

Note to readers with disabilities: *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to [508 standards](#) due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehp508@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

Supplemental Material

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

Amélie Crépet, Paule Vasseur, Julien Jean, Pierre-Marie Badot, Fabrice Nesslany, Jean-Paul Vernoux, Cyril Feidt, and Sakina Mhaouty-Kodja

Table of Contents

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

Supplemental material

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

The institutional HBGVs supported by human epidemiological studies are described below for methylmercury and PCDD/F.

Methylmercury. A tolerable weekly intake (TWI) of 1.3 µg/kg bw/week expressed as Hg, equivalent to an intake of 0.19 µg Hg/kg bw/day, was established by the EFSA (2012) on the basis of the auditory function deficit in relation to hypothyroidism and neurodevelopmental effects (Davidson et al. 2008; Grandjean et al. 1997; Murata et al. 2004). An uncertainty factor of 6.4 for inter-individual variation was applied to the daily dietary intake associated with no adverse effects on hair/blood parameters related to methylmercury intake used in modeling.

ΣPCDD/F. A chronic oral RfD of 0.7 pg/kg bw/day (US EPA 2012) was based on higher TSH levels in newborns of mothers after the Seveso accident in 1976 compared to children born to age-matched women from the surrounding non contaminated area (Baccarelli et al. 2008), and on lower sperm count and motility in men exposed to TCDD as boys than the reference group of males (Mocarelli et al. 2008). The lowest-observed-adverse-effect (LOAEL) was 0.020 ng/kg/day for both thyroid and sperm endpoints. PBPK modeling was used to estimate oral intakes from TCDD exposures reported as serum concentrations corresponding to the LOAEL. An uncertainty factor of 30 [3 for inter-individual variability, 10 for LOAEL to no-observed-adverse-effect level (NOAEL) extrapolation] was assigned to the LOAEL to obtain the RfD.

Institutional HBGVs based on animal experimental studies were reported for mirex and ΣPBDE.

Mirex. An RfD value of 0.2 µg/kg bw/day was determined by the US EPA (IRIS 1992) based on the thyroid effects induced following chronic exposure of rats to mirex (two-year NTP study, 1990). The NOAEL dose of 70 µg/kg bw/day was used with an uncertainty factor of 300 (10 for inter-species variation, 10 for intra-species variability, and 3 for incomplete data).

ΣPBDE. An acute oral minimal risk level (MRL) of 0.06 µg/kg bw/day was established by the ATSDR (2017) for neurobehavioral (Kuriyama et al. 2005), thyroid (Kuriyama et al. 2007), and reproductive effects (Talsness et al. 2005) in F1 offspring of rats (ATSDR, 2017). Collectively, these studies indicated a LOAEL of 60 µg/kg/day. This LOAEL value was used to derive the MRL using an uncertainty factor of 1,000 (10 for inter-species variation, 10 for intra-species variability, and 10 for LOAEL extrapolation to NOAEL).

TTs for the thyroid endpoint were constructed for As, Σchlordane-nonachlor, ΣDDT, HCB, ΣPBBS, PBDE-209, ΣPCBi, PeCB and PFOS.

Arsenic. A TT of 5 ng/kg bw/day was deduced from disruption of thyroid homeostasis recorded in juvenile mice exposed to AsV or AsIII at 10 or 100 µg/L in drinking water for 8 weeks (Sun et al. 2017). The authors reported an effective dose of 10 µg/L on the thyroid system. The LOAEL of 1.5 µg/kg bw/day was calculated on the basis of 3 mL of absorbed water per day and per 20 g mice, which corresponded to 30 ng of ingested arsenic per 20 g mice. This obtained LOAEL value was then divided by applying an uncertainty factor of 300 (10 for intra-species variability, 10 for inter-species sensitivity, and 3 for extrapolating LOAEL to NOAEL).

ΣChlordane-nonachlor. As a major metabolite of chlordane and a main constituent of technical chlordane, the toxicological threshold of trans-nonachlor was used as a substitute for chlordane (lack of data). A toxicological threshold value of 4.2 µg/kg bw/day was determined based on changes in thyroxine levels and thyroid histopathology in rats in a 90-day feeding study (Bondy et al. 2004). The NOAEL of 1,250 µg/kg bw/day was used with an uncertainty factor of 300 accounting for intra-species (10) and inter-species (10) variabilities, and infant sensitivity (3).

ΣDDT. A self-built value of 0.012 µg/kg bw/day was based on studies showing hypothyroidism in pubertal rats exposed to PND1 until six weeks of age (Yaglova et al. 2016; 2018). It was derived from the LOAEL (3.7 µg/kg bw/day) using an uncertainty factor of 300 (10 for inter-species variation, 10 for intra-species sensitivity, and 3 for LOAEL to NOAEL extrapolation).

HCB. A toxicological threshold of 0.53 µg/kg bw/day was built from the studies showing induced hypothyroidism in adult rats exposed for 4 weeks to HCB (Chalouati et al. 2016; Hadjab et al. 2004). Altered thyroid function paralleled ototoxicity (Hadjab et al. 2004) and was shown to be irreversible at the tested doses (Chalouati et al. 2016). Dose-related effects were recorded from 4 mg/kg bw/day, which was considered to be the LOAEL. The NOAEL dose of 160 µg/kg/day (Hadjab et al. 2004) was used to derive the toxicological threshold with an uncertainty factor of 300 [accounting for inter-species (10) and intra-species (10) variations, and for infant sensitivity (3)].

ΣPBB. A self-built value of 1.25 µg/kg bw/day was based on the reduced thyroid hormone levels induced following gestational and lactational exposure (GD8 to PND4) to a PBB mixture in sows (Werner and Sleight 1981). The authors reported a NOAEL of 125 µg/kg bw/day for the thyroid effects. This value was used to calculate the threshold toxicological value, with an uncertainty factor of 100 (10 for inter-species variation, and 10 for intra-species variability).

PBDE-209. A toxicological threshold of 16.7 µg/kg bw/day was based on reduced thyroid hormone levels in adult male rats after 28 days of oral exposure (Wang et al. 2019). The NOAEL was 5 mg/kg bw/day, and an uncertainty factor of 300 was used to account for intra-species (10) and inter-species (10) variabilities, and infant sensitivity (3).

ΣPCBi. A toxic threshold of 0.1 µg/kg bw/day for total PCBs was based on the observed postnatal hypothyroidism induced in rats perinatally exposed to Aroclor 1,254 from GD0 to PND15 or 30 (Provost et al. 1999). The LOAEL of 0.1 mg/kg bw/day was used with an uncertainty factor of 1,000, accounting for intra-species (10) and inter-species (10) variabilities, and extrapolation of LOAEL to NOAEL (10). The value of 0.05 µg/kg/day was calculated for the sum of the 6 PCB indicators, which represent 50% of total PCBs.

PeCB. A toxicological threshold of 2.7 µg/kg bw/day was determined on the basis of hypothyroxinemia induced in adult rats and mice of both sexes exposed through diet in a 13-week NTP study (1991). This value was derived from the LOAEL in male rats (2.4 mg/kg

bw/day) using an uncertainty factor of 900 (10 for inter-species and 10 for intra-species variability, 3 for LOAEL to NOAEL extrapolation, and 3 for infant sensitivity).

PFOS. An RfD of 0.05 µg/kg bw/day was established on the basis of maternal and developmental toxicities associated with hypothyroxinemia in rats and mice exposed from GD1 to GD20 (Lau et al. 2003; Thibodeaux et al. 2003). In neonatal rats, both total T4 and free T4 were depressed in all PFOS-treated groups of pregnant rats (LOAEL of 1 mg/kg bw/day). Serum PFOS concentrations in neonates were converted to a human equivalent dose (HED) using a pharmacokinetic model (PK-HED). An uncertainty factor of 30 (3 for inter-species variation, and 10 for intra-individual variation) was applied to the POD value, which corresponded to the PK-HED of 1.4 µg/kg/day modeled from animal data, thereby resulting in an RfD of 0.05 µg/kg bw/day for thyroid endpoint.

S2.2. Neurodevelopmental effects

Institutional HBGVs based on neural effects were established for six substances including ΣDDT, ΣHeptachlor, PBDE 209, and ΣPCBi, as well as methylmercury and ΣPBDE, which were already discussed in the thyroid section, and are not commented further in this section.

ΣDDT. An acute oral MRL of 0.5 µg/kg bw/day was established by the ATSDR (2002) based on a series of experiments by Eriksson et al. (1990, 1992), who conducted behavioral testing and neurochemical investigations. Hyperactivity and altered muscarinic cholinergic transmission were recorded after treatment at a critical period of neurodevelopment of mice aged 10 days. The LOAEL of 0.5 mg/kg bw/day for neurodevelopmental effects was used with an uncertainty factor of 1,000 (10 for animal to human extrapolation, 10 to account for intra-human variation, and 10 for use of a LOAEL) to define the acute oral MRL.

ΣHeptachlor. An intermediate-duration oral MRL of 0.1 µg/kg bw/day was calculated by the ATSDR (2007) on the basis of behavioral and immune system alterations occurring at the same level of exposure. Moser et al. (2001) reported neurobehavioral changes in the offspring of rats prenatally and postnatally exposed to heptachlor. The MRL was obtained by dividing the LOAEL of 30 µg/kg bw/day by an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for use of a minimal LOAEL).

PBDE 209. An acute oral MRL of 10 µg/kg bw/day was determined by the ATSDR (2017). It was based on the study of Johansson et al. (2008), which showed that exposure of NMRI mice on PND 3 to a single dose of PBDE 209 (1.34, 2.22, 13.4 and 20.1 mg/kg bw/day) induced long-term changes in the adult brain. The changes in spontaneous activity and the altered susceptibility of the cholinergic system were dose-response related. The behavioral defects could be mechanistically related to the functioning of the cholinergic system. An uncertainty factor of 100 (10 for inter-species variation, and 10 for intra-species variability) was assigned to the NOAEL of 1.34 mg/kg bw/day to derive the acute MRL value.

∑PCBi. A TDI of 0.020 µg/kg bw/day was established for total PCBs based on developmental neurotoxicity and immunotoxicity by the WHO (2003) and ANSES (2007). This value was based on the studies of Tilson et al. (1990) reporting neural and developmental changes in infants exposed prenatally and through breastmilk, and on the studies of Rice and Hayward (1997, 1999) describing behavioral consequences of postnatal exposure of monkeys (birth to 20 weeks old) through breastfeeding to a PCB mixture representative of the PCBs typically found in human breastmilk. The NOAEL for hypotonicity and psychomotor delay in humans was 0.093 µg/kg bw/day. An uncertainty factor of 6 (3 for intra-species variation, and 2 extra factor) was applied by ANSES (2007) to obtain a TDI of 0.020 µg/kg bw/day. In monkey studies, the LOAEL was 7.5 µg /kg bw/day for developmental neurotoxicity and converged with immunotoxicity. Using an uncertainty factor of 300 (3 for inter-species variation, 10 for intra-species variation, and 10 for extrapolation from a LOAEL to a NOAEL), a tolerable intake of 0.020 µg/kg bw/day was derived for total PCBs, which corresponds to a TDI of 0.010 µg/kg/day for the sum of the 6 PCBi.

The TTs for neurodevelopment were established for ∑aldrin-dieldrin, arsenic, ∑chlordan-nonachlor, HCB, ∑HCH, inorganic mercury, ∑PBB, ∑PCDD/F, PFHxS, PFOA, and PFOS.

∑Aldrin-dieldrin. A toxicological threshold of 0.03 µg/kg bw/day was built on the basis of disrupted learning acquisition in adult rhesus monkeys after oral exposure for 55 days to low doses of dieldrin (Smith et al. 1976). This value was obtained by applying an uncertainty factor of 300 (for inter-species (10) and intra-species (10) variabilities, and 3 for infant sensitivity) to the NOAEL of 10 µg/kg bw/day.

As. The toxicological threshold of 0.2 µg/kg bw/day was based on neurodevelopmental effects of low arsenic exposure reported in a corpus of epidemiological studies reviewed by Tsuji et al. (2015). The authors calculated speciated arsenic intake associated with urinary arsenic level and 1-point decrease in verbal IQ in girls (Hamadani et al. 2011) and selected a LOAEL in the range 1.1 to 1.47 µg/kg bw/day. The application of an uncertainty factor of 6 (3 for intra-species variability, and 2 as an extra factor) to the lowest value 1.1 µg/kg bw/day resulted in the toxicity threshold of 0.2 µg/kg bw/day.

∑Chlordane-nonachlor. A toxicological threshold of 0.33 µg/kg bw/day was determined based on the study of Cassidy et al. (1994) reporting changes in sex steroid-modulated behaviors and functions in rats after oral chlordane exposure from GD4 until adulthood (PND80). The low dose exposed groups exhibited dose-related responses in a variety of behavioral tests (Cincinnati maze, auditory startle, open field, and mating) from the dose of 100 µg/kg bw/day in males and females. An uncertainty factor of 300 (10 for inter-species variation and intra-species variability; 3 for LOAEL extrapolation to NOAEL) was applied to this LOAEL to derive a toxicological threshold for neurodevelopment.

HCB. A toxicological threshold of 6.4 µg/kg bw/day for neurobehavioral effects was deduced from the study of Lilienthal et al. (1996) in rat offspring after pre- and postnatal exposure to HCB lasting from 90 day pre-mating to weaning. Locomotor activity and active avoidance learning were not affected; dose-response dependent changes in operant behavior were observed from 0.64 mg/kg/day, but a significant decrease was detected at 1.28 mg/kg/day. An uncertainty factor of 100 (10 for inter-species and 10 for intra-species variabilities) was assigned to the NOAEL (0.6 mg/kg bw/day) to derive the toxicological threshold (6.4 µg/kg bw/day).

ΣHCH. A toxicological threshold value of 0.62 µg/kg bw/day was based on behavioral changes induced by prenatal exposure of rats (GD5 to GD21) to lindane (Johri et al. 2007). The threshold value was obtained by dividing the NOAEL of 62.5 µg/kg/day by an uncertainty factor of 100 accounting for inter-species (10) and intra-species (10) variability.

Hg inorganic. A toxicity threshold of 1.23 µg/kg bw/day, expressed as Hg, was determined on the basis of the study of Huang et al. (2011). Neurobehavioral defects in developing offspring mice exposed *in utero* and postnatally consisted in increased locomotor activity, motor equilibrium impairment, and auditory dysfunction. The LOAEL of 0.5 mg/kg bw/day (oral dose, equivalent to 0.37 mg/kg bw/day expressed as Hg) was derived using an uncertainty factor of 300 (10 for inter-species variation, 10 for intra-species variability, and 3 for LOAEL extrapolation to NOAEL) to obtain a toxicological threshold for neurodevelopment of 1.66 µg/kg bw/day (equivalent to 1.23 µg/kg bw/day expressed as Hg).

ΣPBB. A toxicological threshold of 0.7 µg/kg bw/day was built from neurobehavioral changes reported in adult rat offspring following pre- and postnatal exposure (GD6 to PND24) to FireMaster BP-6 (Henck and Rech 1986). PBB-related deficits in acquisition and performance were observed using an autoshaping paradigm from the dose of 0.2 mg/kg bw/day (LOAEL). An uncertainty factor of 300 (inter-species (10), intra-species (10) and extrapolation LOAEL to NOAEL (3)) was applied to the LOAEL to derive the toxicological threshold.

ΣPCDD-F. A toxicological threshold of 0.0007 µg/kg bw/day was derived from the study of Zhang et al. (2018). Gestational exposure (GD8 to GD14) to TCDD induced premature sensorimotor development from 200 ng/kg bw/day, and led to advanced eye opening in preweaned male offspring at the higher dose in rats. Serious deficits of spatial memory and learning ability were observed at the higher dose in adult male offspring. An uncertainty factor of 300 (10 for inter-species and 10 for intra-species variabilities, 3 for LOAEL extrapolation to NOAEL) was applied to the LOAEL of 200 ng/kg bw/day to derive a toxicological threshold for neurobehavioral development (0.7 ng/kg bw/day).

PFHxS. A toxicological threshold of 6.1 µg/kg bw/day was estimated on the basis of dose-related and irreversible changes in spontaneous behavior and cognitive function in both male and female adult mice exposed at a critical developmental period (PND10) to a single dose of PFHxS (Viberg et al. 2013). The toxicological threshold was derived from the NOAEL value of

6.1 mg/kg bw/day using an uncertainty factor of 1,000 (10 for intra-species, 10 for inter-species variabilities, and 10 for paucity of the database on neurodevelopment).

PFOA: A toxicological threshold of 0.3 µg/kg bw/day was determined on the basis of neurobehavioral effects in male offspring of pregnant mice treated by gavage during gestation (GD1 to GD17) (Goulding et al. 2017). An effect on locomotor activity at PND18-20 in male offspring and on dopamine-dependent motor behavior at adulthood was recorded (at 1 mg PFOA/kg/day). The toxicological threshold was derived from the NOAEL of 0.3 mg/kg bw/day using an uncertainty factor of 1,000 (10 for intra-species, 10 for inter-species, and 10 for paucity of the database regarding neurodevelopment).

PFOS. A toxicological threshold for the neurodevelopmental endpoint of 0.03 µg/kg bw/day was established on the basis of functional and morphological changes in the nervous system of rats exposed during gestation and lactation (GD0 to PND20) to PFOS (Butenhoff et al. 2009). The NOAEL in male offspring for increased motor activity and reduced habituation on PND 17 was 0.3 mg/kg/day of maternal treatment. A human equivalent dose (HED) associated with no adverse effects on the developmental endpoint was calculated using pharmacokinetically modeled average serum values. An uncertainty factor of 30 (10 for intra-individual variability, and 3 for toxicodynamic differences between animals and humans) was applied to the PK-HED (0.00084 mg/kg/day as POD value) as calculated by the US EPA (2016), resulting in the retained value of 0.028 µg/kg bw/day, i.e. 0.03 µg/kg bw/day.

Supplemental Figures:

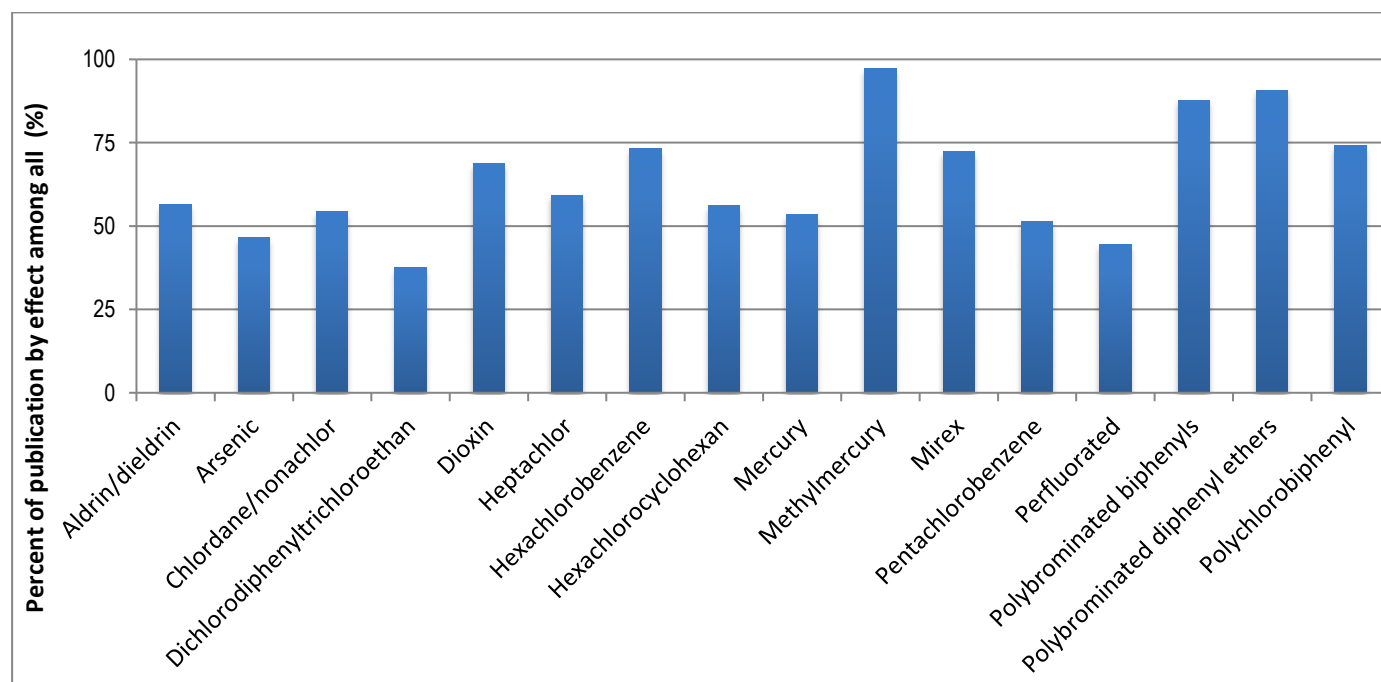


Figure S1: Percent of publications from Pubmed calculated by dividing the sum of publications obtained with the keyword « substance name AND toxicity AND endpoint » by the number of publications gathered using the keywords « substance name AND toxicity». The selected endpoints were hepatic, immune, thyroid,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

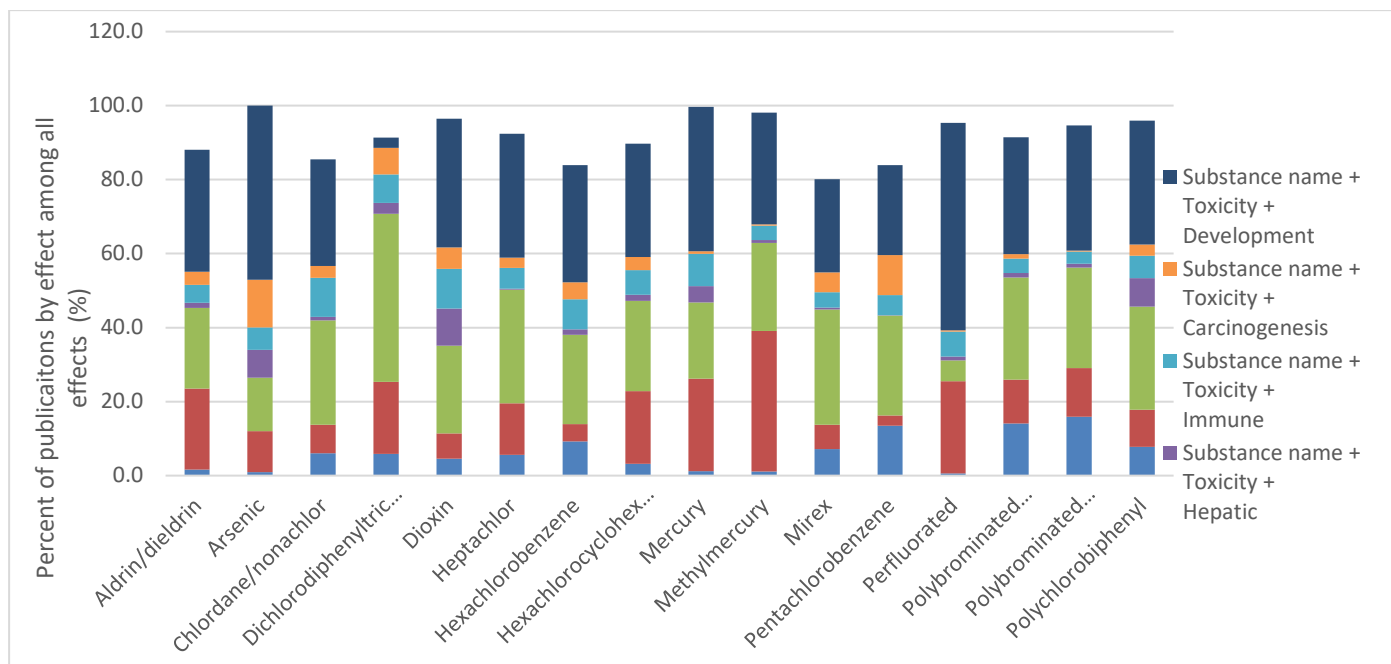


Figure S2. Percent of publications from Pubmed calculated in dividing the sum of publications obtained with the keyword « substance name AND toxicity AND endpoint » by the number of publications gathered using the keywords « substance name AND toxicity AND all endpoints». The selected endpoints were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

References

- ANSES 2007 Request No. 2006-SA-0305. Establishment of relevant maximum levels for non dioxin-like polychlorobiphenyls (NDL-PCB) in some foodstuffs. <https://www.anses.fr/en/content/opinion-french-food-safety-agency-establishment-relevant-maximum-levels-non-dioxin>
- ATSDR 2002. Toxicological profile for DDT, DDE, and DDD. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
- ATSDR 2007. Toxicological profile for Heptachlor and Heptachlor Epoxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
- ATSDR 2017. Toxicological profile for polybrominated diphenyl ethers (PBDEs). <https://www.atsdr.cdc.gov/toxprofiles/tp207.pdf>
- 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. doi: 10.1371/journal.pmed.0050161.
- Bondy G, Curran I, Doucet J, Armstrong C, Coady L, Hierlihy L, Fernie S, Robertson P, Barker M. 2004. Toxicity of trans-nonachlor to Sprague-Dawley rats in a 90-day feeding study. *Food Chem Toxicol* 42:1015-1027. doi: 10.1016/j.fct.2004.02.014.

- Bowers WJ, Nakai JS, Chu I, Wade MG, Moir D, Yagminas A, Gill S, Pulido O, Mueller R. Early developmental neurotoxicity of a PCB/organochlorine mixture in rodents after gestational and lactational exposure. *Toxicol Sci.* 2004 Jan;77(1):51-62. doi: 10.1093/toxsci/kfg248.
- Butenhoff JL, Ehresman DJ, Chang S-C, Parker GA, Stump DG. 2009. Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: Developmental neurotoxicity. *Reprod Toxicol* 27:319-330. doi: 10.1016/j.reprotox.2008.12.010.
- Cassidy RA, Vorhees CV, Minnema DJ, Hastings L. 1994. The effects of chlordane exposure during pre- and postnatal periods at environmentally relevant levels on sex steroid-mediated behaviors and functions in the rat. *Toxicol Appl Pharmacol* 126:326-337. doi: 10.1006/taap.1994.1123.
- Chalouati H, Gamet-Payrastre L, Ben Saad M. 2016. Irreversible thyroid disruption induced after subchronic exposure to Hexachlorobenzene in male rats. *Toxicol Ind Health* 32:822-831. doi: 10.1177/0748233713511511.
- Chu I, Bowers WJ, Caldwell D, Nakai J, Wade MG, Yagminas A, Li N, Moir D, El Abbas L, Håkansson H, Gill S, Mueller R, Pulido O. Toxicological effects of in utero and lactational exposure of rats to a mixture of environmental contaminants detected in Canadian Arctic human populations. *J Toxicol Environ Health A.* 2008;71(2):93-108. doi: 10.1080/15287390701612811.
- Crofton KM, Craft ES, Hedge JM, Gennings C, Simmons JE, Carchman RA, et al. 2005. Thyroid-hormone-disrupting chemicals: Evidence for dose-dependent additivity or synergism. *Environmental health perspectives* 113:1549-1554. doi: 10.1289/ehp.8195.
- Davidson PW, Jean Sloane R, Myers GJ, Hansen ON, Huang LS, Georger LA, Cox C, Thurston SW, Shamlaye CF and Clarkson TW. 2008. Association between prenatal exposure to methylmercury and visuospatial ability at 10.7 years in the Seychelles child development study. *Neurotoxicology* 29:453-459. doi: 10.1016/j.neuro.2008.02.009.
- Elabbas LE, Esteban J, Barber X, Hamscher G, Nau H, Bowers WJ, et al. 2014. In utero and lactational exposure to a mixture of environmental contaminants detected in Canadian arctic human populations alters retinoid levels in rat offspring with low margins of exposure. *Journal of Toxicology and Environmental Health, Part A* 77:223-245. doi: 10.1080/15287394.2013.861776.
- Eriksson P, Ahlbom J, Fredriksson A. 1992. Exposure to DDT during a defined period in neonatal life induces permanent changes in brain muscarinic receptors and behaviour in adult mice. *Brain Res* 582:277-281. doi: 10.1016/0006-8993(92)90144-x.
- Eriksson P, Archer T, Fredriksson A. 1990. Altered behaviour in adult mice exposed to a single low dose of DDT and its fatty acid conjugate as neonates. *Brain Res* 514:141-142. doi: 10.1016/0006-8993(90)90446-i.
- Eriksson P, Fischer C, Fredriksson A. Polybrominated diphenyl ethers, a group of brominated flame retardants, can interact with polychlorinated biphenyls in enhancing developmental neurobehavioral defects. *Toxicol Sci.* 2006 Dec;94(2):302-9. doi: 10.1093/toxsci/kfl109.

- Ernest SR, Wade MG, Lalancette C, Ma YQ, Berger RG, Robaire B, Hales BF. Effects of chronic exposure to an environmentally relevant mixture of brominated flame retardants on the reproductive and thyroid system in adult male rats. *Toxicol Sci.* 2012 Jun;127(2):496-507. doi: 10.1093/toxsci/kfs098.
- EFSA 2012. EFSA Panel on Contaminants in the Food Chain (CONTAM). Scientific opinion on the risk for public health related to the presence of mercury and methylmercury in Food 1. *EFSA J.* 10.2903/j.efsa.2012.2985.
- Fischer C, Fredriksson A, Eriksson P. Coexposure of neonatal mice to a flame retardant PBDE 99 (2,2',4,4',5-pentabromodiphenyl ether) and methyl mercury enhances developmental neurotoxic defects. *Toxicol Sci.* 2008 Feb;101(2):275-85. doi: 10.1093/toxsci/kfm271.
- Flippin JL, Hedge JM, DeVito MJ, LeBlanc GA, Crofton KM. 2009. Predictive modeling of a mixture of thyroid hormone disrupting chemicals that affect production and clearance of thyroxine. *International Journal of Toxicology* 28:368-381. doi: 10.1177/1091581809341883.
- Goulding DR, White SS, McBride SJ, Fenton SE, Harry GJ. 2017. Gestational exposure to perfluorooctanoic acid (PFOA): Alterations in motor related behaviors. *Neurotoxicology* 58:110-119. doi: 10.1016/j.neuro.2016.11.008.
- Gralewicz S, Wiaderna D, Lutz P, Sitarek K. Neurobehavioural functions in adult progeny of rat mothers exposed to methylmercury or 2,2', 4,4', 5,5'-hexachlorobiphenyl (PCB 153) alone or their combination during gestation and lactation. *Int J Occup Med Environ Health.* 2009;22(3):277-91. doi: 10.2478/v10001-009-0020-9.
- Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R and Jorgensen PJ, 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol*, 19:417-428. doi: 10.1016/s0892-0362(97)00097-4.
- Hadjab S, Maurel D, Cazals Y, Siaud P. 2004. Hexachlorobenzene, a dioxin-like compound, disrupts auditory function in rat. *Hear Res* 191:125-134. doi: 10.1016/j.heares.2003.12.017.
- Hallgren S, Darnerud PO. Polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs) and chlorinated paraffins (CPs) in rats-testing interactions and mechanisms for thyroid hormone effects. *Toxicology.* 2002 Aug 15;177(2-3):227-43. doi: 10.1016/s0300-483x(02)00222-6.
- Hamadani JD, Tofail F, Nermell B, Gardner R, Shiraji S, Bottai M, Arifeen SE, Huda SN, Vahter M. 2011. Critical windows of exposure for arsenic-associated impairment of cognitive function in pre-school girls and boys: A population-based cohort study. *Int J Epidemiol* 40:1593-1604. doi: 10.1093/ije/dyr176.
- He P, Wang A, Niu Q, Guo L, Xia T, Chen X. Toxic effect of PBDE-47 on thyroid development, learning, and memory, and the interaction between PBDE-47 and PCB153 that enhances toxicity in rats. *Toxicol Ind Health.* 2011 Apr;27(3):279-88. doi: 10.1177/0748233710387002.

- Henck JW, Rech RH. 1986. Effect of perinatal polybrominated biphenyl exposure on acquisition and performance of an autoshaping paradigm. *Neurotoxicology* 7:651-663.
- Huang C-F, Liu S-H, Hsu C-J, Lin-Shiau S-Y. 2011. Neurotoxicological effects of low-dose methylmercury and mercuric chloride in developing offspring mice. *Toxicol Lett* 201:196-204. doi: 10.1016/j.toxlet.2010.12.016.
- Integrated Risk Information System (IRIS). 1992. Mirex. Integrated Risk Information System. Chemical assessment summary. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0251_summary.pdf. October 18, 2017.
- Johansson N, Viberg H, Fredriksson A, Eriksson P. 2008. Neonatal exposure to decabrominated diphenyl ether (PBDE 209) causes dose-response changes in spontaneous behaviour and cholinergic susceptibility in adult mice. *Neurotoxicology* 29:911-919. doi: 10.1016/j.neuro.2008.09.008.
- Johri A, Yadav S, Dhawan A, Parmar D. 2007. Overexpression of cerebral and hepatic cytochrome P450s alters behavioral activity of rat offspring following prenatal exposure to lindane. *Toxicol Appl Pharmacol* 225:278-292. doi: 10.1016/j.taap.2007.08.006.
- Kuriyama SN, Talsness CE, Grote K, Chahoud I. 2005. Developmental exposure to low dose PBDE 99: Effects on male fertility and neurobehavior in rat offspring. *Environ Health Perspect* 113:149-154. doi: 10.1289/ehp.7421.
- Kuriyama SN, Wanner A, Fidalgo-Neto AA, Talsness CE, Koerner W, Chahoud I. 2007. Developmental exposure to low-dose PBDE-99: tissue distribution and thyroid hormone levels. *Toxicology* 242:80-90. doi: 10.1016/j.tox.2007.09.011.
- Lau C, Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Stanton ME, Butenhoff JL, Stevenson LA. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicol Sci.* 74:382-392. doi: 10.1093/toxsci/kfg122.
- Lilienthal H, Benthe C, Heinzow B, Winneke G. 1996. Impairment of schedule-controlled behavior by pre- and postnatal exposure to hexachlorobenzene in rats. *Arch Toxicol* 70:174-181. doi: 10.1007/s002040050257.
- Liu C, Ha M, Li L, Yang K. PCB153 and p,p'-DDE disorder thyroid hormones via thyroglobulin, deiodinase 2, transthyretin, hepatic enzymes and receptors. *Environ Sci Pollut Res Int.* 2014 Oct;21(19):11361-9. doi: 10.1007/s11356-014-3093-3.
- Miller VM, Sanchez-Morrissey S, Brosch KO, Seegal RF. Developmental coexposure to polychlorinated biphenyls and polybrominated diphenyl ethers has additive effects on circulating thyroxine levels in rats. *Toxicol Sci.* 2012 May;127(1):76-83. doi: 10.1093/toxsci/kfs089.
- 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. doi.org/10.1289/ehp.10399.
- Moser VC, Shafer TJ, Ward TR, Meacham CA, Harris MW, Chapin RE. 2001. Neurotoxicological outcomes of perinatal heptachlor exposure in the rat. *Toxicol Sci* 60:315-326. doi: 10.1093/toxsci/60.2.315.
- Murata K, Weihe P, Budtz-Jorgensen E, Jorgensen PJ and Grandjean P, 2004. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J Pediatr* 144:177-183. doi: 10.1016/j.jpeds.2003.10.059.
- NTP (National Toxicology Program). 1990. Toxicology and carcinogenesis Studies of MIREX (CAS No. 2385-85-5) in F344/N Rats (Feed Studies). NTP TR 313.
- NTP (National Toxicology Program). 1991. NTP report on the toxicity studies of Pentachlorobenzene in F344/N rats and B6C3F1 mice (feed studies). NTP Tox 6, U.S. Dept. of Health and Human Services, Research Triangle Park, North Carolina.
- Pelletier G, Masson S, Wade MJ, Nakai J, Alwis R, Mohottalage S, Kumarathasan P, Black P, Bowers WJ, Chu I, Vincent R. Contribution of methylmercury, polychlorinated biphenyls and organochlorine pesticides to the toxicity of a contaminant mixture based on Canadian Arctic population blood profiles. *Toxicol Lett.* 2009 Feb 10;184(3):176-85. doi: 10.1016/j.toxlet.2008.11.004.
- Provost TL, Juárez de Ku LM, Zender C, Meserve LA. 1999. Dose- and age-dependent alterations in choline acetyltransferase (ChAT) activity, learning and memory, and thyroid hormones in 15- and 30-day old rats exposed to 1.25 or 12.5 PPM polychlorinated biphenyl (PCB) beginning at conception. *Prog Neuropsychopharmacol Biol Psychiatry* 23:915-928. doi: 10.1016/s0278-5846(99)00035-4.
- Reardon AJF, Karathra J, Ribbenstedt A, Benskin JP, MacDonald AM, Kinniburgh DW, Hamilton TJ, Fouad K, Martin JW. Neurodevelopmental and Metabolomic Responses from Prenatal Coexposure to Perfluorooctanesulfonate (PFOS) and Methylmercury (MeHg) in Sprague-Dawley Rats. *Chem Res Toxicol.* 2019 Aug 19;32(8):1656-1669. doi: 10.1021/acs.chemrestox.9b00192.
- Rice DC, Hayward S. 1997. Effects of postnatal exposure to a PCB mixture in monkeys on nonspatial discrimination reversal and delayed alternation performance. *Neurotoxicology* 18:479-494.
- Rice DC, Hayward S. 1999. Effects of postnatal exposure of monkeys to a PCB mixture on concurrent random interval-random interval and progressive ratio performance. *Neurotoxicol Teratol.* 21:47-58. doi: 10.1016/s0892-0362(98)00032-4.
- Roegge CS, Wang VC, Powers BE, Klintsova AY, Villareal S, Greenough WT, Schantz SL. Motor impairment in rats exposed to PCBs and methylmercury during early development. *Toxicol Sci.* 2004 Feb;77(2):315-24. doi: 10.1093/toxsci/kfg252.

- Sitarek K, Gralewicz S. Early developmental effects of separate or combined perinatal exposure to methylmercury (MeHg) and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB 153) in the rat. *Int J Occup Med Environ Health*. 2009;22(2):89-105. doi: 10.2478/v10001-009-0015-6.
- Smith RM, Cunningham Jr WL, van Gelder GA, Karas GG. 1976. Deldrin toxicity and successive discrimination reversal in Squirrel Monkeys (*Saimiri Sciureus*). *J Toxicol Environ Health* 1:737-747. doi: 10.1080/15287397609529372.
- Sun H-J, Li S-W, Chao Li, Wang W-Q, Li H-B, Ma LQ. 2017. Thyrotoxicity of arsenate and arsenite on juvenile mice at organism, subcellular, and gene levels under low exposure. *Chemosphere* 186:580-587. doi: 10.1016/j.chemosphere.2017.08.042.
- Talsness CE, Shakibaei M, Kuriyama SN, et al. 2005. Ultrastructural changes observed in rat ovaries following in utero and lactational exposure to low doses of a polybrominated flame retardant. *Toxicol Lett* 157:189-202. doi: 10.1016/j.toxlet.2005.02.001.
- Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Barbee BD, Richards JH, Butenhoff JL, Stevenson LA, Lau C. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: maternal and prenatal evaluations. *Toxicol Sci* 74:369-381. doi: 10.1093/toxsci/kfg121.
- Tilson HA, Jacobson JL, Rogan WJ. 1990. Polychlorinated biphenyls and the developing nervous system: Cross-species comparisons. *Neurotoxicol Teratol* 12:239-248. doi: 10.1016/0892-0362(90)90095-t.
- Tsuji JS, Garry MR, Perez V, Chang ET. 2015. Low-level arsenic exposure and developmental neurotoxicity in children: A systematic review and risk assessment. *Toxicology* 337:91-107. doi: 10.1016/j.tox.2015.09.002.
- US-EPA. 2012. EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments, Volume 1. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/supdocs/dioxinv1sup.pdf
- Viberg H, Lee I, Eriksson P. 2013. Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose. *Toxicology* 304:185-191. doi: 10.1016/j.tox.2012.12.013.
- Wade MG, Parent S, Finson KW, Foster W, Younglai E, McMahon A, Cyr DG, Hughes C. Thyroid toxicity due to subchronic exposure to a complex mixture of 16 organochlorines, lead, and cadmium. *Toxicol Sci*. 2002 Jun;67(2):207-18. doi: 10.1093/toxsci/67.2.207.
- Wang Y, Chen T, Sun Y, Zhao X, Zheng D, Jing L, Zhou X, Sun Z, Shi Z. 2019. A comparison of the thyroid disruption induced by decabrominated diphenyl ethers (BDE-209) and decabromodiphenyl ethane (DBDPE) in rats. *Ecotoxicol Environ Saf* 174:224-235. doi: 10.1016/j.ecoenv.2019.02.080.
- Werner PR, Sleight SD. 1981. Toxicosis in sows and their pigs caused by feeding rations containing polybrominated biphenyls to sows during pregnancy and lactation. *Am J Vet Res* 42:183-188.

WHO 2003. Polychlorinated biphenyls: Human health aspects. CICAD doc 55, Geneva.

Yaglova NV, Sledneva YP, Nazimova SV, Obernikhin SS, Yaglov VV. 2018. Sex differences in the production of SLC5A5, thyroid peroxidase, and thyroid hormones in pubertal rats exposed to endocrine disruptor dichlorodiphenyltrichloroethane (DDT) during postnatal ontogeny. *Bull Exp Biol Med* 164:430-433. doi: 10.1007/s10517-018-4005-1.

Yaglova NV, Sledneva YP, Yaglov VV. 2016. Morphofunctional changes in the thyroid gland of pubertal and postpubertal rats exposed to low dose of DDT. *Bull Exp Biol Med* 162:260-263. doi: 10.1007/s10517-016-3590-0.

Zhang H-J, Liu Y-N, Xian P, Ma J, Sun Y-W, Chen J-S, Chen X, Tang N-J. 2018. Maternal exposure to TCDD during gestation advanced sensory-motor development, but induced impairments of spatial learning and memory in adult male rat offspring. *Chemosphere* 212:678-686. doi: 10.1016/j.chemosphere.2018.08.118.