

# EPA's Response to Major Interagency Comments on the Interagency Science Discussion Draft IRIS Dioxin Reanalysis, Volume 1

February 2012

## **Purpose:**

The Integrated Risk Information System (IRIS) assessment development process of May 2009 includes two steps (i.e., Step 3 and 6b) in which White House offices and other federal agencies can comment on draft assessments.<sup>1</sup> The following are EPA's responses to major interagency review comments received during the Interagency Science Discussion step (i.e., Step 6b) for EPA's draft IRIS *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume 1*, referred to as "Dioxin Reanalysis, Volume 1" herein. All interagency comments provided were taken into consideration prior to posting of the final Dioxin Reanalysis. The Interagency Science Discussion draft assessment and the complete set of interagency comments are available on the IRIS Web site ([www.epa.gov/iris](http://www.epa.gov/iris)).

Comments were received from the Council on Environmental Quality (CEQ), National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), National Aeronautics and Space Administration/Environmental Management Division Headquarters (NASA), Center for Disease Control and Prevention /Agency for Toxic Substances and Disease Registry (CDC/ATSDR), Department of Agriculture/Office of Budget and Program Analysis (USDA), and Department of Defense/Deputy Under Secretary for Defense Installations and Environment (DoD).

## **Comments on Study Inclusion Criteria**

### ***Topic #1 – Revisions to EPA's epidemiologic study inclusion criteria following Science Advisory Board (SAB) review***

While NIEHS/NTP found the rationale for narrowing down the number of studies under consideration to be clearly articulated, DoD commented that changes were made in the epidemiologic study selection criteria after the SAB review that were not subjected to external peer review and public comment. DoD also requested additional explanation of chemical-specific study selection criteria and asked whether these were to be used for other chemicals undergoing assessments as part of the IRIS process. In addition, DoD was concerned that EPA included several selected studies in the Dioxin Reanalysis that were published in the peer-reviewed literature after EPA's literature review ended in October 2009.

### ***EPA Response***

The study inclusion criteria in the SAB external review draft Dioxin Reanalysis have not undergone significant revision. The SAB asked for, and EPA responded, by providing, clarifying text in several places. These clarifications include additional text on the use of null epidemiologic studies and on the definition of the critical exposure window (see additional details on these issues under Topics 2 and 8, respectively, below).

EPA developed the study selection process, including the epidemiologic study inclusion criteria for TCDD, in direct response to the NAS ([2006](#)) recommendation for "improved transparency

---

<sup>1</sup> For a complete description of the IRIS process, including Interagency Science Discussion, visit the IRIS Web site at [www.epa.gov/iris](http://www.epa.gov/iris)

and clarity in the selection of key data sets for dose-response analysis.” The study inclusion criteria are unique to the TCDD assessment given the types of health endpoints that have been studied and the expansive TCDD database. The study selection process that was developed allowed EPA to focus on the most relevant studies.

Finally, thirteen studies that were published after the October 2009 literature cut-off date in the draft Dioxin Reanalysis appear in the final Dioxin Reanalysis, Volume 1; none was used quantitatively in the derivation of the TCDD reference dose (RfD).

***Topic #2 – Consideration of null epidemiologic studies during study selection and TCDD noncancer dose-response analysis***

DoD commented that EPA ignored epidemiologic studies reporting no association between TCDD and the health endpoint of interest (i.e., null epidemiologic studies) in its evaluation of the potential for TCDD to cause health effects, and that EPA was not responsive to the SAB’s recommendation that “EPA provide more discussion and clarity on the exclusion of null epidemiologic studies” as implemented in EPA’s study selection process. Specifically, DoD stated that EPA did not address the ability of a null study to establish an upper limit on the potency of TCDD or the utility of null studies to identify “false positive” results.

***EPA Response***

EPA fully evaluated all studies, including null studies, in the determination of the potential hazard associated with TCDD toxicity. In addition, as suggested by the SAB, EPA augmented the text related to epidemiologic study selection criteria with a discussion of the use of null studies in the context of developing the TCDD RfD (see Section 2.3.1 of the Dioxin Reanalysis, Volume 1).

It is well-recognized that null studies can provide useful information for dose-response assessment. For example, a no-observed-adverse-effect level (NOAEL) can be identified from a null study and can be used to identify an exposure limit for the absence of adverse health outcomes. However, when other studies are available that demonstrate adverse health outcomes, as is the case with TCDD, then those studies are typically used for RfD derivation and a null study would not be used to identify an upper limit. The large TCDD database provides many positive studies that are considered stronger candidates for derivation of an RfD than studies for which only a NOAEL can be identified. Therefore, EPA used the epidemiologic null studies qualitatively to discuss the biological significance of the critical endpoint(s) that form the basis for deriving the RfD (e.g., see Section 4.3.6.1 of the Dioxin Reanalysis, Volume 1, for a discussion of the literature on thyroid hormone levels and exposure to TCDD and dioxin-like compounds (DLCs)). False positive studies, by definition, are only a concern when the negative evidence (i.e., evidence suggesting no association between an exposure and a health outcome) is overwhelming. As stated above, because of the numerous positive epidemiologic studies and toxicological bioassays, this is clearly not the case for TCDD.

### ***Topic #3 – EPA’s evaluation of studies from the Seveso Women’s Cohort Study (SWCS)***

DoD commented that EPA was inconsistent in the evaluation of exposure information for different studies from the Seveso Women’s Cohort. DoD stated two concerns: 1) that EPA was inconsistent in its evaluation of whether the women from this cohort were exposed primarily to TCDD; and 2) that DoD was unsure why “effective exposure” could be estimated in Eskenazi et al. (2002b), which was selected for TCDD quantitative dose-response analysis, but could not be estimated in four of the Eskenazi et al. studies (2007; 2005; 2003; 2002a) that were not selected.

#### ***EPA Response***

EPA consistently applied the study inclusion criteria to the SWCS publications. DoD’s concerns pertain to two of EPA’s epidemiologic study inclusion criteria as shown here:

Criterion #2. The exposure is primarily to TCDD, rather than DLCs, and can be quantified so that dose-response relationships can be assessed for non-fatal adverse endpoints.

Criterion #3. The effective dose and oral exposure must be quantifiable. The timing of the measurement of health endpoints (i.e., the response) also must be consistent with current biological understanding of the endpoint and its progression.

Regarding DoD’s first concern, EPA correctly applied the study inclusion criteria, but in the interagency review draft had incorrectly marked the ‘TCDD Only’ column (Criterion #2) in Table C-2 of Appendix C for three studies from the SWCS, Bertazzi et al. (2001), Landi et al. (2003), and Consonni et al. (2008); this has been corrected in the final Dioxin Reanalysis, Volume 1 document. These three studies were not selected for TCDD quantitative dose-response analysis as they failed Criterion #3. Regarding DoD’s second concern, these three studies and the four Eskenazi studies cited by DoD were those for which a critical exposure window (see Topic #8 below) could not be identified (Criterion #3), eliminating them from quantitative dose-response assessment. The Seveso cohort studies that passed all criteria had identifiable critical exposure windows for the endpoints that served as points of departure for the RfD [e.g., the 9 months of pregnancy for exposed mothers clearly defined the window of exposure for the fetus in Baccarelli et al. (2008)]. Such a critical exposure window could not be identified for the endpoints (e.g., endometriosis, age of menopause, uterine fibroids) in the Eskenazi et al. studies. . For the endpoints in those studies, averaging the TCDD serum concentrations for the entire period between exposure and effect evaluation was considered to be too conservative and possibly biologically implausible.

### ***Comments on EPA’s Analyses of Dioxin Epidemiologic Studies***

#### ***Topic #4 – Adversity of sperm effects observed in Mocarelli et al. (2008)***

The Mocarelli et al. (2008) study was one of the co-principal studies that EPA used to derive the dioxin RfD. EPA identified the lowest exposed group as a LOAEL in this study. NIEHS/NTP commented that “The EPA suggests that this is a LO[A]EL because in the Seveso accident, individuals 1 standard deviation below the mean had sperm concentrations of 21.8 million/mL and that this concentrations falls at the low end of the range of reduced fertility suggested by Skakkebaek (2010). It should be noted that for the control group, individuals 1 standard deviation below the mean had sperm concentrations of 31.7

million/mL, which is also within the range of reduced fertility suggested by Skakkebaek (2010).” NIEHS/NTP suggested that EPA should consider designating the lowest exposed group as a NOAEL rather than a LOAEL.

### ***EPA Response***

The SAB agreed with EPA’s determination of a LOAEL for this study. EPA’s designation of the LOAEL from Mocarelli et al. (2008) was not based on sperm concentrations at 1 standard deviation from the comparison group mean. EPA’s designation of LOAEL was based on a statistically significant 24% reduction in sperm cell concentration and statistically significant 12% reduction in percent motile sperm; it was not based solely on decreased sperm cell concentration. The SAB supported EPA’s use of these reductions in sperm concentration and sperm motility for determining the RfD. The SAB commented “While the shifts observed in sperm counts may or may not pose a significant health effect in a single individual, such shifts on a population basis could presumably lead to an increased incidence of adverse health outcomes” (SAB, 2011). In addition, in Section 4 of the Dioxin Reanalysis, Volume 1, EPA discusses Skakkebaek et al. (2010), who report that sperm concentrations in the range of 15-40 million/ml potentially result in decreased fertility.

### ***Topic #5 – Evaluation of the Baccarelli et al. (2008) study***

DoD suggested that EPA provide a more critical review of Baccarelli et al. (2008) in relation to the reported increased neonatal thyroid stimulating hormone (TSH) levels and use of this study as a co-principal study for derivation of the RfD. DoD also commented that an SAB panel member stated that there are potentially many causes of elevated neonatal TSH, which should be considered, including iodide uptake inhibition (e.g., from insufficient iodine in the diet, from ingestion and/or environmental exposure to thiocyanate or nitrate), exposure to other common ubiquitous and persistent chemicals besides TCDD, food intake, prematurity, severe illness, maternal thyroid disease, and gestational age.

### ***EPA Response***

The SAB agreed with EPA’s designation of Baccarelli et al. (2008) as a co-principal study for derivation of the RfD but asked EPA to provide further discussion of this study. EPA has expanded the discussion of the Baccarelli et al. (2008) study in Section 4.3 and Appendix C of the Dioxin Reanalysis, Volume 1 to include additional details of the study.

The potential contributing factors attributed by DoD to an SAB panelist were apparently not included in the SAB report. Based on the information provided by the study authors, there is no evidence to suggest that factors other than TCDD exposure were responsible for the increased neonatal TSH levels reported by Baccarelli et al. (2008). The study authors addressed other factors by adjusting their analyses for gender, birth weight, birth order, maternal age at delivery, hospital, and type of delivery. Additionally, Baccarelli et al. (2008) provided a discussion of iodine sufficiency in the Seveso population and concluded that it was not a concern. Baccarelli et al. (2008) also evaluated exposures to dioxin-like compounds (DLCs) and examined the association between these exposure measures and neonatal TSH levels. EPA presents an evaluation of the Baccarelli et al. (2008) DLC analyses as a component of the sensitivity analysis in Section 4.5. Exposure to chemicals other than DLCs that could alter neonatal TSH levels was not evaluated in Baccarelli et al. (2008), but there is also no reason to suspect that other chemical exposures would be correlated with TCDD exposure in this study.

### ***Topic #6 – Observed thyroid stimulating hormone (TSH) levels in other epidemiologic studies of DLCs***

Both DoD and NASA commented that other epidemiologic studies evaluating the outcomes associated with DLC exposures [in particular, those reviewed in Goodman et al. (2010)] do not support EPA's conclusion regarding associations between maternal dioxin exposures and elevated neonatal TSH levels. Four studies were cited by NASA that are part of a review by Goodman et al. (2010) of studies assessing DLC exposure and thyroid hormone levels in children.

#### ***EPA Response***

The studies reviewed in Goodman et al. (2010), with the exception of Baccarelli et al. (2008), are not relevant to the derivation of an RfD for TCDD. EPA has critically reviewed Goodman et al. (2010) in Section 4 of the Dioxin Reanalysis, Volume 1. EPA has also confirmed that there were no additional studies identified in Goodman et al. (2010) that met the selection criteria outlined in Section 2 of the Dioxin Reanalysis, Volume 1.

Goodman et al. (2010) reviewed 21 epidemiologic studies and concluded that background DLC exposures are not clearly or consistently correlated with differences in thyroid hormone levels, including TSH levels, in neonates and children less than 12 years of age. EPA concluded that detection of consistent patterns in the studies reviewed in Goodman et al. (2010) would be unlikely because of the relatively low DLC exposures in the studied populations and important study differences, such as different exposure matrices and timing of measurements. The studies evaluated in Goodman et al. (2010) measured TSH at a variety of time points (ranging from birth up to age 12) in cord blood and/or blood samples collected from neonates, infants and children. The exposure matrices used to evaluate background exposures to DLCs included maternal milk, maternal blood, maternal sera, cord plasma, and child's sera.

The only study reviewed in Goodman et al. (2010) with elevated TCDD levels (i.e., above background) relevant to TCDD dose-response assessment was Baccarelli et al. (2008). The studies summarized in Goodman et al. (2010) measured TSH at a variety of time points. However, TSH levels generally peak about 2 hours after birth then decline rapidly to typical long-term levels over the next few days (Steinmaus et al., 2010). In Baccarelli et al. (2008), blood samples were consistently collected from heel stick at neonatal day 3 and analyzed in the same laboratory.

### ***Comments on Dose-Response Modeling***

#### ***Topic #7 – Benchmark Dose (BMD) modeling of TCDD dose-response***

DoD commented that the statement in Section 4 of the Dioxin Reanalysis, Volume 1, "For continuous endpoints, the preference was for models with an asymptote term (plateau for high-dose-response) because continuous measures do not continue to rise (or fall) with dose forever; this phenomenon is particularly evident for TCDD," is not consistent with EPA's BMD technical guidance (U.S. EPA, 2000). DoD also objected to EPA limiting the benchmark responses (BMRs) to 10% extra risk for dichotomous endpoints and 1 standard deviation from the mean for continuous endpoints. DoD commented that for those data sets where there was no response near the BMR EPA should have selected a BMR suitable for the data in accordance with the BMD technical guidance, rather than trying other means to obtain an adequate fit. In addition, DoD objected to the statement in Section 4.2 that the

models in EPA's BMD software package (BMDS) do not allow for incorporation of covariates (for modeling of epidemiologic data), stating that, "EPA's software includes a nested analysis that is specifically designed to model the co-variation between offspring in a litter from one mother as contrasted with offspring in different litters." NIEHS/NTP commented that EPA's approach is consistent with the NAS comments ([p. 72, NAS, 2006](#)) and that the rationale for the different BMR choices was clearly described in the Dioxin Reanalysis, Volume 1.

#### ***EPA Response***

EPA's BMD modeling of TCDD data was consistent with the methods in the BMD technical guidance ([U.S. EPA, 2000](#)). EPA's focus on continuous BMDS models with plateau terms was implemented because high-dose effect plateaus are particularly evident for TCDD data sets. To clarify this in the Dioxin Reanalysis, Volume 1, a statement has been added to Section 4.2 to indicate that this was a TCDD-specific decision. The EPA BMD technical guidance does allow for use of *lower* BMRs when the lowest response levels are below the standard BMRs. However, that is not the case for the TCDD data sets referenced by DoD, in which the first response was well above 10% or 1 standard deviation from the mean. Higher BMRs are not appropriate. The BMDS nested-analysis model cannot be used for modeling epidemiologic covariate data, because it is specific for data from rodent developmental studies when the responses are reported on a litter basis.

#### ***Topic #8 – EPA's use of a critical exposure window to estimate TCDD exposures***

In the Dioxin Reanalysis, Volume 1, EPA defines a biologically-relevant "critical exposure window" as an exposure period during a specific life stage over which an individual is susceptible to TCDD for a particular health endpoint. The ability to define a critical exposure window was an element of EPA's epidemiologic study inclusion criteria. DoD commented that the terminology of "critical exposure window" was not well defined in the Dioxin Reanalysis, Volume 1. DoD commented that the requirement of a "critical exposure window" suggests that the study inclusion criteria for epidemiologic studies are based on the assumption that reproductive effects would be the most sensitive. Further, DoD stated that EPA should refrain from using criteria that impose conditions that are not appropriate for all toxicological endpoints. NIEHS/NTP commented that although the exact window of sensitivity is unknown for these studies, EPA had made reasonable assumptions on each of the individual critical exposure windows.

#### ***EPA Response***

EPA has added a text box defining "critical exposure window" to Section 2 of the Dioxin Reanalysis, Volume 1 (Text Box 2-2) that more clearly articulates the concept. EPA's study inclusion criteria for epidemiologic studies are not based on the assumption that reproductive effects are the most sensitive. Rather, the critical window of exposure criterion was included to identify studies with appropriate exposure measures for use in dose-response analysis. This criterion is not specific to any one type of toxicological endpoint.



## Comments on Kinetic Modeling

### **Topic #9 – Physiologically-based pharmacokinetic (PBPK) modeling of TCDD**

DoD and NASA commented that EPA did not respond adequately to the SAB comments on the Hill coefficient and the fat:blood partition coefficient ( $PC_{FB}$ ) in the Emond human PBPK model. DoD cited the SAB review comment that "use of a Hill coefficient value well below unity would lead to a nonlinear model behavior that is biologically implausible (hypersensitivity to induction at doses near zero)." DoD also stated that EPA should explain more clearly how the Hill equation used by Walker et al. (1999), who derived a Hill coefficient of 0.94, differs from the Emond model. DoD suggested that EPA should recalculate the RfD based on a Hill coefficient of 1 and/or a  $PC_{FB}$  of 200 or 160. DoD also commented that the Emond model does not account for higher child elimination rates, citing Kerger et al. (2006).

#### ***EPA Response***

The SAB agreed with EPA's choice of PBPK model and its application in derivation of the RfD but requested that additional quantitative sensitivity analyses be conducted on the PBPK models. In response, EPA has added a series of sensitivity analyses for the Emond PBPK model in Sections 3.3.4.3.2 and 4.5 of the Dioxin Reanalysis, Volume 1. These analyses include evaluations of the impact that alternative values for the Hill coefficient and  $PC_{FB}$  would have on estimating TCDD blood levels in humans. At DoD's request, EPA also added an evaluation of how the point of departure (POD) for the RfD (0.02 ng/kg-day) would change using a Hill coefficient value of 1.

Section 4.5.1.1.1 of the Dioxin Reanalysis, Volume 1, shows the impact of setting the Hill coefficient to 1 on the POD derived from Mocarelli et al. (2008). In Appendix A of the Dioxin Reanalysis, Volume 1, EPA has clarified the differences in the Emond model and the Walker et al. (1999) findings, with respect to the Hill coefficient. Walker et al. (1999) uses a different model structure than the Emond model, in which the model parameters represent different physiologic measures, such that the Hill coefficient values in these two models are not comparable. In Section 3 of the Dioxin Reanalysis, Volume 1, EPA has evaluated the impact of changing  $PC_{FB}$  on modeled TCDD blood concentrations.

The Emond PBPK model accounts for the higher elimination rate in children by modeling growth and age-related changes in fat content and physiology. The TCDD half-life calculations in Kerger et al. (2006) are based on blood levels rather than whole-body measurements and do not account for changes in body mass due to growth. This issue was considered by the SAB as a public comment but was not addressed in the final SAB report.

### **Topic #10 – Mouse PBPK model**

NASA commented that using the mouse PBPK model to estimate TCDD disposition in the body did not follow established EPA guidance of relying only on peer reviewed models in IRIS assessments. DoD suggested EPA should wait to release the Dioxin Reanalysis, Volume 1, until the mouse PBPK model is externally peer-reviewed.

#### ***EPA Response***

EPA did not rely on the mouse model in the derivation of the RfD. The TCDD RfD is based on human epidemiologic studies and the human PBPK model, not the mouse PBPK model. Further,

the SAB agreed that EPA appropriately adapted the mouse PBPK model from the peer-reviewed Emond rat PBPK model and that the mouse PBPK model was adequate for use in estimating dose metrics needed in the Dioxin Reanalysis.

While the SAB commented that publication of the mouse PBPK model in the peer-reviewed literature would strengthen and enhance the scientific credibility of the model, SAB did not recommend when this should be completed. EPA will continue to encourage the primary author to publish the mouse PBPK model in the peer-reviewed, scientific literature.

### **Comments on the Sensitivity Analyses**

#### ***Topic #11 – Sensitivity analysis issues***

DoD commented that EPA only evaluated changes to individual variables related to TCDD RfD derivation in its sensitivity analysis and did not consider the impact of the changes when considered together. DoD stated that while some of the individual changes may have relatively minor effects on the outcome, the combined effects may substantially affect the outcome. CEQ stated that the quantitative sensitivity analysis was an important addition and directly responsive to the NAS.

#### ***EPA Response***

EPA did not evaluate the impact of multiple variables considered together because adequate data are not available in the literature for such an analysis. A combined analysis would require detailed knowledge of the uncertainty distributions and correlation structure of the variables under consideration. The common approach to such an endeavor is a Monte Carlo analysis, which SAB suggested was not necessary. However, the SAB recommended several approaches EPA could potentially use to analyze quantitative uncertainty, including sensitivity analyses, which were implemented by EPA.

### **Comments on the Scope of the Dioxin Reanalysis, Volume 1**

#### ***Topic #12 – Treatment of exposure and risk characterization issues***

DoD and NASA requested that EPA characterize current US exposures or risk associated with dioxin exposures in the US population and asked why the “University of Michigan Dioxin Exposure Studies” were not included in the Dioxin Reanalysis, Volume 1.

#### ***EPA Response***

Section 1 of the Dioxin Reanalysis, Volume 1 states that the focus of the document is on health effects study selection for quantitative TCDD dose-response analyses, dioxin pharmacokinetics, and non-cancer dose-response assessment. Dioxin exposure and risk characterization issues are not included in this document. The University of Michigan study and the publications from this study contain no TCDD dose-response information and, therefore, do not meet EPA’s study inclusion criteria for TCDD quantitative dose-response assessment. Thus, studies of dioxin exposures, such as the University of Michigan study publications, are not included in the Dioxin Reanalysis, Volume 1.



***Topic #13 – Separating the Dioxin Reanalysis into 2 Volumes***

NASA and DoD both requested an explanation of why EPA is separating the Dioxin Reanalysis into Volumes 1 and 2. CEQ commented that the decision to issue the Dioxin Reanalysis in two volumes is reasonable and appropriate.

***EPA Response***

EPA's dioxin assessment was extensively peer reviewed by outside experts. While the reviewers applauded EPA's analysis of the non-cancer health effects, they recommended that EPA do some further work on the cancer part of the science assessment. Based on this advice, EPA decided to finish and release the non-cancer part of the assessment now and will work as quickly as possible to finish the cancer part of the assessment. In response to interagency comments, EPA has clearly stated in Volume 1 that the cancer information should not be used for decision-making and that Volume 2 will follow providing the final cancer assessment. Americans deserve the best and most up-to-date information about chemicals in the environment. The non-cancer assessment updates the science and provides important new information to the public.

## References

- [Baccarelli, A; Giacomini, SM; Corbetta, C; Landi, MT; Bonzini, M; Consonni, D; Grillo, P; Patterson, DG; Pesatori, AC; Bertazzi, PA.](#) (2008). Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. *PLoS Med* 5: e161.
- [Bertazzi, PA; Consonni, D; Bachetti, S; Rubagotti, M; Andrea Baccarelli, A; Zocchetti, C; AC, P.](#) (2001). Health effects of dioxin exposure: a 20-year mortality study. *Am J Epidemiol* 153: 1031-1044.
- [Consonni, D; Pesatori, AC; Zocchetti, C; Sindaco, R; D'Oro, LC; Rubagotti, M; Bertazzi, PA.](#) (2008). Mortality in a population exposed to dioxin after the Seveso, Italy, accident in 1976: 25 years of follow-up. *Am J Epidemiol* 167: 847-858. <http://dx.doi.org/10.1093/aje/kwm371>.
- [Eskenazi, B; Mocarelli, P; Warner, M; Samuels, S; Vercellini, P; Olive, D; Needham, LL; Patterson DG, J, r; Brambilla, P; Gavoni, N; Casalini, S; Panazza, S; Turner, W; Gerthoux, PM.](#) (2002a). Serum dioxin concentrations and endometriosis: A cohort study in Seveso, Italy. *Environ Health Perspect* 110: 629-634.
- [Eskenazi, B; Warner, M; Mocarelli, P; Samuels, S; Needham, LL; Patterson, DG, Jr; Lippman, S; Vercellini, P; Gerthoux, PM; Brambilla, P; Olive, D.](#) (2002b). Serum dioxin concentrations and menstrual cycle characteristics. *Am J Epidemiol* 156: 383-392.
- [Eskenazi, B; Mocarelli, P; Warner, M; Chee, WY; Gerthoux, PM; Samuels, S; Needham, LL; Patterson, DG, Jr.](#) (2003). Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy. *Environ Health Perspect* 111: 947-953.
- [Eskenazi, B; Warner, M; Marks, AR; Samuels, S; Gerthoux, PM; Vercellini, P; Olive, DL; Needham, L; Patterson, D, Jr; Mocarelli, P.](#) (2005). Serum dioxin concentrations and age at menopause. *Environ Health Perspect* 113: 858-862.
- [Eskenazi, B; Warner, M; Samuels, S; Young, J; Gerthoux, PM; Needham, L; Patterson, D; Olive, D; Gavoni, N; Vercellini, P; Mocarelli, P.](#) (2007). Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study. *Am J Epidemiol* 166: 79-87. <http://dx.doi.org/10.1093/aje/kwm048>.
- [Goodman, M; Squibb, K; Youngstrom, E; Anthony, LG; Kenworthy, L; Lipkin, PH; Mattison, DR; Lakind, JS.](#) (2010). Using systematic reviews and meta-analyses to support regulatory decision making for neurotoxicants: Lessons learned from a case study of PCBs. *Environ Health Perspect* 118: 727-734. <http://dx.doi.org/10.1289/ehp.0901835>.
- [Kerger, BD; Leung, HW; Scott, P; Paustenbach, DJ; Needham, LL; Patterson, DG, Jr; Gerthoux, PM; Mocarelli, P.](#) (2006). Age- and concentration-dependent elimination half-life of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Seveso children. *Environ Health Perspect* 114: 1596-1602. <http://dx.doi.org/10.1289/ehp.8884>.
- [Landi, MT; Bertazzi, PA; Baccarelli, A; Consonni, D; Masten, S; Lucier, G; Mocarelli, P; Needham, L; Caporaso, N; Grassman, J.](#) (2003). TCDD-mediated alterations in the AhR-dependent pathway in Seveso, Italy, 20 years after the accident. *Carcinogenesis* 24: 673-680. <http://dx.doi.org/10.1093/carcin/bgg002>.
- [Mocarelli, P; Gerthoux, PM; Patterson, DG, Jr; Milani, S; Limonata, G; Bertona, M; Signorini, S; Tramacere, P; Colombo, L; Crespi, C; Brambilla, P; Sarto, C; Carreri, V; Sampson, EJ; Turner, WE; Needham, LL.](#) (2008). Dioxin exposure, from infancy through puberty, produces endocrine disruption and affects human semen quality. *Environ Health Perspect* 116: 70-77. <http://dx.doi.org/10.1289/ehp.10399>.
- [NAS](#) (National Academy of Sciences). (2006). Health risks from dioxin and related compounds: Evaluation of the EPA reassessment. Washington, DC: National Academy Press. [http://www.nap.edu/catalog.php?record\\_id=11688](http://www.nap.edu/catalog.php?record_id=11688).
- [SAB](#) (U.S. EPA Science Advisory Board). (2011). SAB review of EPA's reanalysis of key issues related to dioxin toxicity and response to NAS comments. (EPA-SAB-011-014). Washington, DC: U.S. Environmental Protection Agency. [http://yosemite.epa.gov/sab/sabproduct.nsf/2A45B492EBA8553852578F9003ECBC5/\\$File/EPA-SAB-11-014-unsigned.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/2A45B492EBA8553852578F9003ECBC5/$File/EPA-SAB-11-014-unsigned.pdf).
- [Skakkebaek, NE.](#) (2010). reference ranges for semen quality and their relations to fecundity. *Asian J Androl* 12: 95-98.
- [Steinmaus, C; Miller, MD; Smith, AH.](#) (2010). Perchlorate in drinking water during pregnancy and neonatal thyroid hormone levels in California. *J Occup Environ Med* 52: 1217-1524. <http://dx.doi.org/10.1097/JOM.0b013e3181fd6fa7>.
- [U.S. EPA](#) (U.S. Environmental Protection Agency). (2000). Benchmark dose technical guidance document [external review draft]. (EPA/630/R-00/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <http://www.epa.gov/raf/publications/benchmark-dose-doc-draft.htm>.
- [Walker, NJ; Portier, CJ; Lax, SF; Crofts, FG; Li, Y; Lucier, GW; Sutter, TR.](#) (1999). Characterization of the dose-response of CYP1B1, CYP1A1, and CYP1A2 in the liver of female Sprague-Dawley rats following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicol Appl Pharmacol* 154: 279-286. <http://dx.doi.org/10.1006/taap.1998.8595>.