Protocol to Update to the Haws et al. (2006) Database of Mammalian Relative Potency Estimates for Dioxin-like Compounds

Background

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDD/Fs), and dioxin-like polychlorinated biphenyls (DL-PCBs) are persistent and bioaccumulative compounds which are considered to be relatively ubiquitous in the diet and environment. A subset of these – seventeen laterally-substituted PCDD/F congeners, and 12 non-/mono-ortho chlorine-substituted PCBs commonly referred to as dioxin-like compounds (DLCs) – are of interest to a variety of stakeholders due to their potential health effects and importance in risk assessment and site remediation.[1] In order to assess the potential health effects from individual congeners, the World Health Organization (WHO) has developed Toxic Equivalency Factors (TEFs) based on relative estimates of potency (REPs) reported in the literature. TEFs represent a single value informed by many REPs, which may span a very large range (i.e., orders of magnitude) for each congener. The WHO TEFs are a key component of the human health risk assessment process utilized by USEPA for PCDD/Fs and DL-PCBs. REP values for DLCs were first summarized by scientists at the Karolinska Institute in 1997 (unpublished), which ultimately served as the basis for the establishment of WHO TEFs for mammals, birds, and fish.[2] This database was later updated by Haws et al. (2006), which includes REPs generated through the end of 2004, and was utilized by WHO in the development of the current set of TEFs.[3] Of note, the current WHO TEFs were established based solely on qualitative scientific judgment and represent single point estimates of potency. As a result, the variability in the underlying REP distributions is not captured, and uncertainty inherent to human health risk estimates based on current TEFs cannot be characterized quantitatively. To address this limitations, WHO has suggested that "*…in the future weighted distributions could be used for derivation of TEF values, but establishing consensus values for these REP weighting factors would require additional expertise.*" Further, the WHO expert panel recognized that the methods used to derive REPs were different, and implementation of a more uniform approach to characterizing REPs (i.e., dose-response comparisons) would be ideal.

This review involves updating the Haws et al., (2006) REP database by adding data published in the scientific literature between 2005 and 2018, as well as addressing recommendations from the WHO expert panel in regard to weighting and REP derivation methods. A literature search using PubMed and Embase (scientific literature databases) will be conducted, and studies that provide

[1] Haws, L.C., et al., 2006. Development of a refined database of mammalian relative potency estimates for dioxin-like compounds. Toxicol Sci 89(1):4-30.
[2] van den Berg, M., et al., 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs, for humans and wildlife. Environ Health Perspect. 106, 775.
[3] van den Berg, M., et al., 2006. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 93(2):223-241.

concentration- or dose-response data suitable for the calculation of a REP will be included in the updated database. Specifically, this involves the systematic identification and extraction of data from studies that evaluate any DLC, in addition to a reference compound (i.e., TCDD or PCB126) at the outcome or endpoint level (as opposed to the study- or model-level). Author-reported data will then by synthesized in a manner which addresses weighting for quality and relevance as well as implements computational advances in dose-response techniques to address consistency in REP derivation method. The result will be a REP database that is updated through the end of 2018. It is anticipated that this research may be used to inform an update of current WHO TEFs, as well as to inform the variability and uncertainty around TEF estimates.

Research Objective

The research question (boxed) reflects the review question in population, exposure, comparator, and outcome (PECO) format, recognizing that the overall research project is being facilitated by systematic review though will require use of techniques and methods that are not standard in the practice of systematic review for clinical medicine but rather refined methods unique to toxicology[4].

Review objective:
Systematically identify and characterize data that informs the relative potency of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), or dioxin-like polychlorinated biphenyls (PCBs) in mammals across outcomes, study types, and species, based on synthesis via an updated REP database and integration using weighting criteria specific to the reliability and relevance for DLC REPs and Bayesian methods for characterizing dose-response.

PECO and Inclusion/Exclusion Criteria

The study PECO and inclusion criteria were developed based on that applied for the Haws et al., 2006 database with minor modifications.

Population (P): mammalian species with biological relevance to humans

Include studies evaluating effects of DLCs in:

- Mammalian experimental animals (e.g., rodents, non-human primates)
- *in vitro* assays with human or mammalian cells, or those which have been transfected with a biologically relevant sequence (e.g., DR CALUX)
- QSAR studies

[4] Wikoff, D. S., and Miller, G. W. (2018). Systematic Reviews in Toxicology. *Toxicol Sci* 163(2), 335-337.

Exclude studies evaluating effects of DLCs in

- non-mammalian or marine mammalian species

Exposure (E): exposure to a single DLC at more than one dose or concentration

Include studies evaluating controlled exposure to TCDD or PCB126 and at least one of the following congeners:

- 1,2,3,7,8-pentachlorodibenzodioxin (12378PeCDD);
- 1,2,3,4,7,8-hexachlorodibenzodioxin (123478HxCDD);
- 1,2,3,7,8,9-hexachlorodibenzodioxin (123789HxCDD);
- 1,2,3,6,7,8-hexachlorodibenzodioxin (123678HxCDD);
- 1,2,3,4,6,7,8-heptachlorodibenzodioxin (1234678HpCDD);
- 1,2,3,4,6,7,8,9-Octachlorodibenzodioxin (OCDD);
- 2,3,7,8-tetrachlorodibenzofuran (TCDF);
- 1,2,3,7,8-pentachlorodibenzofuran (12378PeCDF);
- 2,3,4,7,8-pentachlorodibenzofuran (23478PeCDF);
- 1,2,3,4,7,8-hexachlorodibenzofuran (123478HeCDF);
- 1,2,3,7,8,9-hexachlorodibenzofuran (123789HeCDF);
- 1,2,3,6,7,8-hexachlorodibenzofuran (123678HeCDF);
- 2,3,4,6,7,8-hexachlorodibenzofuran (234678HeCDF);
- 1,2,3,4,6,7,8-heptachlorodibenzofuran (1234678HeCDF);
- 1,2,3,4,7,8,9-heptachlorodibenzofuran (1234789HpCDF);
- 1,2,3,4,6,7,8,9-Octachlorodibenzofuran (OCDF);
- 3,3',4,4'-tetrachlorobiphenyl (PCB77);
- 3,4,4',5-tetrachlorobiphenyl (PCB81);
- 2,3,3',4,4'-pentachlorobiphenyl (PCB105);
- 2,3,4,4',5-pentachlorobiphenyl (PCB114);
- 2,3',4,4',5-pentachlorobiphenyl (PCB118);
- 2,3',4,4',5'-pentachlorobiphenyl (PCB123);
- 3,3',4,4',5-pentachlorobiphenyl (PCB126);
- 2,3,3',4,4',5-hexachlorobiphenyl (PCB156);
- 2,3,3',4,4',5'-hexachlorobiphenyl (PCB157);
- 2,3',4,4',5,5'-hexachlorobiphenyl (PCB167);
- 3,3',4,4',5,5'-hexachlorobiphenyl (PCB169);
- 2,3,3',4,4',5,5'-heptachlorobiphenyl (PCB189);
- 2,3,7,8-tetrachlorodibenzodioxin (TCDD)

Exclude:

- Studies evaluating effects of co-exposure to other substances, or a mix of DLCs
- Studies evaluating a single concentration of the congener or reference compound
- Studies without controlled exposure (e.g., observational studies in human populations)

Comparator (C): Vehicle or untreated control group and TCDD and/or PCB126

Include: Studies that include both a vehicle or untreated control group AND controlled exposure to a reference compound

Exclude: Studies evaluating effects of a congener but not TCDD or PCB126 (i.e., a reference compound)

Outcome (O): Any statistically significant toxic or biochemical effect, as compared to the negative control

Include studies that report outcomes in the following manner:

- Author-calculated REPs
- Concentration-/dose-response data (defined as at least 2 dose levels of the test compound)
- Benchmark values

Exclude:

- studies reporting effects by the sum of dl-compounds
- any statistically insignificant toxic or biochemical effect

Reference criteria:

Include

- References reporting original, peer-reviewed study data

Exclude

- Case reports/studies
- Conference abstracts
- Reviews
- Papers not readily available in English

Search Syntax

The search strategy was developed by an Information Specialist (SF), informed by input from topic experts. The searches were conducted using PubMed and EMBASE. Syntax is provided below.

Search efforts were restricted to articles published in English after January 1, 2005. The search was implemented on May 29, 2018. EMBASE searches were exclusive of MEDLINE, which is included in PubMed. Search strategies were validated using returned records in comparison to highly relevant articles identified by a topic expert (DW).

The reviewers do not intend to contact authors of primary studies or reviews for further information.

PubMed strategy:

(dioxins and dioxin like compounds[MeSH Terms] OR Pentachlorodibenzo-p-dioxin OR pentachlorodibenzodioxin OR “40321 76 4”[EC/RN] OR "40321-76-4" OR Hexachlorodibenzo-p-dioxin OR hexachlorodibenzodioxin OR “39227 28 6”[EC/RN] OR "39227-28-6" OR “19408 74 3”[EC/RN] OR “19408-74-3” OR “57653 85 7”[EC/RN] OR “57653-85-7” OR “70648 26 9”[EC/RN] OR “70648-26-9” OR “72918 21 9”[EC/RN] OR “72918-21-9” OR “57117 44 9”[EC/RN] OR “57117-44-9” OR “60851 34 5”[EC/RN] OR “60851-34-5” OR Heptachlorodibenzo-p-dioxin OR heptachlorodibenzodioxin OR “35822 469”[EC/RN] OR “35822-46-9” OR “67562-39-4” OR “55673-89-7” OR “67562 39 4”[EC/RN] OR “55673 89 7”[EC/RN] OR Octachlorodibenzo-p-dioxin OR octachlorodibenzodioxin OR “3268 87 9”[EC/RN] OR “3268-87-9” OR Tetrachlorodibenzofuran OR “55722 27 5”[EC/RN] OR “83704 25 0”[EC/RN] OR “55722-27-5” OR “83704-25-0” OR Pentachlorodibenzofuran OR “57117 41 6”[EC/RN] OR “57117-41-6” OR “57117 31 4”[EC/RN] OR “57117-31-4” OR Octachlorodibenzofuran OR OCDF OR “39001-02-0” OR “39001 02 0”[EC/RN] OR “PCB 77” OR “PCB 81” OR Tetrachlorobiphenyl OR “32598-13-3” OR “32598 13 3”[EC/RN] OR “70362-50-4” OR “70362 50 4”[EC/RN] OR “PCB 126” OR “PCB 105” OR “PCB 114” OR “PCB 118” OR “PCB 123” OR Pentachlorobiphenyl OR “57465-28-8” OR “57465 28 8”[EC/RN] OR “32598-14-4” OR “32598 14 4”[EC/RN] OR “74472-37-0” OR “74472 37 0”[EC/RN] OR “31508-00-6” OR “31508 00 6”[EC/RN] OR “65510-44-3” OR “65510 44 3”[EC/RN] OR “PCB 169” OR “PCB 156” OR “PCB 157” OR “PCB 167” OR Hexachlorobiphenyl OR “32774-16-6” OR “32774 16 6”[EC/RN] OR “38380-08-4” OR “38380 08 4”[EC/RN] OR “69782-90-7” OR “69782-90-7”[EC/RN] OR “52663-72-6” OR “52663 72 6”[EC/RN] OR “PCB 189” OR Heptachlorobiphenyl OR “39635-31-9” OR “39635 31 9”[EC/RN] OR TCDD OR Dioxin OR tetrachlorodibenzo-p-dioxin OR tetrachlorodibenzodioxin OR PCDD OR “1746-01-6” OR “1746 01 6”[EC/RN]) AND (“PCB 126” OR Pentachlorobiphenyl OR “57465-28-8” OR “57465 28 8”[EC/RN] OR TCDD OR Dioxin OR tetrachlorodibenzo-p-dioxin OR tetrachlorodibenzodioxin OR PCDD OR “1746-01-6” OR “1746 01 6”[EC/RN]) AND to[sh]

Embase search strategy:

('dioxin'/exp OR 'pentachlorodibenzo p dioxin' OR pentachlorodibenzodioxin OR '40321 76 4':rn OR '40321-76-4' OR 'hexachlorodibenzo p dioxin' OR hexachlorodibenzodioxin OR '39227 28 6':rn OR '39227-28-6' OR '19408 74 3':rn OR '19408-74-3' OR '57653 85 7':rn OR '57653-85-7' OR '70648 26 9':rn OR '70648-26-9' OR '72918 21 9':rn OR '72918-21-9' OR '57117 44 9':rn OR '57117-44-9' OR '60851 34 5':rn OR '60851-34-5' OR 'heptachlorodibenzo p dioxin' OR heptachlorodibenzodioxin OR '35822 469':rn OR '35822-46-9' OR '67562-39-4' OR '55673-89-7' OR '67562 39 4':rn OR '55673 89 7':rn OR 'octachlorodibenzo p dioxin' OR octachlorodibenzodioxin OR '3268 87 9':rn OR '3268-87-9' OR tetrachlorodibenzofuran OR '55722 27 5':rn OR '83704 25 0':rn OR '55722-27-5' OR '83704-25-0' OR pentachlorodibenzofuran OR '57117 41 6':rn OR '57117-41-6' OR '57117 31 4':rn OR '57117-31-4' OR octachlorodibenzofuran OR ocdf OR '39001-02-0' OR '39001 02 0':rn OR 'pcb 77' OR 'pcb 81' OR tetrachlorobiphenyl OR '32598-13-3' OR '32598 13 3':rn OR '70362-50-4' OR '70362 50 4':rn OR 'pcb 126' OR 'pcb 105' OR 'pcb 114' OR 'pcb 118' OR 'pcb 123' OR pentachlorobiphenyl OR '57465-28-8' OR '57465 28 8':rn OR '32598-14-4' OR '32598 14 4':rn OR '74472-37-0' OR '74472 37 0':rn OR '31508-00-6' OR '31508 00 6':rn OR '65510-44-3' OR '65510 44 3':rn OR 'pcb 169' OR 'pcb 156' OR 'pcb 157' OR 'pcb 167' OR hexachlorobiphenyl OR '32774-16-6' OR '32774 16 6':rn OR '38380-08-4' OR '38380 08 4':rn OR '69782-90-7' OR '69782-90-7':rn OR '52663-72-6' OR '52663 72 6':rn OR 'pcb 189' OR heptachlorobiphenyl OR '39635-31-9' OR '39635 31 9':rn OR tcdd OR dioxin OR 'tetrachlorodibenzo p dioxin' OR tetrachlorodibenzodioxin OR pcdd OR '1746-01-6' OR '1746 01 6':rn) AND ('pcb 126' OR pentachlorobiphenyl OR '57465-28-8' OR '57465 28 8':rn OR tcdd OR dioxin OR 'tetrachlorodibenzo p dioxin' OR tetrachlorodibenzodioxin OR pcdd OR '1746-01-6' OR '1746 01 6':rn) AND ('toxicity'/exp/mj OR 'aromatic hydrocarbon receptor'/exp/mj OR 'toxic equivalency factor' OR 'tef' OR 'tefs' OR 'rep' OR 'reps' OR 'relative potency estimates' OR 'relative effect potency' OR 'relative effect potencies') AND [english]/lim AND [2005-2018]/py AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Data Extraction

Titles and abstracts of records retrieved using the search strategy were uploaded to DistillerSR and screened by SF or WR for inclusion/exclusion criteria outlined above. A third reviewer (JU) reassessed any record for which inclusion was uncertain. The full text of the potential studies was retrieved and added to the appropriate DistillerSR record. Full-text screening will be performed simultaneous to data extraction in order to increase efficiency and reduce unnecessary repetition.

A piloted data extraction form will be used to collect data from the included studies via DistillerSR. Collected data will include: citation information, study details (e.g., objective), experimental details (e.g., compounds, animal model, endpoints). If available, dose-response data, benchmark values, and REP calculations for each endpoint conducted by the study author will also be collected. Should data be reported graphically (i.e., in figures), reviewers will utilize GraphClick to estimate data points. Graphical data extraction will be noted when these methods are applied.

In addition to extraction of new data, references previously included in the Haws et al. (2004) database will be reviewed for updated information (e.g., finalized reports vs. interim reports). Should updated REPs or data be identified, old data will be retained for record keeping, but replaced by updated information for further analysis. Studies included in the Haws et al. (2004) database will also be reviewed for identification and extraction of dose-response data, including that reported in figures.

Information/categorizations pertaining to the consensus-based weighting criteria based on study quality and relevance will also be recorded. These include: study type, experimental model), details about experimental pharmacokinetics, author-derived REP derivation method, REP derivation quality (i.e., maximum response, statistical reliability), and biological relevance.

A 100% QC will be performed for all extracted data. Identified errors will be noted by the project team and corrected in the original DistillerSR record.

Synthesis and Evaluation

As an interim between extraction and synthesis, data processing will be performed to prepare data for synthesis. Individual studies will be reviewed to ensure that data from repetitive endpoints are removed, retaining only the most applicable. For example, if a study reports data for both CYP1A1 mRNA expression and EROD induction, data for the latter will be retained as it is a better measure of the same endpoint. Database authors will discuss best approaches for new endpoints (e.g., -omics or similar).

The data underlying each REP in the database will be appraised based on six, consensus-based study characteristics that are important descriptors of REP quality and reliability (i.e., study type, experimental model, pharmacokinetics, REP derivation method, REP derivation quality, and endpoint relevance) as described by Wikoff et al. (in progress).

To address the needs of the WHO expert working group, extracted data will be synthesized and evaluated both in context of: (1) REP weighting and (2) REP derivation method. REP weighting for quality and relevance will be implemented via a random-forest (RF) model trained on the 2004 REP database to relate study attributes to quality categories (*publication in process*).

For REP derivation, it is anticipated that an iterative approach will be implemented; the approach (or approaches) will be dependent on the number of REPs with dose-response data as well the granularity of dose-response data available. Approaches will consider best-science methods for evaluating dose response relationships, building on, for example, those applied by the National Toxicology Program in the current database, while also considering techniques which also allow for combined characterization weighting and full dose-response datasets (vs point estimates on a curve), such as Bayesian fixed-effects meta-analysis. Where possible, concentration-/dose-response data will be modeled via R Statistical Software. Summary statistics describing the distribution of dose-response relationships across REP datasets will be generated. It is anticipated that these calculations will also be applied to subsets based on the number of REPs available for each congener, *in vivo* vs *in vitro* models, endpoint or outcome categories, or any other logical subset that is identified. Further comparisons of REPs between this database update and the Haws et al. (2004) database may also be employed.