



## Correlation of chemical structure with reproductive and developmental toxicity as it relates to the use of the threshold of toxicological concern

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### ARTICLE INFO

#### Article history:

Received 25 May 2011

Available online 10 October 2011

#### Keywords:

Threshold of toxicological concern

Developmental toxicity

Reproductive toxicity

Cramer Class

Chemical structure

### ABSTRACT

In the absence of toxicological data on a chemical, the threshold of toxicological concern (TTC) approach provides a system to estimate a conservative exposure below which there is a low probability of risk for adverse health effects. The original toxicology dataset underlying the TTC was based on NOELs from repeat dose studies. Subsequently there have been several efforts to assess whether or not these limits are also protective for reproductive/developmental effects. This work expands the database of chemicals with reproductive and developmental data, presents these data in a comprehensive and transparent format and groups the chemicals according to the TTC “Cramer Class” rules. Distributions of NOAELs from each of these classes were used to assess whether the previously proposed TTC values based on repeat dose data are protective for reproductive/developmental toxicity endpoints as well. The present analysis indicates that, for each Cramer Class, the reproductive and developmental endpoints would be protected at the corresponding general TTC tiers derived by Munro et al. (1996).

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### 1. Introduction

The threshold of toxicological concern (TTC) approach is used to estimate a conservative threshold of human exposure to a chemical below which “there would be no appreciable risk to human health” (Kroes et al., 2004). This approach relies on existing toxicological data on chemicals to make conservative inferences about the toxicological potential of substances of untested toxicity, providing a system to identify an acceptable level of exposure to a chemical when toxicological data are limited or missing. The establishment and application of widely accepted TTC values could reduce animal use for toxicity testing and safety evaluations when exposures are below such a threshold, and could facilitate prioritization of testing resources for situations where no alternatives currently exist. This also focuses limited resources on the evaluation of substances with the greatest potential to pose risks to human health. As the ban on animal testing of cosmetic ingredients in the European Union (EU) is currently being phased in with a 2013 target for the banning of repeat dose testing, and as the regulation on Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) legislation continues to be implemented requiring the toxicological assessment of large numbers of chemicals, the pressure to reduce

and eliminate animal testing will continue to increase along with the need to prioritize testing resources. In conjunction with these trends, the importance of non-animal risk assessment approaches like TTC will continue to expand.

The first application of a TTC-based approach by a regulatory agency was the Threshold of Regulation (ToR), which was a single value developed from carcinogenicity data and formally adopted in the mid-1990s by the US FDA as a tool for expediting the assessment of low level migrants from food contact materials. Expansion of the ToR approach resulted in a decision tree that describes TTC values for both cancer and non-cancer endpoints in a tiered system. This was developed as the outcome of an Expert Group of the European branch of the International Life Sciences Institute (ILSI-Europe) and is described in Kroes et al. (2004). It has become the basis for much of the current application of TTC. The application of TTC approaches by other regulatory agencies includes the evaluation of flavoring substances (EFSA, 2004; JECFA, 1996), guidance for thresholds for genotoxic impurities in pharmaceuticals (EMA, 2006, 2007; CDER, 2008), and chemical residues in drinking water (Bruschweiler, 2010; EPHC/NHMRC/NRMMC, 2008). TTC approaches designed to be protective for both cancer and non-cancer endpoints have been proposed for use beyond food contact materials in a number of diverse industries, including cosmetics, consumer and household products (Blackburn et al., 2005; Kroes et al., 2007).

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The framework for the non-cancer tiers in the integrated decision tree described by Kroes et al. (2004) was based on an analysis by Munro et al. (1996) of chronic toxicity data on 613 chemicals. The chemicals were classified according to the Cramer et al. (1978) decision tree placing each chemical into one of three classes (Class I, II, and III) associated with increasing levels of potential toxicity according to their chemical structure. The cumulative distributions of no observed effect levels (NOELs) for the chemicals in each Cramer Class were examined and toxicity thresholds were derived by identifying the 5th percentile NOEL<sup>1</sup> for each distribution, assuming a 60 kg body weight and applying a composite 100× uncertainty factor (UF).

The EU Scientific Committee on Food (SCF, 1996), when it first considered TTC use, raised questions on whether the initial TTC value of 1.5 micrograms per day ( $\mu\text{g}/\text{day}$ ) derived from the cancer database, would adequately cover neurotoxicity, developmental toxicity, endocrinologic effects and immunotoxicity. In the course of evaluating the data to respond to the questions raised by the SCF (1996), Kroes et al. (2000) examined 81 chemicals from the Munro et al. (1996) database with data on developmental toxicity to determine if the distribution of NOELs for the developmental toxicity endpoint indicated more toxicity than the NOEL distribution from the chronic studies for Cramer Class III chemicals as a whole. It was concluded that the cumulative distribution of NOELs from the developmental endpoint database was not significantly different from the cumulative distribution reported by Munro et al. (1996) for the Class III chemicals.

The idea of identifying an exposure threshold for reproductive and developmental toxicity has also been considered as a tool to prioritize the need for conducting a reproductive/developmental toxicity study to meet a regulatory requirement (e.g., under REACH). This was examined by Bernauer et al. (2008) who assembled a database of 91 chemicals with finalized and draft EU Risk Assessment Reports (RARs) available from the EU existing chemicals program in June 2007 with data on fertility or developmental toxicity. From this database of chemicals, Bernauer et al. identified 58 no observed adverse effect levels (NOAELs) for fertility and 62 NOAELs for developmental toxicity. Because of the limited number of data points, the lowest value in the distribution was used to derive the thresholds as opposed to identifying a percentile-based value as was done by Munro et al. (1996). Thresholds were derived by applying a 1000× uncertainty factor (10× for interspecies differences, 10× for human variability, and 10× for uncertainty from a small dataset and severity of the health effects) to the lowest NOAELs from the datasets for each endpoint to give TTC values of 1.5 micrograms per kilogram body weight per day ( $\mu\text{g}/\text{kg}/\text{day}$ ) for fertility and 1.0  $\mu\text{g}/\text{kg}/\text{day}$  for developmental toxicity.

More recently, van Ravenzwaay et al. (2011) utilized a proprietary database of BASF oral developmental toxicity studies to identify and compare TTC values derived for developmental toxicity and corresponding maternal toxicity. Analysis of the cumulative distribution of 93 NOAELs from developmental studies was used to identify the 5th percentile NOAEL. To this 5th percentile NOAEL, a composite UF of 500× (10× for interspecies differences, 10× for human variation, and 5× to account for chemical classes that may be underrepresented in their database) was applied to calculate a TTC of 10  $\mu\text{g}/\text{kg}/\text{day}$ . Using maternal toxicity data on the same chemicals, 92 NOAELs for maternal toxicity were similarly examined to identify a TTC of 8  $\mu\text{g}/\text{kg}/\text{day}$ . Additionally, in order to expand their dataset, van Ravenzwaay et al. (2011) combined their developmental toxicity dataset with data from Kroes et al. (2004)

to give a combined database of 111 chemicals and derived a TTC value of 8  $\mu\text{g}/\text{kg}/\text{day}$ .

A limitation for each of these previous works was the relatively small number of chemicals used in the analyses. Kroes et al. (2000) evaluated the developmental toxicity data of 81 chemicals, while Bernauer et al. (2008) looked at fertility and developmental toxicity data of 91 chemicals; there are 121 unique chemicals between the two datasets. van Ravenzwaay et al. (2011) analyzed 93 chemicals, expanded to 111 with the Kroes data; unfortunately van Ravenzwaay et al. (2011) did not report what chemicals were included in their dataset so examining the overlap with the other analyses is not possible. In addition, the previous evaluations of endpoint specific thresholds for reproductive and developmental toxicity derived the thresholds from distributions of NOAELs without considering the chemical structure component, thereby preventing application of the tiered framework established by Kroes et al. (2004).

The present work looks to expand on the analyses begun by Kroes et al. (2000), Bernauer et al. (2008), and van Ravenzwaay et al. (2011) using a larger dataset of nearly 300 chemicals with data on reproductive and developmental endpoints. This dataset combines the chemicals previously looked at by Kroes et al. (2000) and Bernauer et al. (2008) with additional data available in the published literature. In addition, by incorporating a structural analysis as was done by Munro et al. (1996) using the Cramer et al. (1978) decision tree, a comparison of the structure based endpoint-specific thresholds with the existing Cramer Class-based thresholds is possible.

## 2. Methods

### 2.1. Data set compilation and inclusion criteria

To build a robust distribution of highly reliable NOAELs, we updated the information for chemicals from related published analyses and supplemented this compilation with data for additional chemicals. The selected chemicals were obtained from previous research (Kroes et al., 2000; Bernauer et al., 2008), primary (published) literature, and authoritative reviews (see Table 1). The database of NOAELs was limited to toxicity studies following dose administration by the oral route (i.e., gavage, dietary, or drinking water studies) in traditional laboratory animal species.

To be included in the analysis, the dataset for a particular chemical had to include at least one reproductive or developmental toxicity study using a standard testing protocol. However, sub-chronic or chronic systemic toxicity studies that identified effects for reproductive endpoints or organs were also included, and in some cases were selected as the critical study if effects on the reproductive organs in these studies resulted in a lower NOAEL than using the NOAEL from the reproductive or developmental toxicity study (e.g., 2-chlorophenol, cyclohexylamine hydrochloride, hexachlorobenzene, ronidazole). Studies were reviewed sequentially by two reproductive toxicity experts, followed by a detailed quality review by a group with risk assessment expertise. It is noted that the database was not limited to chemicals for which reproductive or developmental toxicity was identified in a relevant study, but was inclusive of all chemicals for which studies have been identified for these endpoints (including those with no effects identified).

#### 2.1.1. Study quality inclusion criteria

Although the initial literature search and data compilation included all reproductive and developmental toxicity studies that were identified, the studies were then culled based on study quality considerations for final inclusion in the database. Studies were considered of adequate quality for inclusion when they were:

<sup>1</sup> Note that earlier publications referred to the values as NOELs, but it is unclear from the methods description if in fact these were NOELs or NOAELs. For example, they are referred to as NOELs here but in our analysis, we specifically looked to establish no observed adverse effect levels (NOAELs) when available.

**Table 1**  
Authoritative reviews.

Organization*	Document type	Sources
ATSDR	Toxicological Profiles	<a href="http://www.atsdr.cdc.gov/toxprofiles/index.asp">http://www.atsdr.cdc.gov/toxprofiles/index.asp</a>
EU	International Uniform Chemical Information Database (IUCLID); Risk Assessment Reports (EU RARs)	<a href="http://ecb.jrc.ec.europa.eu/esis/">http://ecb.jrc.ec.europa.eu/esis/</a>
OECD	Screening Information Data Set (SIDS) initial assessment documents	<a href="http://www.oecd.org/">http://www.oecd.org/</a>
US EPA	Integrated Risk Information System (IRIS); Reregistration Eligibility Decision (RED) documents	<a href="http://www.epa.gov/iris/">http://www.epa.gov/iris/</a> ; <a href="http://www.epa.gov/opp00001/reregistration/status.htm">http://www.epa.gov/opp00001/reregistration/status.htm</a>
WHO	Environmental Health Criteria documents	<a href="http://www.who.int/ipcs/publications/ehc">http://www.who.int/ipcs/publications/ehc</a>

\* ATSDR, Agency for Toxic Substances and Disease Registry; EU, European Union; OECD, Organization for Economic Cooperation and Development; US EPA, U.S. Environmental Protection Agency; WHO, World Health Organization.

(1) conducted under optimum conditions (i.e., conducted according to internationally accepted guidelines) and followed good laboratory practice (GLP), (2) conducted under a recognized guideline and well documented, or (3) provided sufficient information on methods and results to adequately evaluate the data. Based on such evaluation, each study was assigned a Klimisch score (Klimisch et al., 1997a) and studies assigned a score of 1 (reliable) or 2 (reliable with restriction) were included in the final database for the selection of a critical reproductive or developmental NOAEL. Based on these quality control criteria, edetic acid and tetrasodium ethylenediaminetetraacetate (EDTA) from the original Bernauer et al. (2008) and disodium EDTA from the Kroes et al. (2000) datasets were excluded because available studies were single dose and/or non-guideline studies.

#### 2.1.2. Chemical inclusion criteria

In developing chemical inclusion criteria, we applied guidance for application of the TTC concept published by the ILSI-EU Expert Group (Kroes et al., 2004). For this analysis, any chemicals that were excluded from TTC use by Kroes et al. (2004) were not included. These included heavy metals, organometallic compounds, polyhalogenated dibenzo-*p*-dioxins, polyhalogenated dibenzofurans, polyhalogenated biphenyls, other compounds known to accumulate in the body, and polymers. In addition, compounds that lack a CAS Registry Number or representative structure (such as complex mixtures) were excluded, as this precluded assigning a relevant Cramer classification (see details below). Based on these criteria, seven chemicals from the Kroes et al. (2000) dataset were excluded from evaluation (alkylate 215, Arochlor 1016 and 1254, brominated vegetable oil, sodium lauryl glyceryl ether sulfonate, sucrose polyester, and T2-toxin). Also excluded from this data set was heptachlor epoxide (no core grade study available). Seventeen chemicals from the Bernauer et al. (2008) dataset were excluded because they were heavy metals and/or their salts, while another set of 11 chemicals from the same dataset were excluded because the reproductive/fertility and/or developmental endpoints were identified from inhalation studies and there were insufficient data to reliably extrapolate results to an equivalent oral NOAEL.

Applying the above criteria yielded a final database of 283 chemicals with reliable NOAEL estimates for reproductive or developmental toxicity endpoints (see Appendix A, Table A1). This database includes: (1) 59 chemicals from the Kroes et al. (2000) dataset; (2) 40 chemicals from the Bernauer et al. (2008) dataset as well as an additional 21 chemicals identified from the source used by these authors that have been added since June 2007; and (3) 163 additional chemicals identified from a new literature search of oral developmental toxicity, reproductive toxicity, teratology, embryotoxicity, fetotoxicity and fertility studies found on PubMed Central, the DART database on Toxnet, NTP, IUCLID and SIDS Data sets up to 2006.

The critical studies identified in the Kroes et al. (2000) and Bernauer et al. (2008) datasets were evaluated and/or verified

against authoritative reviews (see Table 1) to ensure that these studies meet the data quality criteria listed above. In addition, a supplemental literature search was conducted on each chemical in these datasets to identify any relevant data from more recent (published and unpublished) studies using the DART database on the U.S. National Library of Medicine's Toxicology Data Network (TOXNET). A number of newer studies or analyses were identified from authoritative reviews that were used to update the datasets for chemicals evaluated by Kroes et al. (2000) or Bernauer et al. (2008). For example, critical studies identified for methoxychlor, linuron, iprodione, hexachlorobenzene, etc. (from Kroes et al. dataset) were replaced with studies identified in US EPA review documents, while studies for 2-(2-butoxyethoxy)ethanol, di-isononyl phthalate, piperazine (from Bernauer et al. dataset) were replaced with studies identified in the EU RAR for these chemicals. Newer critical studies from the updated literature search for a number of chemicals (e.g., methylacetate, ronidazole, and folpet) also were found that impacted the final NOAEL selection. For the Kroes et al. (2000) chemicals, 25 different NOAELs were identified based on authoritative reviews (IRIS, WHO and ATSDR). In these cases, 17 of the NOAELs were lower than those reported by Kroes et al. (2000), while 8 were higher either due to the selection of inappropriate endpoints (e.g., delayed hypersensitivity or systemic toxicity) or NOAEL calculation differences (see Appendix A2, Table A2). For five chemicals (acesulfame potassium, folpet, losartan, ronidazole, and sulfur mustard) without authoritative reviews, NOAELs different from those used in Kroes et al. (2000) were identified using either the same study cited by Kroes et al. (2000) or another study identified during the literature search (see Appendix). While the NOAELs identified for these chemicals trended towards lower values than those used in Kroes et al. (2000), the overall cumulative distribution of the dataset was minimally affected (see Fig. 1).

#### 2.2. Selection of critical study and database NOAELs

Selection of a critical study and effect level (e.g., NOAEL) for the reproductive and developmental endpoint for each chemical was based on generally accepted risk assessment methods (Barnes and Dourson, 1988; US EPA, 2002). As the focus of the analysis was the reproductive and developmental endpoints, maternal toxicity or systemic toxicity was not used as a critical effect for this evaluation. The basic approach included arraying the NOAEL and LOAEL for all reliable studies and selecting the NOAEL for the most sensitive reproductive or developmental endpoint. Since detailed mode of action analyses were not done, health protective assumptions were often made in selecting the critical NOAEL as a default approach. For example, we did not generally favor one species (e.g., primate over rodent studies) or select dosing regimens that might be more relevant to human exposure (e.g., drinking water over gavage studies). Rather we considered all these studies relevant and selected the more sensitive species and dosing regimen.

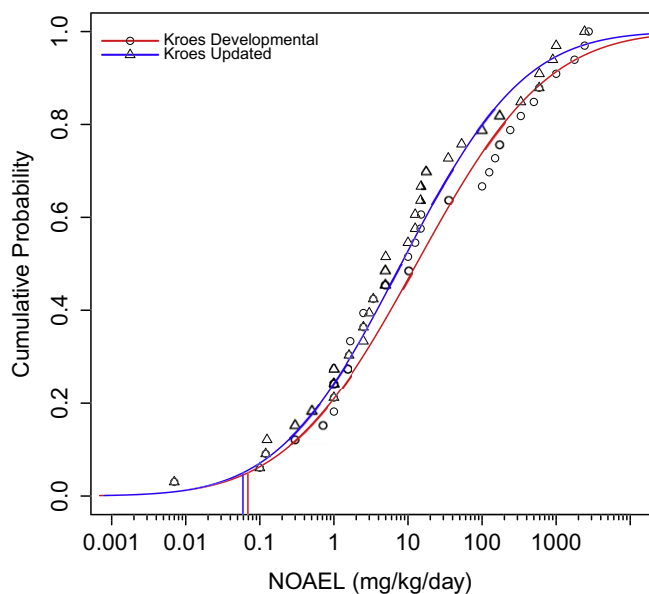


Fig. 1. Cumulative distribution of the Kroes et al. (2000) dataset with historical and updated NOAELs.

For 86 out of 283 chemicals the highest dose tested did not cause any reproductive or developmental toxicity. For example, for hydrochlorothiazide, the highest dose tested in both rats and mice in the available gavage studies did not elicit any developmental toxicity, indicating that these doses are free-standing NOAELs for these endpoints. In these instances, the highest dose tested in the most sensitive species (i.e., the lowest among the pool of free standing NOAELs) was selected as the critical NOAEL for inclusion in the TTC analysis.

For 20 out of 283 chemicals, the lowest dose tested caused adverse reproductive or developmental effects, indicating that only a LOAEL, but not a NOAEL, could be identified from the available literature. It is noted that the analyses by Kroes et al. (2000), Bernauer et al. (2008), and van Ravenzwaay et al. (2011) did not include chemicals for which a NOEL was not identified. It was decided to include these to ensure the dataset was not biased by leaving out chemicals that were shown to be reproductive or developmental toxicants and may be among the more toxic chemicals in the database. Where the dataset was sufficient for modeling, a benchmark dose (BMD) model was calculated using the US EPA Benchmark Dose Software, v. 2.1.2 (available at <http://www.epa.gov/ncea/bmds/>). The BMDL (95% lower confidence limit) was modeled at a 10% response level, with the exception of fetal or pup weight, which were at a 5% level. The BMDL from the best fitting model was chosen, and where more than one model fit well, the value with the best AIC (Akaike's Information Criterion) was chosen. For chemicals where data were not sufficient for BMD modeling, an uncertainty factor of 10 was applied to adjust from the LOAEL to derive a surrogate NOAEL. It is acknowledged that the appropriate size of the UF for LOAEL to NOAEL extrapolation depends on the dose spacing, the shape and slope of the dose-response curve, and the extent and severity of the effect seen at the LOAEL for the specific chemical and that a factor of 3 has been shown to be the median value when ratios of NOAELs and LOAELs are compared (Dourson et al., 1996). Instead of evaluating the dose spacing and severity of effect for each case, in the instances in this database where a LOAEL was used to derive a NOAEL surrogate a factor of 10 was chosen as a conservative default uncertainty factor that is consistent with the uncertainty factors used by Munro et al. (1996) in the existing TTC literature.

The final database includes one NOAEL from a subchronic toxicology study for 2,3-epoxypropyltrimethylammonium chloride. This

NOAEL was for reproductive organ histopathology, and was also the study cited in the EU RAR used in Bernauer et al. (2008). Although an additional factor of 3 for subchronic to chronic extrapolation was used by Munro et al. (1996), in this case an additional uncertainty factor was not applied since the time frame in the selected study is consistent with the time frame generally required for expression of effects on the reproductive organs and is consistent with the less than chronic dosing times for standard reproductive toxicity protocols (US EPA, 2009).

### 2.3. Structural analysis and assignment of Cramer Classes

Each of the 283 chemicals in the combined dataset was classified according to the decision tree method of Cramer et al. (1978) using the Toxtree v1.51 software program (Ideacon Ltd., 2009). This classification identified 203 chemicals in Cramer Class III, 11 chemicals in Cramer Class II, and 69 chemicals in Cramer Class I. It is noted that the distribution of chemicals by Cramer Class from this dataset is consistent with ratios reported by Munro et al. (1996) where the majority of chemicals fell into Class III (448/613) and fewer in Class II (28/613) and Class I (137/613).

## 3. Results

The cumulative distributions of NOAELs for each Cramer Class are shown in Fig. 2. As can be seen in Fig. 2 there is a separation of the distributions for each class indicating a clear effect of structure on toxicity.

The 5th percentile NOAEL was calculated from the distribution for each Cramer Class in a manner consistent with the analysis done by Munro et al. (1996). The 5th percentile NOAELs were found to be 13.1, 1.87, and 0.31 mg/kg/day for Cramer Classes I, II, and III, respectively. From these NOAELs a human exposure threshold was calculated using the same assumptions used by Munro et al. (1996), which include an uncertainty factor of 100x (10x for interspecies differences and 10x for human variation) and a body weight of 60 kg. The human exposure thresholds derived for the reproductive and developmental endpoints are shown in Table 2 with the corresponding values calculated by Munro et al. (1996). In each case the reproductive/developmental threshold was greater than the corresponding Munro et al. (1996) threshold Figs. 3–5.

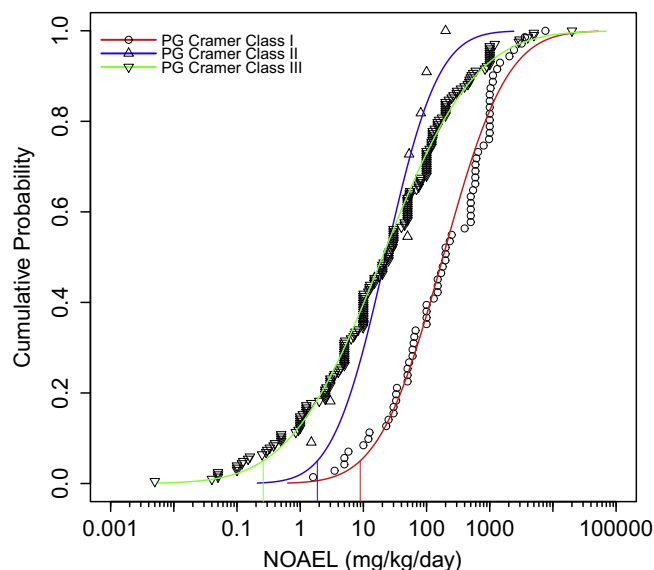


Fig. 2. Cumulative distributions of NOAELs for reproductive and developmental endpoints grouped by Cramer Class for this database.

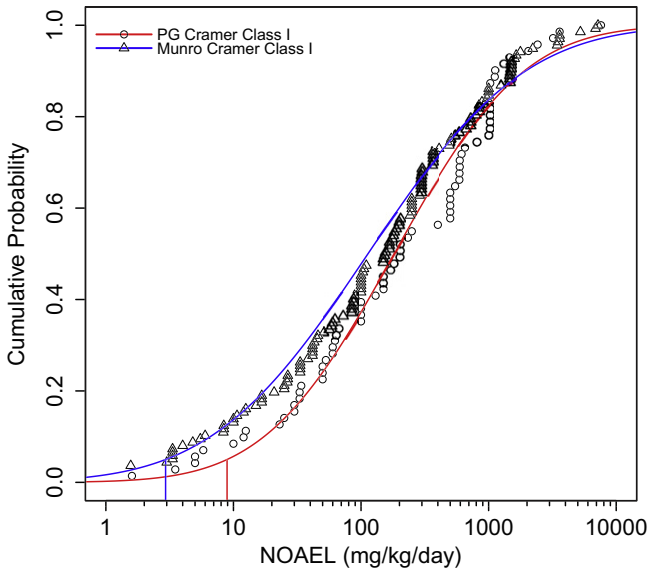


Fig. 3. Overlay of cumulative distributions of Cramer Class I from Munro et al. (1996) and this analysis.

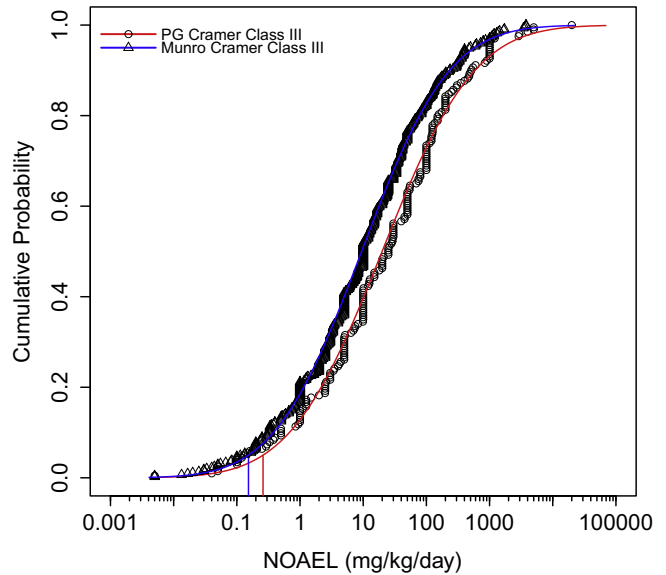


Fig. 5. Overlay of cumulative distributions of Cramer Class III from Munro et al. (1996) and this analysis.

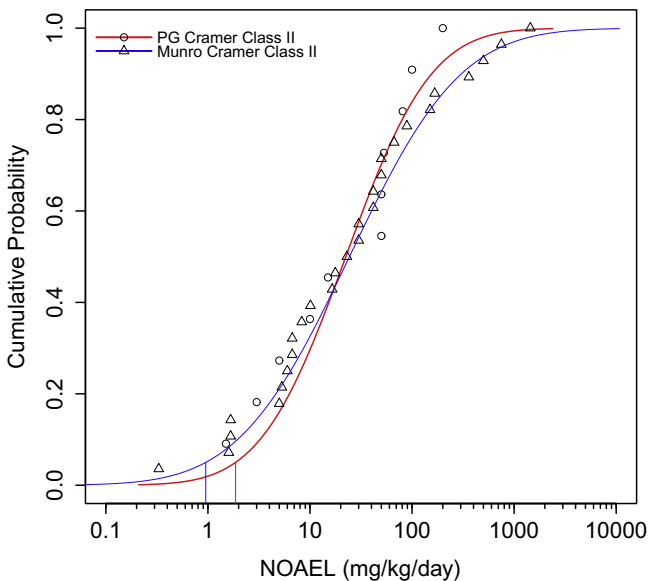


Fig. 4. Overlay of cumulative distributions of Cramer Class II from Munro et al. (1996) and this analysis.

The uncertainty factors were selected to reflect what was used to derive the existing Cramer Class-based thresholds. The rationale for these factors reported by Munro et al. (1996) was that the 100-fold factor, consistent with the factor that would typically be used in establishing safe intake levels, would provide a sufficient margin of safety because the thresholds are based on a large dataset with good supporting toxicological data. In deriving endpoint-specific thresholds for fertility and developmental toxicity, Bernauer et al.

Table 3

Comparison of endpoint-specific thresholds and UFs applied.

	5th Percentile NOAEL (mg/kg/day)	UF applied	Threshold (µg/day)
Fertility (Bernauer)	1.5*	1000	90
Developmental (Bernauer)	1*	1000	60
Developmental (van Ravenzwaay)	4	500	480
Reproductive/developmental (present analysis)	0.57	100	342
Reproductive/developmental Class III	0.31	100	186
Reproductive/developmental Class II	1.87	100	1122
Reproductive/developmental Class I	13.1	100	7860

\* It is noted that Bernauer et al. (2008) did not use a 5th percentile NOAEL, but rather used the lowest NOAEL from their database because of the limitations imposed by the small dataset.

(2008) used an additional uncertainty factor of 10× due to the small dataset (91 substances) and severity of the effects. van Ravenzwaay et al. (2011) included an additional factor of 5× to account for chemical classes that may be underrepresented in their database for a total safety factor of 500. With the larger dataset in the database compiled for this analysis and the conservative nature of our assumptions it was concluded that a 100× uncertainty factor is sufficient.

In order to be able to do a direct comparison to the exposure thresholds derived by Bernauer et al. (2008) and van Ravenzwaay et al. (2011), the 5th percentile NOAEL was calculated from the dis-

Table 2

Comparison of 5th percentile NOAELs and human exposure thresholds.

Class	Reproductive/developmental 5th percentile NOAEL (mg/kg/d)	Munro 5th percentile NOAEL (1996) (mg/kg/d)	Derived reproductive/developmental TTC level (µg/day)	Munro et al. (1996) TTC levels (µg/day)
III	0.31	0.15	186	90*
II	1.87	0.91	1122	540
I	13.1	3	7860	1800

\* It is noted that Munro et al. (2008) have recommended that the TTC for Cramer Class III be raised from 90 to 180 µg/day, based on a reanalysis of the NOAELs after removing the organophosphates from Cramer Class III.

**Table A1**

Reference database of chemicals with reproductive and developmental toxicity data.

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
<i>Cramer Class III</i>								
Chloroform	67-66-3	Dev	Increased implantations, decreased fetal weight	Rat	50	50	126	Thompson et al. (1974)
(R)-Camphor	464-49-3	Dev	No effect	Rabbit	400	400	NA	NTP (1992a)
(1,4)-Dioxino(2,3-b)-1,4-dioxin-2,3,6,7-tetrol, hexahydro-	4405-13-4	Dev	No effect	Rabbit	50	50	NA	NTP (1993a)
1,2,4-Trichlorobenzene	120-82-1	Dev	Alteration of embryonic parameters	Rat	120	120	360	Kitchin and Ebron (1983)
1,3-Benzodioxole-5-propanal, alpha-methyl-	1205-17-0	Dev	No effect	Rat	250	250	NA	Api et al. (2006)
1,3-Dinitrobenzene	99-65-0	Dev	Testicular atrophy	Rat	1.1	1.1	2.7	Linder et al. (1990)
1,4-Dichlorobenzene	106-46-7	2-Gen	Decrease in number of pups between day 1-4 in F1/F2	Rat	30	30	90	Bornatowicz et al. (1994)
1,4-Dioxane	123-91-1	Dev	Embryotoxicity	Rat	517	517	1034	Giavini et al. (1985)
1,6-Diaminohexane	124-09-4	Dev	Embryotoxicity	Rat	112	112	184	Johannsen and Levinskas (1987)
<sup>1</sup> H-Indole-1,3(2H)-dione,2-methyl	550-44-7	1-Gen	Reduced post-weaning body weights and delays in acquisition of puberty in males	Rat	5.0*	NA	50	U.S. EPA (2005)
1-Methoxy-2-hydroxypropane	107-98-2	Dev	Delayed ossification of skull	Rat	0.4	0.4	0.8	Stenger et al. (1972)
1-Methyl-2-pyrrolidinone	872-50-4	Dev	Increased incidence of resorptions; imperforate anus; absence of tail; anasarca; malformations of the great vessels and of cervical arches; decreased fetal body weight; increase in complete ossification of skull bones and of sternebrae	Rat	125	125	250	Saillenfait et al. (2002)
1-Vinyl-2-pyrrolidone	88-12-0	3-Mos drinking water	No effect	Rat	8.3	8.3	NA	BASF (1986), Klimisch et al. (1997b)
2,2',6,6'-Tetrabromo-4,4'-isopropylidenediphenol	79-94-7	2-Gen	No effect	Rat	1000	1000	NA	MPI Research (2002b, 2003)
2,2-Bis(chloromethyl) trimethylene bis[bis(2-chloroethyl) phosphate (V6)]	38051-10-4	2-Gen	Increase in the number of runts	Rat	29	29	86	TNO Quality of Life (2007a)
2,3-Dihydroxynaphthalene	92-44-4	Dev	No effect	Rabbit	450	450	NA	DiNardo et al. (1985)
2,4-Dichlorophenol	120-83-2	1-Gen	Decreased mean litter size	Rat	3	3	30	Exon and Koller (1985)
2,4-Dinitrotoluene	121-14-2	3-Gen	Severe reductions in fertility	Rat	5	5	35	Ellis et al. (1979)
2-Chlorophenol	95-57-8	Subchr Repro	Increase in number of stillborns and decrease in the size of the litters	Rat	5	5	50	Exon and Koller (1982)
2-Furaldehyde	98-01-1	Dev	Possible reduction in fetal body weight	Rat	100	100	150	Nemec (1997)
2-Methoxypropanoic acid	4324-37-2	Dev	Increase in resorption rates; decrease in fetal body weight; increases in incidence of retrocavalureter, paraovarian cysts, irregular pattern of sternebrae ossification; and delayed ossification of distal limb bones and hyoid	Rabbit	26	26	78	Carney et al. (2003)
2-Nitrotoluene	88-72-2	Repro/dev screen	Equivocal retardation in pup growth	Rat	5.0*	NA	50	Huntingdon (1994)
3,4-Dichloroaniline	95-76-1	Dev	Slight but not statistically significant increase in resorptions and consequently post-implantation loss; delay in ossification	Rat	25	25	125	Clemens and Hartnagel (1990)
2,3-Epoxypropyltrimethylammonium chloride (EPTAC)	3033-77-0	28-Day tox	Dose-related incidence and severity of focal atrophy of the testes (males) and follicular atrophy and persistent corpora lutea (females).	Rat	10	10	31.6	Degussa (1990)
4,4'-Isopropylidenediphenol	80-05-7	3-Gen	Reduction in the number of pups per litter	Rat	50	50	500	Tyl et al. (2000)
4-Chloro-2-methyl phenol	1570-64-5	Comb. repeat dose/repro screen	No effect	Rat	600	600	NA	Hansen (1996)
4-Methyl-m-phenylenediamine (toluene, 2,4-diamine)	95-80-7	10 Week tox	Reduced male fertility and impaired spermatogenesis	Rat	5	5	15	Thysen et al. (1985)
4'-Tert-butyl-2',6'-dimethyl-3',5'-dinitroacetophenone	81-14-1	Peri/postnatal tox	Marginal, but statistically significant decrease in body weight gain in F1 males	Rat	2.5	2.5	7.5	Makin and Bottomley (1997)

Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
5-Tert-butyl-2,4,6-trinitro-m-xylene	81-15-2	Peri/postnatal tox	Slight pup toxicity (slightly later day of attainment of air righting and slightly reduced body weight gain)	Rat	7.5	7.5	25	Brooker et al. (1998)
Acephate	30560-19-1	2-Gen	Decreased viability index	Rat	2.5	2.5	25	Chevron Chemical Co. (1987)
Acesulfame potassium	33665-90-6	Dev	No effect	Rabbit	900	900	NA	Baeder and Horstmann (1977)
Acetonitrile	75-05-8	Peri/postnatal	No effect	Rabbit	30	30	NA	Argus Research Labs, Inc. (1984)
Acrylonitrile	107-13-1	3-Gen	Reduced viability (F1a, F1b and F3a) and lactations (F1a, F1b, F2a, F3a) indexes at each dose. Reduced pup body weight (F1–3) 35 mg/kg	Rat	4.1**	NA	8.5	Beliles et al. (1980)
Alar	1596-84-5	3-Gen	No effect	Rat	15	15	NA	Uniroyal Chemical (1966)
Albendazole	54965-21-8	3-Gen	Limb defects	Rat	5	5	6.62	Killeen and Rapp (1975a,b), (1976), Christian (1984), Christian (1987a,b), Hogan and Rinehart (1977), Schroeder and Rinehart (1978)
Aldicarb	116-06-3	Dev	Poor ossification of the sixth sternbra and significant decreases in fetal body weight	Rat	0.125	0.125	0.5	Rhone-Poulenc Ag (1988)
Alfadex	10016-20-3	Dev	No effect	Rat	20000	20000	NA	NTP (1994a)
Alkanes, C10–13, chloro-	85535-84-8	Dev	Increases in the number of post-implantation losses and decrease in viable fetuses per dam	Rat	500	500	2000	Serrone et al. (1987), Unpublished Report 102, ICI Report CTL/C/1171, 10.09.82, 1982
Amitraz	33089-61-1	Dev	Increased fetal death and postimplantation loss; decreased litter size and fetal body weight; increased fetal external, visceral, and skeletal abnormalities; reduced fetal ossifications in many skeletal districts	Rat	3	3	10	Kim et al. (2007)
Ammonium perchlorate	7790-98-9	Dev	Developmental delays in the number of ossification sites in the caudal vertebrae, ribs, sternal centra, and forelimb phalanges	Rat	1	1	30	York et al. (2003)
Aniline	62-53-3	Dev	Reduced postnatal viability	Rat	21	21	100	Price et al. (1985a)
Anthracene, pure	120-12-7	90-Day oral	No effect	Mice	1000	1000	NA	US EPA (1989)
Aspartame	22839-47-0	Dev	No effect	Mice	4000	4000	NA	McAnulty et al. (1989)
Atrazine	1912-24-9	2-Gen	Equivocal decrease in body weights of the F2 male pups	Rat	3.5	3.5	35	Ciba-Geigy Corporation (1987b)
Avermectin B1	65195-55-3	2-Gen	Increased retinal folds in weanlings, decrease viability and lactation indices, decreased pup body weight, increase of dead pups at birth	Rat	0.12	0.12	0.4	Merck and Company (1984)
Azadirachtin	11141-17-6	Dev	No effect	Rat	50	50	NA	Srivastava and Raizada (2007)
Baythroid	68359-37-5	3-Gen	Decreased viability index	Rat	2.5	2.5	7.5	Mobay Chemical Corporation (1983c)
Benomyl	17804-35-2	3-Gen	Decreased pup weanling weights	Rat	5	5	25	E.I. duPont de Nemours and Co. (1968)
Benzidine sulfate	21136-70-9	Dev	No effect	Rat	50	50	NA	DiNardo et al. (1985)
Benzophenone	119-61-9	Dev	Reduced fetal body weight	Rabbit	25	25	45	NTP (2004a)
Berberine chloride dihydrate	5956-60-5	Dev	Decreased fetal body weight, significant for male offspring only	Mice	841	841	1000	Jahnke et al. (2006)
Beta-Thujaplicin	499-44-5	Dev	Increase in postimplantation loss; decreased body weight	Rat	15	15	45	Ema et al. (2004)
Bidrin	141-66-2	3-Gen	Decreased pup survival	Rat	0.1	0.1	0.25	Shell Chemical Company (1965a)
Biphenyl	92-52-4	Dev	No effect	Rat	1000	1000	NA	Khera et al. (1979)
Bis(hydroxylammonium)sulfate (BHAS)	10039-54-0	Dev	No effect	Rat	20	20	NA	BASF (1994)
Bisphenol A	80-05-7	Dev	No effect	Rat	640	640	NA	NTP (1985a)

Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
Boric acid	10043-35-3	Dev	Decrease in fetal body weight per litter; increased incidence of short rib XIII	Rat	55	55	74	Heindel et al. (1992), Price et al. (1996)
Bromodichloromethane	75-27-4	Dev	Minimal delay in ossification of forepaw phalanges and hindpaw metatarsals and phalanges	Rat	45	45	82	Christian et al. (2001)
Bromoform	75-25-2	Cont. breed	Increased neonatal mortality and decreased pup body weight	Mice	100	100	200	NTP (1989a)
But-2-yne-1,4-diol	110-65-6	Dev	No effect	Rat	40	40	80	BASF (1999)
Butylate	2008-41-5	2-Gen	Decrease in mean pup weights; litter size decrease	Rat	10	10	50	Stauffer Chemical Company (1986)
Cacodylic acid	75-60-5	Dev	Diaphragmatic hernia	Rat	12	12	36	Irvine et al. (2006)
Caffeine	58-08-2	Dev	Sternebral and skeletal ossification deficiencies	Rat	10.1	10.1	27.4	Collins et al. (1983)
Captan	133-06-2	1- and 3-Gen	Decreased pup litter weights	Rat	12.5	12.5	25	Stauffer Chemical Company (1982), Chevron Chemical Company (1982)
Carbendazim	10605-21-7	Dev	Increased resorption rate	Rat	5	5	10	Mantovani et al. (1998)
Carbosulfan	55285-14-8	3-Gen	Decreased pup weight and viability	Rat	1	1	12.5	FMC Corporation (1982b)
Chloridazon	1698-60-8	3-Gen	No effect	Rat	135	135	NA	Huntingdon Research Centre (1977)
Chloroacetic acid	79-11-8	13-Week tox	No effect	Rat	150	150	NA	NTP (1992b)
Chlorothalonil	1897-45-6	Dev	No effect	Rabbit	10	10	NA	Farang et al. (2006)
Chlorpromazine hydrochloride	69-09-0	Dev	Increase of malformations (open eye, cleft palate, hydronephrosis, missing rib(s), or fused ribs)	Mice	5	5	15	NTP (1983a)
Chlorpyrifos	2921-88-2	Dev	Pinna detachment, vaginal patency and preputial separation, concurrently with reduced body weight, and decreased pup viability (mainly on days 1-5 postpartum).	Rat	1	1	5	Maurissen et al. (1999)
Chocolate brown HT	4553-89-3	Dev	No effect	Rat	1000	1000	NA	Grant and Gaunt (1987)
Codeine	76-57-3	Dev	Decrease in fetal body weight	Hamster	20	20	100	NTP (1987d)
Cyclohexylamine hydrochloride	108-91-8	Chr oral	Testicular damage	Rat	18	18	60	Gaunt et al. (1976)
Cyclohexylbenzothiazol-2-sulphanamide	95-33-0	Dev	Decreased mean fetal body weights	Rat	69.1	69.1	288.8	Ema et al. (1989)
Cyclophosphamide	50-18-0	2-Gen	Decreased fertility	Rat	3.4	3.4	5.1	Hales et al. (1992)
Cyhalothrin/karate	68085-85-8	3-Gen	Reduced body weight gain in offspring during weaning period	Rat	0.5	0.5	1.5	Coopers Animal Health, Inc. and Imperial Chemical Industries, Ltd. (1984)
Dapsone	80-08-0	Dev	Increase in number of resorptions per litter and gross fetal alterations	Mice	100	100	200	NTP (2004b)
Debendox	8064-77-5	Dev	Delayed ossification of caudal vertebrae	Rat	500	500	800	NTP (1984a)
Decabromobiphenyl ether	1163-19-5	Dev	Decrease in amplitude of the lateral head (ALH) displacement and mitochondrial membrane potential (MMP) and increased generation of hydrogen peroxide in the sperm of adult	Rat	100	100	500	Tseng et al. (2006)
Dibromoacetic acid	631-64-1	2-Gen	Reduced pup body weights	Rat	4.4	4.4	11.6	Christian et al. (2002)
Dichloroacetic acid	79-43-6	1-Gen	Reduced epididymis weight; increase in fused caput sperm; alterations in spermiation, sperm morphology and motility	Rat	54	54	160	Linder et al. (1997)
Didanosine	69655-05-6	Dev	No effect	Mice	2880	2880	NA	NTP (2004c)
Diethanolamine	111-42-2	Dev	Postimplantation loss and mortality	Rat	50	50	125	Price et al. (2005)
Diglyme	111-96-6	Dev	Increase in resorptions; higher incidence of major malformations among surviving fetuses	Rabbit	25	25	50	NTP (1987e)
Diltiazem hydrochloride	33286-22-5	Dev	Increase in supernumerary ribs; cleft palate; decreased fetal weight and gravid uterus weight; number of live fetuses reduced and resorptions increased at 80 mg/kg; no live fetuses at 120 mg/kg/	Mice	5.1**	NA	5	Rogers et al. (1986)



Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
			day					
Dimethyl sulfone	67-71-0	Dev	No effect	Rat	1000	1000	NA	Østergaard (1999)
Dimethyl-4-phenylenediamine	99-98-9	Dev	No effect	Rat	150	150	NA	DiNardo et al. (1985)
Dimethyldioctadecylammonium chloride	107-64-2	Repro/dev screen	Increase in postimplantation losses; lower rate of live borns	Rat	125	125	500	RBM (1999)
Dinitrotoluene	25321-14-6	Dev	Increase in prenatal mortality	Rat	100	100	150	Price et al. (1985b)
Dinoseb	88-85-7	3-Gen	Decreased fetal weight	Rat	0.1*	NA	1	Dow Chemical Company (1981a)
Diphenhydramine hydrochloride	147-24-0	Dev	Reduced fetal body weight	Rat	50	50	100	NTP (1983b)
Diphenyl ether, octabromo der.	32536-52-0	Dev	Slight decrease of the fetal body weight	Rabbit	2	2	5	Breslin et al. (1989)
Diphenyl ether, pentabromo derivate	32534-81-9	Dev	Significant reduction in serum T4 in dams and offspring	Rat	1	1	10	Zhou et al. (2002)
Dipropylene glycol	25265-71-8	Dev	No effect	Rabbit	1200	1200	NA	NTP (1992c)
Disodium 5'-inosinate	4691-65-0	3-Gen	No effect	Rat	2964	2964	NA	Palmer et al. (1975)
Disodium tetraborate, anhydrous	1330-43-4	Dev	Reduction in mean fetal body weight/litter and fetal skeletal effects	Rat	45	45	NA	Price et al. (1996)
Dup 697	88149-94-4	Dev	Intrauterine growth retardation; increase in skeletal variations (delayed and asymmetrical ossification)	Rat	0.05	0.05	3.5	Buridan et al. (2003)
Emodin	518-82-1	Dev	No effect	Rat	80	80	NA	Jahnke et al. (2004)
Endothall	145-73-3	3-Gen	F2B pup mortality	Rat	5	5	125	Pennwalt Corporation (1965)
Ethanol,2-((2'-amino-4'-nitro(1,1'-biphenyl)-2-yl)amino)-	96512-75-3	Dev	No effect	Rat	200	200	NA	DiNardo et al. (1985)
Ethanone,1-((3R,3aS,7R,8aS)-2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)-	32388-55-9	Dev	No effect	Rat	100	100	NA	Lapczynski et al. (2006)
Ethion	563-12-2	3-Gen	No effect	Rat	1.25	1.25	NA	FMC Corp. (1985)
Ethylene dichloride	107-06-2	Dev	Embryotoxicity (increase in non-viable implants and resorption sites per litter)	Rat	158	158	198	Paya et al. (1995)
Ethylenediamine	107-15-3	Dev	No effect	Rabbit	80	80	NA	NTP (1993b)
Express	101200-48-0	2-Gen	Decreased body weight gain during lactation for F1b and F2b pups	Rat	1.25	1.25	12.5	E.I. du Pont de Nemours and Company, Inc. (1986b)
Fenpropathrin (Danitol)	39515-41-8	3-Gen	Changes in pup weight	Rat	1.25	1.25	12.5	Sumitomo Chemical America, Inc. (1979b)
Fenthion	55-38-9	2-Gen	Marginal increase in resorptions	Rat	0.16	0.16	1.12	Kowalski et al. (1989)
Fluoxetine hydrochloride	56296-78-7	Dev	No effect	Rat	12.5	12.5	NA	Byrd and Markham (1994)
Flurprimidol	56425-91-3	2-Gen	Decreased fertility (male and female) and gestation survival with an associated decrease in litter size	Rat	7.3	7.3	74	Eli Lilly and Company (1986a)
Flutolanil	66332-96-5	3-Gen	Reduced fetal body weights	Rat	6.4*	NA	63.7	Nor-Am Chemical Co. (1982a)
Folpet	133-07-3	Dev	Increased in number of fetuses and litters with hydrocephalus with associated skull malformations	Rabbit	10	10	20	Feussner (1984)
Formamide	75-12-7	Dev	Reduced fetal body weight; mild developmental delay	Rat	50	50	100	George et al. (2000)
Fosetyl-al	39148-24-8	3-Gen	Lower weight gains of F2b generation, lower litter and mean weight in late lactation	Rat	300	300	600	Rhone-Poulenc (1981)
Galaxolide	1222-05-5	Dev	Reduced fetal body weight	Rat	150	150	500	Christian et al. (1999)
Genistein	446-72-0	Dev	Increased resorptions; decreased fetal body weight	Rat	100	100	500	McClain et al. (2007)
Gentian violet	548-62-9	Dev	Decreased fetal body weight	Rabbit	0.22**	NA	0.5	NTP (1983f)
Glyphosate	1071-83-6	3-Gen	No effect	Rat	30	30	NA	Monsanto Co. (1981)
Haloxypop-methyl	69806-40-2	3-Gen	Reduced fertility in the F1/F2b generation	Rat	0.005	0.005	0.05	Dow Chemical (1985a)
Hexabromocyclododecane	25637-99-4	2-Gen	Increased pup mortality during lactation	Rat	10	10	100	Ema et al. (2008)
Hexachlorobenzene	118-74-1	Chr feed	Increased pup mortality	Rat	0.29	0.29	1.45	Arnold et al. (1985)
Hexachlorobutadiene	87-68-3	Dev	Slightly reduced body weights	Rat	10*	NA	100	NTP (1990)
Hexachlorocyclopentadiene	77-47-4	Dev	Significant increase in proportion of foetuses with 13 ribs	Rabbit	25	25	75	Murray et al. (1980)
Hexachlorophene	70-30-4	3-Gen	Slight increase in corpora lutea, and slight decrease in mean number of early resorptions; decreased	Rat	1	1	3	Kalo Laboratories, Inc. (1979a)

Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
			number of pups surviving at lactation day 4 of F1a litter; decreased mean pup body weight					
Hydrochlorothiazide	58-93-5	Dev	No effect	Rat	1000	1000	NA	George et al. (1995)
Hydrogen fluoride	7664-39-3	2-Gen	No effect	Rat	10	10	NA	Collins et al. (2001a,b). Sprando et al. (1997, 1998)
Iprodione	36734-19-7	1-Year feed	Decreased prostate weight	Dog	4.2	4.2	15	Rhone-Poulenc (1984)
Iprnidazole	14885-29-1	3-Gen	Repro (damage of testes tubules, lossof spermatogenesis)	Rat	10	10	100	Dale (1976)
Isobutylidene diurea	6104-30-9	Dev	No effect	Rat	1000	1000	NA	Hellwig et al. (1997)
Lactofen	77501-63-4	2-Gen	Reduced mean pup weight	Rat	2.5	2.5	25	PPG Industries (1983a)
Lamivudine	134678-17-4	Dev	No effect	Mice	200	200	1000	NTP (2004d)
Lenalidomide	191732-72-6	Dev	Reduced fetal body weights; increased fetal variations and postimplantation losses and fetal variations	Rat	3	3	10	Christian et al. (2007)
Linuron	330-55-2	Dev	Decrease in fetal body weights and litter size; statistically significant trend in elevation of total skull alterations	Rabbit	0.5*	NA	5	E.I. du Pont de Nemours and Company, Inc. (1986)
Lithium carbonate	554-13-2	Dev	Reduced number of implantation sites; abnormalities including incomplete ossification of sternebrae, wavy ribs, shortening of limb bones, and deformities in scapula and pelvic bones	Rat	50	50	100	Marathe and Thomas (1986)
Losartan	114798-26-4	Dev	Decreased fetal weight and delayed ossification	Rabbit	20	20	40	Hiroyoshi et al. (1994)
Lovastatin	75330-75-5	Dev	Mean fetal weights reduced; increased incidence of skeletal malformations, variations, and incomplete ossifications	Rat	90.4**	NA	100	Lankas et al. (2004)
Melatonin	73-31-4	Dev	No effect	Rat	200	200	NA	Jahnke et al. (1999)
Metam-sodium	137-42-8	Dev	Increased number of dead implantations, reduced number of live fetuses, slight increase in post-implantation loss	Rabbit	10	10	30	BASF AG (1987)
Methacrylonitrile	126-98-7	Dev	No effect	Rabbit	5	5	NA	George et al. (1996)
Methenamine	100-97-0	Repro	No effect	Rat	1.5	1.5	NA	Della Porta et al. (1970)
Methoxsalen	298-81-7	Dev	Increase in percent fetuses with variations (incidence of a rudimentary lumbar rib)	Rat	80	80	120	NTP (1994d)
Methoxychlor	72-43-5	Dev	Excessive loss of litters	Rabbit	5.01	5.01	35.5	Kincaid Enterprises, Inc. (1986)
Methyl bromide	74-83-9	Dev	No effect	Rabbit	10	10	NA	Kaneda et al. (1998)
Methyl chloroform	71-55-6	Dev	Slight increase in mortality	Rat	267	267	2388	NTP (1987f)
Methylarsonic acid	124-58-3	Dev	Skeletal variations	Rabbit	7	7	12	Irvine et al. (2006)
Methylidopa	555-30-6	Dev	Decreased fetal body weight; increased embryotoxicity and fetotoxicity at higher doses.	Rat	50	50	100	NTP (1986b)
Methylene blue	7220-79-3	Dev	Increased percent of resorptions per litter; average fetal body weight reduced	Rat	125	125	200	NTP (1993c)
Methyleugenol	93-15-2	Dev	Intrauterine growth retardation and mildly delayed skeletal ossification	Rat	200	200	500	NTP (2004e)
Metolachlor	51218-45-2	2-Gen	Reduced pup weights	Rat	15	15	50	Ciba-Geigy (1981)
N,N'-methylenebisacrylamide	110-26-9	Dev	Increase in fetal variations per litter	Mice	3	3	10	NTP (1992d)
Naphtha, petroleum, light steam-cracked, debenzenized, C8-16-cycloalkadiene conc.	68478-10-4	Reprod/dev screen	No effect	Rat	100	100	NA	Malley (2003)
Naphthalene	91-20-3	Dev	No effect	Rabbit	120	120	NA	NTP (1992e)
Napropamide	15299-99-7	3-Gen	Decreased body weight gain in pups	Rat	30	30	100	Stauffer Chemical Corporation (1978a)
Nelfinavir	159989-64-	1-Gen	No effect	Rat	1000	1000	NA	Burns-Naas et al. (2003)

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Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
Nicotine	7 54-11-5	Dev	Increased incidence of focal necrosis	Rat	2.6	2.6	4.3	Sheng et al. (2001)
Nitrobenzene	98-95-3	Repro screen	Reduced organ weights for testes and epididymides, decrease in sperm density and sperm motility, increase in percentage of abnormal sperm	Mice	0.94*	NA	9.4	Morrissey et al. (1988a,b)
Nitrofurazone	59-87-0	1-Gen	Copulation and fertility indices decreased; sperm head count reduced; tubular degeneration and interstitial cell hyperplasia; failure of spermiation in tubular epithelia; failure to impregnate female at 25 mg/kg and up [Decreased epididymis weight and inhibited spermiation drove the LOAEL (ARS)]	Rat	5.9**	NA	12.5	Nishimura et al. (1995)
Norflurazon	27314-13-2	Dev	Decreased mean fetal weight, slight delays in ossification of the skull and limbs, and an increase in the incidence of 13th ribs	Rabbit	30	30	60	Hrab et al. (1983a,b)
Oxytetracycline hydrochloride	2058-46-0	Dev	Reduced fetal body weight	Rat	388**	NA	1200	NTP (1983c)
Parathion	56-38-2	Dev	No effect	Rat	1	1	NA	Renhof (1985)
Parathion-methyl	298-00-0	Dev	Developmental delay and marginal increase in resorptions	Rat	0.3*	NA	3	Becker et al. (1987)
Patulin	149-29-1	2-Gen	Increased resorptions	Rat	0.15*	NA	1.5	Dailey et al. (1977)
Pentachlorophenol	87-86-5	Dev	Increased resorptions; reduced live litter size and fetal body weights; increased malformations and variations	Rat	30	30	80	Bernard and Hoberman (2001)
Perboric acid, sodium salt	11138-47-9	Dev	Early fetal resorptions; increase of post implantation loss	Rat	100	100	300	Bussi (1995, 1996)
Phosphoric acid, 1,3-phenylene tetraphenyl ester	57583-54-7	Dev	No effect	Rabbit	1000	1000	NA	Ryan et al. (2000)
Piperazine	110-85-0	2-Gen	Reduced pregnancy index and decreased number of implantation sites, and post implantation losses		125	125	300	Wood and Brooks (1994)
Polysorbate 20	9005-64-5	Dev	No effect	Rat	5000	5000	NA	NTP (1992f)
Polysorbate 80	9005-65-6	Dev	No effect	Rat	5000	5000	NA	NTP (1992f)
Prochloraz	67747-09-5	Dev	Depressed fetal body weight	Rat	5.15	5.15	21.75	Nor-Am Chemical Company (1980)
Propargite	2312-35-8	2-Gen	Postnatal growth retardation	Rat	4	4	20	Kehoe (1990)
Ronidazole	7681-76-7	Chr feed	Testicular atrophy	Rat	10	10	20	Lankas et al. (1988)
Rotenone	83-79-4	2-Gen	Reduced pup weight	Rat	0.38	0.38	1.88	U.S. Fish and Wildlife Service (1983)
Scopolamine hydrobromide anhydrous	114-49-8	Dev	Marginal intrauterine growth retardation and non-dose related trend toward an increase in the incidence of malformations.	Rat	10	10	100	NTP (1987a)
Sethoxydim	74051-80-2	2-Gen	No effect	Rat	54	54	NA	BASF Wyandotte Corporation (1980a)
Sodium chlorate	7775-09-9	Dev	No effect	Rabbit	475	475	NA	NTP (2002)
Sodium fluoride	7681-49-4	Dev	No effect	Rabbit	29	29	NA	NTP (1993d)
Sodium hypochloride	7681-52-9	1-Gen	No effect	Rat	5	5	NA	Carlton et al. (1986)
Sodium selenite	10102-18-8	Chr drinking water	Decrease in epididymal sperm concentration in males	Rat	0.04	0.04	0.13	Nebbia et al. (1987)
Spinosad	168316-95-8	Dev	No effect	Rabbit	50	50	NA	Breslin et al. (2000)
Stavudine	3056-17-5	Dev	Increased prenatal mortality; skeletal or external malformations	Mice	480	480	NA	NTP (2004c)
Sucralose	56038-13-2	Dev	Abortions resulting from maternal gastrointestinal disturbance	Rabbit	350	350	700	Kille et al. (2000)
Sulfamethazine	57-68-1	Dev	Increased incidence of visceral malformations (predominantly hydroureter and hydronephrosis)	Rat	545	545	685	NTP (1985b)

Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
Sulfur mustard (bis(2-chloroethyl)sulfide)	505-60-2	Dev	Reduced ossification of the vertebra and/or sternbrae	Rat	0.05*	NA	0.5	DOA (1987)
Systhane	88671-89-0	Chr feed	Testicular atrophy	Rat	2.49	2.49	9.84	Rohm and Haas Company (1986)
Tebufenozide	112410-23-8	2-Gen	Increase in the number of pregnant females with increased gestation duration and dystocia; decreased number of pups per litter on postnatal days 0 and/or 4	Rat	12.8	12.8	171.1	U.S. EPA (1999)
Tebuthiuron	34014-18-1	2-Gen	No effect	Rat	28	28	NA	Elanco Products (1981)
Tert butyl hydroxyperoxide	75-91-2	Comb. repeat dose/ reproductive/ developmental Screen	No effect	Rat	30	30	NA	Jonker et al. (1993)
Tetrahydrofuran	109-99-9	2-Gen	Reduced pup growth in F1 and F2; delayed eye opening in F2	Rat	305	305	782	BASF (1996)
Theophylline anhydrous	58-55-9	Dev	Fetotoxicity (decreased body weight and reduced number of live fetuses per litter)	Rat	123.8	123.8	217.5	NTP (1985c)
Thiabendazole	148-79-8	Dev	No effect	Mice	200	200	NA	Lankas et al. (2001)
Thiophenol	108-98-5	Dev	Decreased female fetal body weight	Rat	20	20	35	NTP (1994b)
Trichloroethylene	79-01-6	Cont. breed	Reductions in litter size	Rat	75	75	150	NTP (1986a)
Triclopyr butoxyethyl ester	64700-56-7	Dev	Increase in incidence of 14th thoracolumbar rib	Rat	100	100	300	Carney et al. (2007)
Triclopyr-triethylammonium	57213-69-1	Dev	Slightly decreased fetal body weight and reduced skeletal ossification	Rat	100	100	300	Carney et al. (2007)
Tridiphane	58138-08-2	2-Gen	Decreased fertility index	Rat	0.33	0.33	1.67	Dow Chemical (1984)
Trifluralin	1582-09-8	Dev	Abortions; depressed fetal body viability and weight	Rabbit	225	225	500	Byrd et al. (1995)
Triglyme	112-49-2	Dev	Increased fetal mortality	Rabbit	75	75	125	NTP (1987b)
Tris(2-chloro-1-methylethyl) phosphate (TCPP)	13674-84-5	2-Gen	Effects on the uterus weight	Rat	9.9*	NA	99	TNO Quality of Life (2007b)
Tris(2-chloroethyl phosphate) (TCEP)	115-96-8	Repro cont. breed	Reduced litter size in both the F0 and the F1 generations	Mice	175	175	350	Gulati et al. (1991)
Tris(nonylphenyl) phosphite	26523-78-4	Repro/dev screen	Slight reduction of the litter size, on a slight decrease in relative paired epididymides weight in F1 males	Rat	200	200	1000	Tyl et al. (2002)
Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCEP)	13674-87-8	Dev	Increased resorptions and decreased fetal viability index	Rat	100	100	400	Stauffer Chemical Company (1978f)
Zalcitabine	7481-89-2	Dev	Decreased fetal and pup weights	Mice	200	200	400	NTP (1992g)
Zearalenone	17924-92-4	2-Gen	Decreases in fertility, number of viable offspring per litter and numbers of corpora lutea, implantations and resorptions per dam; increases in the incidences of a number of skeletal and soft tissue abnormalities in both the F1B and F2A1 fetuses	Rat	0.1	0.1	1	Becci et al. (1982)
Zidovudine	30516-87-1	Dev	Reduced fetal body weight; skeletal variations (extra ribs on Lumbar I)	Mice	10*	NA	100	NTP (2004b,d)
<i>Cramer Class II</i>								
Acetyl hexamethyl tetralin	21145-77-7	Dev	No effect	Rat	50	50	NA	Christian et al. (1999)
Acrylaldehyde	107-02-8	2-Gen	Reduced pup weight	Rat	3	3	6	Parent et al. (1992)
Acrylamide	79-06-1	80 Days tox	Male mediated implantation loss	Rat	1.5	1.5	2.8	Smith et al. (1986)
Acrylic acid	79-10-7	2-Gen	Reduced pup weight	Rat	53	53	240	BASF (1993)
Benzene, C10-13-alkyl derivs.	67774-74-7	2-Gen	Decreases in litter size, pup viability and weight	Rat	50	50	500	Robinson and Nair (1992)
Benzene, C10-16-alkyl derivs.	68648-87-3	2-Gen	Reduced pup weights	Rat	5	5	50	Robinson and Schroeder (1992)
Butylated hydroxytoluene	128-37-0	2-Gen	Lower body weights at weaning and during lactation period.	Rat	100	100	250	McFarlane et al. (1997)
Ethyl maltol	4940-11-8	Chronic feed	No effect	Rat	200	200	NA	Gralla et al. (1969)

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Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
Gemfibrozil	25812-30-0	Dev	No effect	Rat	81	81	NA	Kurtz et al. (1976)
Phenol, 4-nonyl-, branched	84852-15-3	3-Gen	Slight changes in the oestrous cycle length, the timing of vaginal opening and possibly also in ovarian weight and sperm/spermatid count	Rat	15	15	50	NTP (1997)
Phenol, nonyl-	25154-52-3	2-Gen	Decrease in numbers of implantation sites and live pups, decrease in ovary weight in females; reduced viability of offspring from pnd 0–4 decreased	Rat	10	10	50	Nagao et al. (2001)
<i>Cramer Class I</i>								
1,2,3,4-Butanetetracarboxylic acid	1703-58-8	Dev	No effect	Rat	1000	1000	NA	George et al. (2001a)
1,2-Benzenedicarboxylic acid, di-C6–8-branched alkyl esters, C7-rich	71888-89-6	2-Gen	Reduced bodyweight and reduced anogenital distance in F1 and F2 pups	Rat	64	64	309	McKee et al. (2006)
1,2-Benzenedicarboxylic acid, di-C7–9-branched and linear alkyl esters	68515-41-3	Dev	Increased incidence of supernumerary lumbar ribs	Rat	500	500	1000	Fulcher et al. (2000)
1,2-Benzenedicarboxylic acid, di-C8–10-branched alkyl esters, C9-rich	68515-48-0	Dev	Increased in rudimentary lumbar ribs	Rat	500	500	1000	Waterman et al. (1999)
1,2-Benzenedicarboxylic acid, di-C9–11-branched alkyl esters, C10-rich	68515-49-1	2-Gen	Decrease in survival Indices in the second pup generation (F2)	Rat	33	33	117	Exxon Biomedical Sciences (1997c, 2000)
1,2-Benzenedicarboxylic acid, di-C9–11-branched and linear alkyl esters	68515-43-5	Dev	Increased incidence of supernumerary lumbar ribs; increase in dilated renal pelves	Rat	250	250	500	Fulcher et al. (2000)
1,4-Butanediol	110-63-4	Dev	Decreased fetal body weight	Mice	100	100	300	NTP (1994c)
1-Butanamine, hydrochloride	3858-78-4	Dev	Increased embryonic resorptions; reduced fetal and placental weight; retarded skeletal development; malformations such as filiform/kinked tail, enlarged cardiac ventricular chamber(s), malpositioned heart, aortic arch atresia, and diaphragmatic hernia	Rat	100	100	400	Gamer et al. (2002)
1-Butanol	71-36-3	Dev	Decreased fetal weight	Rat	1454	1454	5654	Ema et al. (2005)
2-(2-Butoxyethoxy)ethanol	112-34-5	1-Gen	Decreased body weight gain of pups during later stages of lactation	Rat	500	500	1000	Nolen et al. (1985)
2-(2-Methoxyethoxy)ethanol	111-77-3	Dev	Decreased in pup survival; visceral malformation of the cardiovascular system	Rat	200	200	600	Yamano et al. (1993)
2,4,4-Trimethylpentene	25167-70-8	Repro/dev screen	No effect	Rat	1000	1000	NA	Huntingdon Life Sciences, Ltd. (1997b)
2-Butanol	78-92-2	2-Gen	Decreased pup body weight	Rat	594	594	1771	Cox et al. (1975)
2-Butoxyethylacetate	112-07-2	Cont. breed	Fertility impairment	Mouse	976	976	1816	Morrissey et al. (1988a,b, 1989), Heindel et al. (1990)
2-Ethoxyethanol	110-80-5	Dev	Increase in the number of early and late prenatal death	Rat	23	23	46.5	Stenger et al. (1971)
2-Ethylhexanol	104-76-7	Dev	Reduced mean fetal body weights; increased frequency of fetuses with skeletal variations and retardations; increased number of resorptions and increased post-implantation loss	Rat	130	130	650	BASF (1991)
2-Ethylhexyl octadecanoate	22047-49-0	Dev	No effect	Rat	1000	1000	NA	Aulmann et al., 2000
3-Xylene	108-38-3	Dev	Increased incidence of resorptions	Mouse	652.5	652.5	867	Nawrot and Staples, 1980
4-Tert-butylbenzoic acid	98-73-7	Cont. breed	Slight reduction of fertility (infertility/inability to impregnate), without histopathological changes	Rat	1.6	1.6	7.9	Hoechst AG (1987)
4-Tertbutylphenol	98-54-4	2-Gen	Effects on fertility: significant decreased body weight gain in F1 males, decrease in pup bw and litter weight in F1 and F2	Rat	67	67	200	Clubb and Jardine (2006)
Allura red AC dye	25956-17-6	Dev	Reduced ossification of the hyoid and average number of foetuses per litter with at least two skeletal variations	Rat	545.7	545.7	939.3	Collins et al. (1989)
Amaranth	915-67-3	3-Gen	No effect	Rat	2420	2420	NA	Collins et al. (1975)

Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
Annatto (Natural Orange)	1393-63-1	Dev	No effect	Rat	500	500	NA	Paumgarten et al. (2002)
Aspirin	50-78-2	Dev	Decreased placental weight, developmental variations (increased incidence of fetuses with runts, exophthalmos, and distended ureter), malformations	Rat	17***	NA	50	Gupta et al. (2003)
Benzoic acid	65-85-0	Dev	Decreased fetal weight gain; significant increases in malformations, development variations, and variations due to retarded development	Rat	30	30	160	Østergaard (1999)
Benzyl butyl phthalate	85-68-7	2-Gen	Reduced anogenital distance in F1 and F2 offspring;	Rat	50	50	250	Tyl et al. (2004)
Butylated hydroxyanisole	25013-16-5	1-Gen	Decreases in testes and ventral prostate weights in F1 rats.	Rat	10	10	100	Jeong et al. (2005)
Butylparaben	94-26-8	10 Weeks tox	No effect	Rat	1088	1088	NA	Hoberman et al. (2008)
Cekanoic C8 acid	25103-52-0	Dev	no effect	Rat	800	800	NA	Ambroso et al. (1999)
D 003 (fatty acids)	312700-63-3	Dev	No effect	Rat	1000	1000	NA	Rodriguez et al. (2003)
Di-(2-ethylhexyl) terephthalate	6422-86-2	1-Gen	Reduction in rate of body weight gain	Rat	614	614	NA	Faber et al. (2007)
Di(ethylhexyl) adipate	103-23-1	1-Gen	Reduced offspring weight gain, total litter weight, and litter size	Rat	170	170	1080	ICI Central Toxicology Laboratory (1988a,b)
Dibutyl phthalate	84-74-2	Dev	Reduced birth weight; reduced number of live pups per litter; reduced body weight gain; reduced male anogenital distance; damage to reproductive system of mature male rats	Rat	50	50	250	Zhang et al. (2004)
Diethyl phthalate	84-66-2	Dev	Increase in skel. variations	Rat	1770	1770	3640	NTP (1984b)
Diethylene glycol	111-46-6	Dev	No effect	Rat	1118	1118	4472	Union Carbide Corporation (1992), Ballantyne and Snellings (2005)
Diethylene glycol diethyl ether	112-36-7	Dev	Decreased body weight of female fetuses	Rabbit	200	200	400	NTP (1987c)
Diethylhexyl phthalate	117-81-7	Dev	Significant increase in bilateral aspermatogenesis	Rat	5.8	5.8	29	David et al., 2000
Di-"isodecyl" phthalate	26761-40-0	2-Gen	Decrease in survival indices	Rat	33	33	114	Exxon Biomedical Sciences (2000)
Di-"isononyl" phthalate	28553-12-0	2-Gen	Decrease in offspring body weight	Rat	53	53	159	Exxon Biomedical Sciences (1996), Nikiforov et al. (1995)
Dimethyl phthalate	131-11-3	Dev	No effect	Rat	3600	3600	NA	NTP (1989b)
Dimethyldicarbonate	4525-33-1	3-Mos tox	No effect	Rat	590	590	NA	Eiben et al. (1983)
Erythritol	149-32-6	2-Gen	No effect	Rat	7600	7600	NA	Waalkens-Berendsen et al. (1996)
Ethyl acetoacetate	141-97-9	Repro/dev screen	No effect	Rat	1000	1000	NA	LPT, 1999 (2000)
Ethylene glycol	107-21-1	Dev	Reduced body weight; fused ribs and arches; poor ossification in thoracic and lumbar centra; increased occurrence of extra 14th rib	Mouse	150	150	500	Neeper-Bradley et al. (1995)
Ethylene glycol diethyl ether	629-14-1	Dev	Increase in malformations including short tail, small spleen, fused sternbrae, and fused rib cartilage	Rabbit	25	25	50	George et al. (1992)
Glycolic acid	79-14-1	Dev	Mean fetal weight reduced; increased incidence of skeletal (ribs, vertebra, sternbra) malformations and variations; fused ribs and fused vertebra	Rat	150	150	300	Munley et al. (1999)
Hydroquinone	123-31-9	Dev	No effect	Rabbit	150	150	NA	Blacker et al. (1993)
Isoeugenol	97-54-1	Dev	Decreased fetal body weight; increased incidence of unossified sternbrae	Rat	500	500	1000	George et al. (2001b)
Limonene	138-86-3	Dev	Increased incidences of lumbar rib, fused rib, delayed ossification, and decreased body weight gain	Mice	591	591	2363	Kodama et al. (1977)
Methacrylamide	79-39-0	Dev	Decreased fetal body weight; increased proportion	Mice	60	60	120	NTP (1991a)

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Table A1 (continued)

Chemical name	CAS#	Study type	Study effect	Species	Risk value for analysis (mg/kg-day)	NOEL/NOAEL (mg/kg-day)	LEL/LOEL/LOAEL (mg/kg-day)	References
Methyl acetate	79-20-9	Dev	of nonlive implants per litter No effect	Rat	3200	3200	NA	Cummings (1993)
Methyl carbamate	598-55-0	Chronic drinking water	No effect	Rat	62.5	62.5	NA	Steinhoff et al. (1977)
Methyl ethyl ketone (MEK)	78-93-3	2-Gen	Decreased pup body weight	Rat	594	594	1771	Cox et al. (1975)
Methyl malonate	108-59-8	1-Gen	No effect	Rat	1000	1000	NA	Degussa AG (2003)
Mono-(2-ethylhexyl)phthalate	4376-20-9	Dev	Increased malformations and mortality per litter	Mice	10.7**	NA	35	NTP (1991b)
<i>n</i> -Butoxyethanol	111-76-2	Dev	Reduced embryo viability	Rat	100	100	200	NTP (1989c)
Octadecenyamine	112-90-3	Dev	No effect	Rabbit	30	30	NA	Springborn Laboratories Inc. (1989b)
Oxtripitan	4350-09-8	Dev	Significant increase in percent resorptions and affected (non-live plus malformed) fetuses per litter; increase in average fetal body weight per litter; Visceral malformations (hydrourerter, hydronephrosis, renal agenesis, hydrocephaly); gross malformations (anophthalmia and microphthalmia); skeletal (short rib and missing rib)	Rat	150	150	300	NTP (1983d)
Pentane	109-66-0	Dev	No effect	Rat	1000	1000	NA	Exxon Biomedical Sciences (1997a,b)
Phenol	108-95-2	Dev	Decreased fetal body weight; increased number of litters with resorptions	Rat	60	60	120	NTP (1983e)
Potassium carbonate	584-08-7	Dev	No effect	Rat	180	180	NA	NTIS (1975)
Resorcinol	108-46-3	2-Gen	No effect	Rat	233	233	NA	WIL Research Laboratories, LLC. (2005)
Sodium benzoate	532-32-1	Dev	Number of dead/resorbed fetuses; body weight of viable fetuses; mild systemic edema; anophthalmia; microphthalmia	Rat	1310	1310	NA	Onodera et al. (1978)
Sodium lauryl trioxethylene sulfate	13150-00-0	2-Gen	No effect	Rat	199	199	NA	Tusing et al. (1962)
Tallow alkylamines	61790-33-8	Repro/dev screen	Lower fertility index and a lower conception rate	Rat	12.5	12.5	50	Instituto di Ricerche Biomediche (2000b)
Thiodiglycol	111-48-8	Dev	Increase in the incidence of dumbbell ossifications of thoracic vertebral bodies	Rat	400	400	1000	BASF AG (1995)
Trolamine	102-71-6	Dev	No effect	Mouse	1125	1125	NA	Environmental Health Research Testing Inc. (1989)
Vinyl acetate	108-05-4	2-Gen	Significant reduction in weight gain of the F1 pups	Rat	100	100	500	Mebus et al. (1995)
Xylene	1330-20-7	Dev	Mean fetal weight decreased; increase in the incidence of cleft palate	Mice	1030	1030	2060	Marks et al. (1982)

\* Risk value derived from LOAEL.

\*\* Risk value derived from BMDL.

\*\*\* BMD modeling resulted in a value greater than the marginal LOAEL, a conservative risk value for analysis was derived from the LOAEL using an UF of 3; reproductive toxicity studies have been specified as 1-, 2- or 3-generation; developmental toxicity studies evaluate adverse effects that may result from exposure prior to conception (either parent), during prenatal development, or postnatally until the time of sexual maturation; peri/postnatal studies include those in which pregnant dams are exposed to the test substance during the late part of gestation, during parturition and lactation.

tribution of NOAELs for the entire dataset assembled for this work and found to be 0.57 mg/kg/day. This provides a human exposure threshold of 342 µg/day (using 60 kg-bw and a composite UF of 100×). Table 3 shows the values identified from the overall distribution for each endpoint-specific threshold derived and it shows that the expanded dataset assembled here adequately covers chemicals in the same toxicity ranges of the previous analyses, and any differences in magnitude of the thresholds stem from choosing different uncertainty factors.

#### 4. Discussion

The goal of this analysis was to develop structure-based exposure thresholds for reproductive and developmental endpoints taking advantage of the concept that the structure of a chemical is an important factor in its toxicity. An expanded dataset of chemicals with toxicity data for reproductive and developmental toxicity was assembled and exposure thresholds for the three Cramer Classes were developed that provide a conservative value for protection of human health with respect to reproductive and developmental endpoints in cases where chemical specific data are lacking. Importantly, this analysis demonstrates that use of the Munro et al. (1996) thresholds provide a conservative value for protection of human health with respect to reproductive and developmental endpoints,

even with the proposed increase of the Cramer Class III threshold to 180 µg/day (Munro et al., 2008). Confidence in this conclusion is increased by the fact that sequential independent analyses have reached similar conclusions. In addition, revisiting values based on older studies and incorporating new data or more recent risk assessment perspectives did not substantively alter the conclusions of the analysis. It is suggested that any additional analyses to evaluate whether or not there is adequate protection using the existing Cramer Class values for other endpoints or for other chemical groupings or structures be conducted in a manner that includes an analysis using the same principles and methods as the original analysis such that the values can be directly compared.

#### Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

#### Acknowledgments

The authors gratefully acknowledge Mariam Nasir for initiating the compilation of the P&G dataset and Dr. Ulrike Bernauer for sharing the database of RARs used in her 2008 analysis allowing us to expand our analysis and do key relevant comparisons.

This work was funded by The Procter & Gamble Company.

**Table A2**

Values updated from Kroes et al. (2000).

Chemical name	CAS#	Cramer Class	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Kroes et al. (2000) NOEL (mg/kg/day)	Kroes et al. (2000) LOEL (mg/kg/day)	References
2,4-Dichlorophenol	120-83-2	III	3	30	0.3	3	Exon and Koller (1985)
2-Chlorophenol	95-57-8	III	5	50	1.66	50	Exon and Koller (1982)
Acrylic acid	79-10-7	II	53	240	240	460	BASF (1993)
Albendazole	54965-21-8	III	5	6.62	1	10	Killeen and Rapp (1975a,b, 1976), Christian (1984, 1987a,b), Hogan and Rinehart (1977), Schroeder and Rinehart (1978)
Aldicarb	116-06-3	III	0.13	0.5	0.7	None	Rhone-Poulenc Ag (1988)
Captan	133-06-2	III	12.5	25	500	None	Chevron Chemical Company (1982)
Cyclohexylamine hydrochloride	108-91-8	III	18	60	100	150	Gaunt et al. (1976)
Cyhalothrin/karate	68085-85-8	III	0.5	1.5	1.5	5	Coopers Animal Health, Inc. and Imperial Chemical Industries, Ltd. (1984)
Dinoseb	88-85-7	III	0.1*	1	10	None	Dow Chemical Company (1981a)
Fenpropathrin (Danitol)	39515-41-8	III	1.25	12.5	3	9	Sumitomo Chemical America, Inc. (1979b)
Hexachlorobenzene	118-74-1	III	0.29	1.45	0.08	0.29	Arnold et al. (1985)
Hydroquinone	123-31-9	I	150	NA	50	150	Blacker et al. (1993)
Methoxychlor	72-43-5	III	5.01	35.5	10	50	Kincaid Enterprises, Inc. (1986)
Methyl ethyl ketone (MEK)	78-93-3	I	594	1771	1771	3122	Cox et al. (1975)
Napropamide	15299-99-7	III	30	100	100	None	Stauffer Chemical Corporation (1978a)
Norflurazon	27314-13-2	III	30	60	18.75	51.25	Hrab et al. (1983a,b)
Prochloraz	67747-09-5	III	5.15	21.75	7.5	31.25	Nor-Am Chemical Company (1980)
Rotenone	83-79-4	III	0.38	1.88	1.88	3.8	U.S. Fish and Wildlife Service. (1983)
Sethoxydim	74051-80-2	III	54	NA	18	54	BASF Wyandotte Corporation. (1980a)
Benomyl	17804-35-2	III	5	25	125	None	E.I. duPont de Nemours and Co. (1968)
Systhane	88671-89-0	III	2.49	9.84	2.32	9.28	Rohm and Haas Company. (1986)
2-Butanol	78-92-2	I	594	1771	1771	3122	Cox et al. (1975)
Linuron	330-55-2	III	0.5*	5	6.25	31.25	E.I. du Pont de Nemours and Co., Inc. (1986)
Patulin	149-29-1	III	0.15*	1.5	0.64	None	Dailey et al. (1977)
Flutolanil	66332-96-5	III	6.4*	63.7	63.7	661.8	Nor-Am Chemical Co. (1982a)
Acesulfame potassium	33665-90-6	III	900	NA	2751	None	Baeder and Horstmann (1977)
Folpet	133-07-03	III	10	20	34.5	160	Feussner (1984)
Glyphosate	1071-83-6	III	30	NA	10	30	Monsanto Co. (1981)
Ronidazole	7681-76-7	III	10	20	60	None	Lankas et al. (1988)
Sulfur mustard (bis(2- chloroethyl)sulfide)	505-60-2	III	0.05*	0.5	0.1	0.4	DOA (1987)

\* Risk value derived from LOAEL.



## Appendix A

See Tables A1 and A2.

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