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Supplemental Material

Integrating Selection and Risk Assessment of Chemical Mixtures: A Novel Approach Applied to a Breast Milk Survey

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S1. Search and evaluation strategy on relevance of dose-additivity

For thyroid effects, the keywords “mixture AND thyroid and rodents” gathered a total of 310 publications using Pubmed search engine up to December 2019. A further selection based on the information available in the abstract was performed in order to retain only *in vivo* experimental studies focusing on thyroid hormone levels and using at least two different substances present in the studied mixture. Twelve studies were selected (Bowers et al. 2004; Crofton et al. 2005; Chu et al. 2008; Pelletier et al. 2008; Flippin et al. 2009; He et al. 2011; Miller et al. 2012; Elabbas et al. 2014; Liu et al. 2014; Wade et al. 2002; Hallgren & Darnerud, 2002; Ernest et al. 2012). Only six of the twelve studies compared the effects of separate or combined exposure, with four of them reporting effects of the mixture following developmental (Crofton et al., 2005; Flippin et al., 2009; Miller et al., 2012) or adult exposure (Hallgren & Darnerud, 2002). Crofton et al. (2005) reported that postnatal exposure of rats to a mixture of TCDD and PCBs reduced thyroxin (T4) levels in an additive manner at low doses; these effects were predicted by a self-generated model approach. Similar additive effects on T4 levels have been described for postnatal or perinatal exposure to mixtures of TCDD/PCBs/pesticides or PCBs/PBDEs in the rat (Flippin et al. 2009; Miller et al. 2012).

Concerning neural effects, the search using the keywords “mixture AND nervous system (or brain) and rodents” gathered around 4,666 publications. Only *in vivo* studies using at least two different substances present in the studied mixture and focusing on neurodevelopmental or behavioral effects were selected. Seven of the ten selected studies compared separate and combined exposure of rats or mice (Roegge et al. 2004; Eriksson et al. 2006; Fischer et al. 2008; Gralewicz et al. 2009; Sitarek & Gralewicz 2009; He et al. 2011; Reardon et al. 2019). In 4 studies, there were no effects of the mixture or the interaction was not studied between the substances (PCB/MeHg: Gralewicz et al. 2009, Sitarek & Gralewicz 2009; PCB/PBDE: He et al. 2011; PFOS/MeHg: Reardon et al. 2019). The three remaining studies suggested additive effects on motor coordination following developmental exposure to mixtures containing PCBs and MeHg, PCBs and PBDEs, or PBDEs and MeHg (Roegge et al. 2004; Eriksson et al. 2006; Fischer et al. 2008).

S2. Study details for defining health-based guidance value (HBGVs and toxicological threshold (TT) values.

The sections S1.1 and S1.2 describe how the retained HBGVs and built toxicological thresholds (TT) were defined on the basis of key studies for thyroid and neurodevelopmental effects.

S2.1. Thyroid effects

S2.2. Neurodevelopmental effects

Figure S1. Percent of publications from Pubmed calculated by dividing the sum of publications obtained with the keyword « substance name AND toxicity AND endpoint » by the number of publications gathered using the keywords « substance name AND toxicity ». The selected endpoints were hepatic, immune, thyroid, nervous system, reproduction, carcinogenesis, development. Data can be found in Excel Table S6.

Figure S2. Percent of publications from Pubmed calculated in dividing the sum of publications obtained with the keyword « substance name AND toxicity AND endpoint » by the number of publications gathered using the keywords « substance name AND toxicity AND all endpoints ». The selected endpoints were hepatic, immune, thyroid, nervous system, reproduction, carcinogenesis, development.

References

Additional File- Excel Document