as it directly impacts risk management measures (US EPA, 1995). Despite LD50s not commonly being used in mammalian hazard assessment, the values are sometimes used as a starting point and then adjusted by a larger ACR in an emergency situation or in a screen-level risk assessment, particularly when there are no other types of data available (e.g., State of Michigan) (State of Michigan, 2017). However, the suitability of applying such default ACRs needs to be examined for various chemical classes. As shown in Table S3, there were acute LD50s available for imidaclothiz and nitenpyram, yet developmental or reproductive toxicity information for these insecticides are lacking. If rodent acute LD50s are used as surrogates and divided by a factor of 10 (or 100), the derived chronic developmental or reproductive toxicity profiles (NOAELs) would only provide 16% (or 66%) or 25% (or 76%) of protection (Table 5). Instead, during the present study ACRs of 112 (32, 464) (TC5 ratio)-411 (280, 623) (90^{th} centile) and 58 (5.8, 858)-246 (141, 547) were estimated for neonicotinoids for rat (oral) from TC5 ratios between acute LD50s and developmental and reproductive chronic NOAELs, respectively (Tables 3–5). In addition, an ACR for mouse (oral) was estimated to be 92 (30, 295) using CTD comparisons approach. Subsequently, such mechanistically derived ACR values may be applied with higher confidence than the arbitrary default values of 10 or 100.

When only subchronic/subacute data are available for an endpoint, an extra exposure duration extrapolation factor (e.g., $UF_{S\text{-}C}$) is normally applied to extrapolate chronic exposure. Within a similar developmental response, UF extrapolations for exposure duration were computed for neonicotinoids, and three 95% CIs of four TC5 ratios overlapped with the unity (except for rodent oral developmental subacute-to-chronic UF of 6.2 (2.0, 24) and 3.0 (1.4, 9.0) using all and common neonicotinoids, respectively; Tables 3 and 4), indicating similar sensitivity for particular endpoints of a species across exposure durations. Interestingly, $UF_{S\text{-}C}$ values were species-dependent and were 4.4 (2.7, 10), 22 (14, 41), and 114 (40, 590) for rat, dog, and mouse, respectively, when considering developmental toxicity data from individual UF probability distribution. It appears $UF_{S\text{-}C}$ could be reduced from 10 to 3.8–4.4 for rats (oral), again based on existing information, since a factor of 10 would provide adequate protection with high confidence (97%; Table 5) when rodent developmental subchronic NOAELs were used as surrogates for chronic NOAELs. Similarly, it may be reasonable to reduce UFs for subacute-to-subchronic and subacute-to-chronic extrapolations from 10 to 1.0–6.9 and 3.0–6.2, respectively, for rats (oral) when considering developmental responses. This observation was similar with previous studies (Rulis and Hattan, 1985; Lewis, 1993; Dourson et al., 1996) that 10-fold $UF_{S\text{-}C}$ provided sufficient (or over) protection and could be reduced on a scientific basis (warranted smaller $UF_{S\text{-}C}$). Conversely, the $UF_{S\text{-}C}$ might be increased from 10 to 22 and 114 for dog and mouse, respective, for extrapolating more conservative chronic NOAELs due to low confidence of protection using a 10-fold UF (82% for dog and 69% for mouse; Table 5).

The $UF_{L\text{-}N}$ is another UF applied to LOAELs to estimate NOAEL values. Numerous studies suggested reducing this factor from 10 to lower values (e.g., 2–3 by ECETOC (1995)) for particular chemical classes in practice (Naumann and Weideman, 1995; Dourson et al., 1996; Wang et al., 2018). Based on existing information for neonicotinoids (Tables 3–5), it appears reasonable (with high confidence) to reduce $UF_{L\text{-}N}$ from 10 to 3.4–5.3, 4.3–5.1 and 3.7 when considering developmental (chronic), reproductive (chronic), and neurological (acute) LOAELs, respectively, as surrogates for corresponding NOAEL for rats, and 2.8–5.4 for rabbits when using developmental subacute LOAELs for NOAELs. However, it is exceptionally important to note that a larger $UF_{L\text{-}N}$ of 247 was identified to be more appropriate for mouse (oral) when considering developmental chronic responses.

In the case that relevant data are deficient for a species or an exposure route of interest, health risks resulting from dermal or inhalation exposures are frequently assessed based on rodent oral toxicity data (Freireich et al., 1966; Geraets et al., 2014). For neonicotinoids, differences in data deficiency were remarkable. While dermal and inhalation data were limited, rodent oral hazard data dominated the datasets (Tables S3 and S4). In the case of species-to-species extrapolations, six UFs were derived from rat to dog, mouse, and rabbit considering all available oral acute LD50s, and developmental subacute, subchronic, and chronic NOAELs (Tables 3 and S8; five UFs when considering common neonicotinoids for both datasets; Tables 4 and S9). Surprisingly, calculated UFs for species-to-species extrapolation on the basis of TC5 ratios were all equal to 1, implying there were no significant differences in sensitivity between rat and mouse (developmental subchronic/chronic), rat and dog (developmental subchronic/chronic), neither rat and rabbit (acute). For purposes of conservatism, UFs of 2.3 and 25 were identified for rat-to-dog extrapolations when considering development subchronic and chronic responses, respectively. Similarly, UFs of 15, 3.2, and 59 could be useful for rat-to-mouse extrapolations when considering acute (lethal) and developmental subchronic and chronic effects, respectively.

Because there were only sufficient rodent data (acute LD50s) of neonicotinoids for constructing dermal and inhalation CTDs, oral-to-dermal and oral-to-inhalation UFs were identified for rats (Tables 3–5). Interestingly, it appears that rodent oral LD50s were often smaller than dermal and inhalation LD50s (left shifted oral CTDs to corresponding dermal/inhalation CTDs; Figs. S3g and h and S5g and h), indicating that rats were more sensitive to neonicotinoids under oral exposure than dermal or inhalation exposures, which avoid first pass metabolism. This observation was characterized by the smaller than 1 TC5 ratios (Tables 3 and 4) and individual UFs (87.5% for oral-to-dermal and 100% for oral-to-inhalation; Fig. 4). Thus, based on the analysis presented here, rodent oral hazard data appears to provide sufficient protection if they are used for inhalation extrapolation, with a factor of 2.7 could be recommended for rodent oral-to-dermal extrapolation (Table 5). Further studies should be conducted when additional dermal or inhalation chronic responses (especially for rabbit) are available to compare the corresponding rodent oral CTDs for a particular response. Further meta-analysis should also be conducted when more hazard data are available,

especially for imidaclothiz, nitenpyram, nithiazine, and paichongding, so as to validate and/or refine our current findings.

4. Conclusions

In the present meta-analysis paper, we reviewed and examined public available hazard data for mammal species (rat, dog, mouse, and rabbit) under oral/dermal/inhalation exposures against neonicotinoids. The PHA approach using CTDs for neonicotinoids was subsequently conducted and corresponding TC and 95% CI values were estimated for a particular dataset under a defined exposure scenario for various common mammalian species. These threshold concentrations from a more robust dataset on a data-driven basis can benefit read across when filling data gaps or conducting screening-level risk assessment for neonicotinoids in the future.

In practice, these derived TCs (or adjusted by a factor) represent initial TTC values for future hazard and risk assessment, or could be useful as surrogates for interim HLVs establishment. These thresholds of neonicotinoids and probability values (likelihood of adverse health effects) are also becoming increasingly important in upper-tier risk assessment. Using available hazard data, uncertainty factors were also identified for neonicotinoids including LD50-to-NOAEL, LOAEL-to-NOAEL, and exposure duration extrapolations within a species, in addition to species-to-species (oral: rat-to-dog/mouse/rabbit) and route-to-route (rats: oral-to-dermal/inhalation) extrapolations. These identified UFs, which can be refined with more data availability, appear beneficial for risk practitioners during data dossier development (read across) or conducting screening-level risk assessment especially for neonicotinoids with little or no toxicity information. Risk assessors or managers can also characterize potential hazard of neonicotinoids using these data-driven UFs, which reflect degrees of uncertainty in various cases and inform influences of uncertainty during risk management decisions with additional scientific judgment.

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Conflict of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.01.040.

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