Analysis of the most appropriate risk management option (RMOA)

Substance Name: 2,2',4,4'-tetrabromodiphenyl ether (BDE-47)

EC Number: -

CAS Number: 5436-43-1

Authority: FR

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Cover Note

In the framework on the French National Strategy on Endocrine Disruptors in 2017, the French Competent Authority requested ANSES to evaluate the ED properties of BDE-47 and verify whether risk management measures should be necessary for this substance.

Anses concisely described in a former expertise all the available data on regulations and uses related to polybrominated compounds, their contamination levels in various marketed products and environmental compartments, and the potential effects for on human health.
This state of the art was used in particular to identify polybrominated compounds for which a health risk assessment may be justified in light of their widespread use and/or persistence in the human body or the environment, and in light of their potential toxicity to humans, particularly for reproductive function and development.

In light of this analysis, the experts considered that certain brominated compounds such as BDE-47 may justify an individual assessment. BDE 47 was therefore selected for an assessment of its ED potential for humans and the environment.

Regarding ED properties, the data available indicate a trend for effect on male reproduction in rats and metabolic disturbances. Environmental data show endocrine disruptor potential of BDE-47. Nevertheless, these data set is insufficient to conclude that BDE-47 is an endocrine disruptor according to the OECD conceptual framework for testing and assessment of endocrine diruptors. Anses consider that BDE-47 is an endocrine disruptor for environment.

As the substance is not registered and already regulated by the POP Convention, no further action is recommended.

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1 IDENTITY OF THE SUBSTANCE

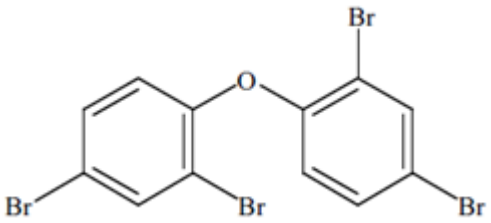
1.1 Other identifiers of the substance

Table 1: Other Substance identifiers

EC name (public):	
IUPAC name (public):	2,2’,4,4’-tétrabromo diphényl éther
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C12H6Br4O
Molecular weight or molecular weight range:	485.8
Synonyms:	BDE-47 Benzene, 1,1'-oxybis(2,4-dibromo)- PBDE 47 2,2',4,4'-Tetrabromodiphenyl ether

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



1.2 Similar substances/grouping possibilities

Not relevant in the frame of this RMOA.

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table 2: Completed or ongoing processes

RMOA		☐ Risk Management Option Analysis (RMOA) other than this RMOA
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restri -ction	☐ Annex XVII[1]
Harmonised C&L		☐ Annex VI (CLP) (see section 3.1)
Processes under other EU legislation		☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009
		☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments
Previous legislation		☐ Dangerous substances Directive Directive 67/548/EEC (NONS)
		☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)
(UNEP) Stockholm convention (POPs Protocol)		☐ Assessment
		☒ In relevant Annex
Other processes/ EU legislation		☐ Other (provide further details below)

[1] Please specify the relevant entry.

Tetrabromodiphenyl ether listed in Annex I Part A of Regulation (EU) No 757/2010 of 24 August 2010 - amending Regulation (EC) No 850/2004 of the European Parliament and of the Council on persistent organic pollutants ("POP") as regards Annexes I and III.

The "POP" Regulation contains provisions regarding production, placing on the market and use of chemicals, management of stockpiles and wastes, and measures to reduce unintentional releases of POPs. Furthermore, Member States must set up emission inventories for unintentionally produced POPs, national implementation plans (NIPs) and monitoring and information exchange mechanisms.

As stated in Annex I Part A, for the purposes of this entry, Article 4(1)(b) shall apply to concentrations of Tetrabromodiphenyl ether equal to or below 10 mg/kg (0,001 % by weight) when it occurs in substances, preparations, articles or as constituents of the flame-retarded parts of articles.

By way of derogation, the production, placing on the market and use of the following shall be allowed:

(a) without prejudice to subparagraph (b), articles and preparations containing concentrations below 0,1 % of tetrabromodiphenyl ether by weight when produced partially or fully from recycled materials or materials from waste prepared for re-use;

(b) electrical and electronic equipment within the scope of Directive 2002/95/EC of the European Parliament and Council (repealed by Directive 2011/65/EU of the European Parliament and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and electronic equipment).

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

Human and environmental hazards properties presented are based on available data from scientific literature.

Human health

Epidemiology

Epidemiological studies are not likely to identify modes and / or mechanisms of action. They can only provide information on the presence of associations between exposure and a specific outcome.

The literature was searched with medline and scopus. It showed the existence of 50 abstracts of articles on BDE-47 (and other PBDEs) published between 2010 and 2017. Time constraints led us to establish from the abstracts a prioritization process for reading and analyzing these articles. On what criteria? We decided to study first the studies which, according to their summary, seemed the most reliable, that is to say those which seemed free of risk of biases.

A bias is a systematic error that more or less distorts the parameter estimator measuring the association between an exposure and a health parameter; a random error leads to a lack of precision.

We have adopted the OHAT method (NTP, 2015) which is based on 11 criteria for identifying the absence of certain biases and / or errors with a probability measured in 4 classes: very strong, possible, unlikely or very unlikely. Some criteria are key criteria (characterization of exposure, characterization of health events and consideration of confounding factors). For each summary, the 11 criteria of the OHAT method were reviewed and were used as a basis for ranking the articles in 4 reading priority classes of the full article.

Priority class 1: the summary is well structured (context, objective of the study, methods, results, conclusions). We understand what is done and how. Given the limited space (<350 words in general), the 11 criteria seem to be respected with a high probability. The number of subjects is important, the methods of measurement as well as analysis are very clear. The study must be read in full for details.

Priority class 2: The probability that the 11 criteria are respected is less important than in case N°1. There is a lack of information and / or the quality criteria are not all specified. For example the number of subjects is low or we do not know how were selected the subjects of the study, the statistical analysis is not specified (but we can guess what it is). The absence of certain information is probably due to the small space devoted to the summary.

Priority class 3: The summary is poorly presented and poorly structured. We hardly understand what is done.

Priority class 4: we can dispense with reading the entire article because the summary is really incomprehensible. Other possibility: the study does not explore an association between an exposition and a health parameter.

The fact that the BDE-47 is associated or not with the health parameter(s) studied does not fall within the prioritization criteria.

Concretely, the rules were as follows:

- If the summary indicated that subjects came from a cohort, the assumption was made that selection bias at inclusion was unlikely because when a cohort is set up,

careful attention is given to this point. If the summary did not indicate how subjects were selected it was an element to decrease the reading priority of the entire article.

- Most articles said what confounding factors had been taken into account. If there was no reference to such factors it was an element to decrease the priority.

- The measurement method of BDE-47 and / or health parameters is not often included in a summary. It was hypothesized that the measurement method was reliable when it came to biological measurements.

- The statistical method used is not always indicated. If it was, or if we guessed from the results what it was, it was a positive point for the prioritization.

- The type of study (cross-section, case-control, cohort) is not a quality criterion for prioritization. It is rather at the moment of the interpretation of a possible association highlighted by the study (causal or not?) that the type of study is important.

Among the 50 studies, 14 were classified in priority class 1, 20 in priority class 2, 9 in priority class 3 and 7 in priority class 4.

Three studies have focused on the male reproductive system. In a prospective study, Meijer *et al* (2012) found no correlation between plasma concentrations of BDE-47 measured in pregnant women and reproductive hormone levels (total and free testosterone, SHBG, LH, FSH, total and free estradiol, Inhibin B) as well as with testicular volume and penis length in their children at ages 3 and 18 months. In a transveral study, Abdelouahab *et al* (2011) found an inverse association between the plasma concentration of BDE-47 measured in men consulting for couple infertility and total T4 blood concentration. However, no corrections for multiple comparison were carried out taking into account the large number of comparisons (n = 77). Finally, in a transversal study, no association was observed between the plasma concentrations of BDE-47 measured in adult fertile men presumed and the main quantitative and qualitative semen characteristics, reproductive hormones and sperm DNA damage (Toft *et al*, 2014).

Two cross-sectional studies have focused on the female reproductive system. One showed no association between BDE-47 measured in breast milk and the characteristics of menstruation before pregnancy (Chao *et al*, 2010). The other shows an inverse association between plasma BDE concentrations in young girls (12-19 years) and age at first rules (Chen A *et al*, 2011). Given the retrospective nature of this study, no causality can be inferred.

Two prospective studies (Lopez-Espinosa *et al,* 2015; Yasmine *et al,* 2016) showed no association between exposure to BDE-47 estimated in the blood during pregnancy and fetal growth during pregnancy or weight at birth.

In a population-based case-control study, no association was found between BDE-47 exposure estimated by its concentration in carpet samples (in the room where the child spent) and risk of childhood acute lymphoblastic leukemia (Ward et al, 2014). A small hospital-based case control study (48 cases and 56 controls) did not shown association between BDE-47 concentration in adipose tissues and risk of breast cancer (Hurley *et al*, 2011).

Nine prospective studies have explored the associations between exposure to BDE-47 and neurodevelopment. No associations were observed in four among them where exposures were estimated in breast milk (Gascon *et al*, 2012, Adjenta *et al*, 2014) or in maternal blood during pregnancy (Donauer *et al*, 2015; Zhang *et al*, 2017). In 4 others studies (Hoffman *et al*, 2012, Chen *et al*, 2014, Cowell *et al*,

2015, Ding *et al*, 2015) exposure to BDE-47 (estimated in maternal blood during pregnancy or cord blood or breast milk) a few inverse associations were observed, sometimes at the limit of statistical significance, with some scores estimating neuro-development. Finally, I one study (Vuonga *et al,* 2017) increased exposure to BDE-47 (estimated in maternal blood during pregnancy and in blood of children at age 1, 2, 3, 5 and 8) was associated to better visual spatial abilities of children at age 5 and 8. Otherwise, in two transversal studies at the age of adolescence (Kiciński *et al*, 2012; Przybyla *et al*, 2016) no associations were associated with neurodevelopment.

A large number of studies have focused their attention on the consequences of BDE-45 exposures on circulating concentrations of thyroid hormones (including free and total thyroxine, free and total triiodothyronine, and thyroid-stimulating hormone). Most of these studies were cross-sectional and conducted in pregnant women, infants, young children, or adults (Kim *et al*, 2005; Miranda *et al*, 2015; Shy *et al*, 2012; Eggesbø *et al* 2011; Lin *et al*, 2011; Stapleton *et al,* 2011; Zota *et al*, 2011; Kim *et al*, 2013; Jacobson *et al*, 2016; Huang *et al*, 2015; Abdelouahab *et al*, 2011; Li *et al*, 2011; Oulhote *et al*, 2016; Makey *et al*, 2016; Johnson *et al*, 2015; Kiciński *et al*, 2015; Leijs *et al*, 2012). Their conclusions were strongly divergent with sometimes the presence of associations in one direction or another, or the absence of association. The only prospective study conducted in a mother-child cohort could not show an association between maternal exposure to BDE-47 and thyroid hormone concentrations in cord blood (Vuong *et al*, 2015).

In conclusion, all of these studies do not suggest an association between exposure to BDE-47 and the occurrence of adverse events to human health.

Pharmacokinetic data

The 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) congener of the Polybrominated diphenyl ethers (PBDEs) has been used in a wide variety of consumer applications as additive flame retardants. Routes of exposure are mostly by inhalation and oral exposure. Recent papers have been published recently improving the knowledge of the pharmacokinetic (PK). 6 papers have been reviewed whose 3 *in vitro* studies, 1 *in vivo* study, and 2 *in silico*. The *in vitro* studies reviewed are important for the understanding of BDE-47 because they describe major metabolites of BDE-47 and provide information about the enzymes implicated and their PK parameters. One paper used the human liver microsomes (HLM) to measure rates of formation of the metabolite by the CYP2B6 enzyme of the P450 family (Erratico *et al*., 2013). In fact, they determined several Vmax and Km implicated in the hydroxylation of BDE-47. Another paper characterizes the *in vitro* metabolism of BDE 47 by HLM and recombinant human CYPs, and to identify the CYP(s) that are active in the oxidative metabolism (Feo *et al*., 2013). Here the authors identify CYP2B6 as the major enzyme implicated in the formation of several metabolites such 6 OH-BDEs, 3 OH-BDE 47, 5 OH-BDE 47, 6 OH-BDE 47, 4 OH-BDE 42, 4´ OH-BDE 49, and suspected the 2´ OH-BDE 66. They also found that the Km of the CYP2B6 varied from 3.8 to 6.4µM and varied from 7.0 to 11.4 µM when a pooled human liver microsomes was used at concentration between 0 to 60 µM. Another paper used pig liver microsomes to study the formation of hydroxylated metabolite such as 3′-OH-BDE-7, 4′-OH-BDE-17, 3-OH-BDE-47 (Li *et al*., 2016). In this species, it seems that CYP3A4 is the major CYP450 for the hydroxylation of the BDE-47. For the *in vivo* study, a recent publication has looked the maternal transfer of BDEs 47 and BDE-209 as predominant congeners found in dust foods, and study the transfer in rat dam-offspring during gestation and lactation periods (Shin *et al*., 2017). The authors exposed female rats in 3 groups (from GD4 to GD14 or PND0 or PND4). Several hydroxy congeners were measured in dams and offspring. The major amount of BDE-47 transfers was during lactation. In addition, the BDE-209 seems

to be accumulated 10-fold more than BDE-47. Two *in silico* model papers have retained the attention. Both had used a PBPK model approach. The first was published in 2013 a description of BDE-47 distribution in mice using a PBPK model (Emond *et al.,* 2013). This model was developed based on a previous one in 2010 developed for rats (Emond *et al*., 2010). The particularity of the 2013 model was the incorporation of transporters. One transporter in blood the M-mup and a second the Pgp present in different compartments. Both seem to be implicated in the pharmacokinetic of BDE-47. The M-mup protein does not seem present in rats which results in different PK as describe in 2010 (Emond *et al*., 2010). The last in silico paper was published recently for humans and describe the PK of BDE-47 and the possible alteration timing of menarche (Song et al., 2016). This model is a 3 compartments model describing the distribution of BDE-47 in human. Contrary on what was concluded in previous publication, the modeling suggested there is no significant bias observed due to the growth dilution and change in the Pk in the reported relationship between BDE-47 and age at menarche.

This paper present observation resulting from modeling simulation, thus this not enough to conclude about an association or not with health effect. Considering the recent information related to the metabolism of BDE-47, it is important to integrate the hydroxylate metabolites of BDE-47 as part of the assessment because suspected to be implicated in developmental toxicity and may be impacting thyroid hormone regulation in vivo (Abdelouahab *et al*., 2013; Macaulay *et al*., 2015).

Toxicological data

Studies addressing the potential *in vivo* effects of BDE-47 exposure since 2011 are summarized and presented below. Whether or not a potential link with an endocrine disrupter mode of action was investigated in these studies is discussed.

- **Immune system**

Maranghi *et al*. (2013) have fed 22-day old female BALB/c mice (n = 10) with a fish-based diet containing BDE-47 (with a dose of 450 µg/kg bw/day). After one month, they have shown only minor histological modifications such as lymphocytic infiltration in liver and spleen, or cellular debris in thyroid follicular lumen. They have also reported an increase of the thymic cortex thickness.

Without functional tests, these histological data cannot be linked to an endocrine disruption and seem not relevant to humans.

- **Metabolism and obesity**

Several studies have explored the effects of BDE-47 on obesity and insulin sensitivity either investigating the impact on adipocyte differentiation or on pancreatic beta cell function, a key player in glucose homeostasis.

Taken as a whole, it sounds likely that BDE-47-induced alterations on metabolism are linked to an endocrine disrupting mode of action.

Sumorov and colleagues (Sumorov *et al*., 2009) explored the hypothesis that BDE-47 could impair the GH-IGF1 axis based on previous reports of the literature on wildlife. To that end, rats were perinatally exposed from embryonic day 15 to postnatal day (PND) 20. Specifically, intravenous injections were performed every 5th day with 0.002 or 0.2 mg/kg bw BDE-47. A follow-up of body weight and length of the pups indicated a significantly higher body length that would explain the

increase in body weight with the highest dose. Effects faded with age and were no longer observed at PND 47 (last age studied). In males but not in females, these effects were accompanied with an increase in plasma IGF-1 (dosed at PND 27). Exposed males (both doses) had better glucose tolerance than controls at PND 75-76. No such effect was observed at PND 40-41 or in females at any age. The authors concluded to a potential male impairment of the GH-IGF1 axis in response to a perinatal exposure to the BDE-47.

Increase in IGF-1 has also been reported by Khalil and colleagues (Khalil *et al*., 2017) in male mice exposed perinatally to BDE-47 (0.2 mg/kg/day given orally with a tip from embryonic day 8 until PND21). In addition, transcriptomic analysis of the liver by 20 weeks of age revealed long-lasting changes in important metabolic set genes and enhanced triglicerides, consistent with involvement of the mTOR (the mammalian target of rapamycin) serine/threonine kinase pathway. In as much as mTOR controls insulin signaling by regulating several downstream components, alteration of mTOR is in agreement with an endocrine disrupting mode of action.

PPAR Gamma is a master transcriptional regulator controlling adipocyte proliferation and differentiation and it has been proposed that the obesogenic properties of environmental pollutants were linked to their PPAR Gamma agonist activities. The authors Fang *et al*. (2015) investigated the PPAR Gamma binding activity of several flame retardants and of their metabolites including BDE-47 and BDE-47 metabolites. In the course of their study, the authors used Rosiglitazone as well as other previously identified PparGamma ligands as positive controls. They also used previously described obesogenic molecules as positive controls including tributyltin (TBT) and DEHP and its metabolite MEHP. Ligand binding activity was determined using a commercially Ppar Gamma competitive binding assay. Results showed that several flame retardants have Ppar Gamma binding activity. A striking result with regards to BDE-47, is that while the parent compound has little binding activity, the metabolite 3-OH-BDE-47 was of high potency and as potent as Rosiglitazone with an IC50 of 0.24 microM. These results do not mean complete activation of transcriptional events leading in fine to enhanced adipocyte differentiation because molecules may act as full or partial agonists or competitive antagonists. However, they are consistent with the study of Kamstra and colleagues (Kamstra *et al*., 2014) showing the potential of BDE-47 to induce adipocyte differentiation in a 3T3-L1 murine preadipocyte differentiation model at low concentrations (10 nM) *via* promoter demethylation of the Pparγ2 gene resulting in enhanced expression of the Pparγ transcription factor. Whether inappropriate activation of Pparγ is per se an endocrine disrupting mechanism of action has yet received no definitive answer. Nonetheless, it could be considered that molecules that enhance adipocyte differentiation result in body weight gain and obesity is a risk factor for diabetes.

Accordingly, McIntyre RL *et al*. (2015) investigated the impact of BDE-47 on hepatic metabolism and systemic glucose metabolism in genetically engineered mice with either Pten or Tsc1 hepatic specific deletion because these mice exhibit varying insulin sensitivities. Pten is a tumor suppressor gene that inhibits Akt activation reducing insulin signaling. Tsc1 loss results in constitutive mTORC1 activation promoting lipogenesis and limiting AKT signaling through feedback inhibition. Thus, Pten hepatic specific deletion results in enhanced insulin sensitivity while Tsc1 hepatic specific deletion results in decreased insulin sensitivity (all *versus* wild-type animals). Using these models, the authors developed an experimental protocol in

which exposure consisted in daily oral gavage of BDE-47 (1 mg/kg/day) or corn oil for 6 weeks (Monday through Friday) starting with 3 to 6 week-old mice (groups of 6 animals). Metabolic tests were performed and at sacrifice, mice were weighed and adipose tissue and liver recovered. Plasma insulin levels and glycaemia were measured. Interestingly, mice deficient for Pten in the liver, which exhibited greater insulin sensitivity than wild-type mice showed decreased insulin sensitivity when exposed to BDE-47. However, this is definitely a very complex model and more straightforward protocols should be set up to determine if insulin sensitivity is targeted by BDE-47.

One such study was recently published by Zhang *et al* (2017). Indeed, the authors investigated the direct impact of BDE-47 on adult male Sprague-Dawley rats. To that purpose, BDE-47 (0.03 or 20mg/kg/day) or corn oil (vehicle) was administered by gavages for 12 weeks. Rats were either fed a normal diet or a high-fat diet to determine if BDE-47 could aggravate the deleterious metabolic consequences of a high-fat diet (HFD). Reproductive parameters were also studied and discussed in the corresponding section. HFD aggravated the accumulation of adipose tissue (both gonadal and retroperitoneal) in rats treated with BDE-47. No effect was observed in rats fed a standard diet. Fasting glucose and plasma insulin levels were significantly increased but only at the highest dose of BDE-47 and independently of the diet. Importantly, plasma levels of triglyceride and of testosterone levels were significantly decreased for both doses of BDE-47 and in both diet conditions, indicating that these 2 endpoints were the most sensitive and consistent with BDE-47 acting as an endocrine and metabolic disruptor. The study of Karandrea and colleagues (Karandrea *et al*., 2017) is consistent with the finding that BDE-47 could alter insulin secretion. Indeed, the authors examined whether BDE-47 and BDE-85 exposure alters the glucose stimulated insulin secretion of INS-1 832/13 cells, a cancer cell line derived from pancreatic β-cells, and the potential molecular mechanisms involved. During the course of the study, the authors use a concentration of BDE compounds ranging from 1µM to 25 µM. Concentration as low as 1µM is effective however 10 µM shows the maximum increase in insulin secretion. This last concentration is higher than the nM ranges of concentrations reported in human tissues. To overcome the negative impact of this concern, they argue that BDEs bio-accumulate and thus it is possible that cells are or will be in the future exposed to similar concentration. Regarding the mode of action, they propose that the BDE effect involves the thyroid hormone receptor and the PI3K/Akt signaling pathway. They show that the alpha isotype of the thyroid hormone receptor is expressed in the INS-1 832/13 cells, but not the beta form. Subsequently, they show that pretreatment with a thyroid hormone antagonist, decreases the effect of BDEs on insulin secretion. As the action of the antagonist is not characterize and can be larger than the action of BDEs. The origin of the effect on BDEs action can be a confounding effect. Finally, they show that thyroid hormones slightly increase Akt phosphorylation and unfortunately the effect of wortmannin (an inhibitor of the PI3K/Akt signaling pathways) was not addressed while it was for the BDEs. Thus, the mode of action proposed here corresponds to the disruption of the type 3 mechanism of action of thyroid hormone receptor in the new nomenclature suggested to clarify the thyroid hormone mechanism of action. Briefly, thyroid hormone receptors located at the plasma membrane act without DNA binding, but interact with and activate kinase to participate in signaling pathways, like the PI3K pathway. **In conclusion, the experiments carried out and the results obtained in this article show a correlation between thyroid**

hormone receptor and Akt signaling and between BDEs and Akt signaling. However, the direct link between thyroid hormone receptor mode of action and BDE mode of action can only be suggested and will need to be further assessed.

Another recent report investigated if flame retardants including the BDE-47 could interact with the estrogen receptor using both wild-type C57BL animals and Ex3αERKO mice carrying global Esr1 exon 3 deletion (Krumm *et al*., 2017). They studied the hypothalamus (especially, the arcuate nucleus (ARC)) because it regulates food behavior and energy expenditure and collected blood and liver. They also performed metabolic tests including glucose tolerance and insulin sensitivity tests. It is of note that all females were ovariectomized in the study. Adult exposure to BDE-47 elevated fasting glucose in males and glucose clearance in females. No effect was observed in KO mice. Different neuropeptides and nuclear receptors for E2, ghrelin, insulin, leptin and fatty acids (Pparγ) of the ARC nucleus had their expressions altered in mice orally dosed with BDE-47 (1 or 10 mg/kg/day) for 28 days depending on sex and on the genotype (WT or ERα-KO). For example, Esr1 expression was reduced in males but not in females and effects disappeared in KO mice; Insr (insulin receptor) and Pparγ expression were enhanced in both sexes and effects disappeared in KO mice; Lepr (leptin receptor) was increased in males but not in females (and effects almost disappeared in KO mice). In the liver, different metabolic genes had also their expression impacted by exposure to BDE-47 in wild-type mice. Examples included xenobiotic receptor and FXR target genes. For example, there was an increase in the expression of Bsep (Abcb11) in both males and females but only of the wildtype genotype. **In summary, adult exposure to BDE-47 can alter hypothalamic and liver gene expression and impact food intake and glucose homeostasis in a sex-dependent manner. These effects involve at least partly the ERα.**

- **Developmental effects**

The study of Zhu *et al*. (2017) evaluated the effect of a BDE-47 exposure (0; 0.36; 3.6 and 36 mg/kg bw/day by gavage during four days) from gestational day (GD) 13.5 to 16.5 on markers of placental function and pregnancy outcomes in mice.

A decrease of the birth weight of low amplitude (4.3 %) was observed only in mice treated with 36 mg BDE-47/kg. The rate of stillborn, calculated for the overall litters, was significantly lower in the high dose treated group, whereas there was no effect of BDE-47 on average number of live newborn per mouse. The biological significance of these low amplitude effects on pregnancy outcomes is questionable.

This study shows that plasma testosterone and progesterone levels were reduced in mice treated with 36 mg BDE-47/kg. The group treated with 3.6 mg/kg of BDE-47 displayed decreased growth hormone (Gh) peptide expression in the placental tissue extracted at GD 17.5. This effect could be mediated by activation of MAPK signaling pathway. **These results suggest a possible endocrine disruptor activity of BDE47 at high dose.**

However, the levels of BDE in placenta, maternal and fetal plasma were not measured. And to evaluate the relevance of the study in terms of human health, it is necessary to compare the BDE-47 internal exposure inducing effect in mice with human internal concentrations in environmental conditions.

Males reproduction effects

The present report is only focused on the identification of an ED MoA of BDE-induced male reproductive adverse effects.

The study by Khalil *et al*. (2017) evidences delayed negative effects of perinatal exposure to BDE-47 on testicular weight and various spermatogenic parameters. Specifically, abnormal spermatozoa morphology with an increase in head size is correlated with decreases in the expression of protamines and transition proteins. This study brings no information about the potential endocrine disrupting MoA of BDE-47.

In the study by Huang *et al*. (2015), adult were exposed to 0.001, 0.03, 1 or 20 mg/kg/d BDE-47 for 8 weeks and observed a reduction in the seminiferous epithelium width from 0.03 mg/kg/d and an increase in apoptosis in early leptotene spermatocytes from 0.03 mg/kg/d. The proteomic analysis showed changes in 64 proteins involved in apoptosis (31%) proliferation (17%), mitochondrial activity (23%). Regarding the potential endocrine disrupting MoA of BDE-47, since this study was not designed to analyse endocrine disruption, it does not evidence such a MoA. However, it is known that androgens act at various steps during spermatogenesis. One of them is the blood testicular barrier i.e. an effect during early leptotene stage. Thus, this study does not disagree with the hypothesis that the spermatogenic BDE-47 effect could result from an androgens deficit, but it does not demontrate such a MoA.

In the study by Zhang *et al*. (2013), the main objective of this study was to demonstrate that CYP3A1 mediated the adverse effects of BDE47 by conversion in 3-OH-BDE. They observed that the liver and the testis are able to metabolize BDE47 into 3-OH-BDE-47, that BDE47 up-regulates CYP3A1 by BDE-47 and that *in vitro* effect of 3-OH-BDE47 is higher than that of BDE-47. Furthermore, a co-treatment with dexamethasone, which known to increase the expression of CYP3A1, enhanced the effects of BDE-47. These are only associative observations and there is no direct evidence that, *in vivo*, BDE-47 acts on testicular functions after conversion into 3-OH-BDE-47.

On the contrary, interestingly, a dose-dependent deleterious effects of BDE-47 on adult spermatogenesis is well demonstrated (disruption of normal histology of the seminiferous epithelium, decrease daily sperm production, increase apoptosis and in ROS in the seminiferous tubules).

Regarding the potential endocrine disrupting MoA of BDE, this study reports a sharp dose dependent reduction in plasma testosterone level. It is known that a reduction in testosterone can be the consequence of an initial reduction of spermatogenesis or the cause of this latter. In this paper, the reduction of testosterone was observed with the lowest tested dose (0.001 mg/kg) whereas not any spermatogenic endpoint was affected with this dose suggesting a primary effect of BDE-47 (or 3-OH-BDE-47) on the Leydig cell functions.

In conclusion, although it was not the aim of the authors, this study allowed highlighting the possibility of a direct effect of BDE (or its metabolites) on the endocrine activity of the testis.

The study by Zhang *et al* (2017) is a key study for the investigation of a potential ED MoA of BDE-47. Adult rats received an intragastric administration of vehicle, 0.03 or 1 mg/kg/d BDE-47 for 12 weeks and were fed a normal diet. Three other groups received the same intragastric administration of BDE-47 and were fed a high-fat diet.

Numerous interesting observations were done.

1) *In vivo* BDE-47 effects.

Reproductive function

In normal diet animals, qualitative testicular and epididymal histological damages were observed (increase vacuolar spaces in the seminiferous epithelium, increase multinucleated giant cells, decrease number of epididymal sperm). Testicular steroidogenic function was affected by BDE (dose-dependent decrease plasma testosterone level from 0.03 mg/kg/d onwards, decrease StAR expression evaluated by immunoblotting with 20 mg/kg/d, increase DAX-1 expression evaluated by immunoblotting with 0.03 and 20 mg/kg/d)

In control High-Fat Diet (HFD) animals, testosterone level, StAR and 3ß-HSD expressions were reduced and increased DAX-1 expression was increased as compared with control animal fed a normal diet. HFD increased the accumulation of BDE47 in the liver and particularly in the testis. HDF aggravated BDE47-induced histological damages and the amplitude of all the effects on testicular steroidogenic function observed with normal diet and described above.

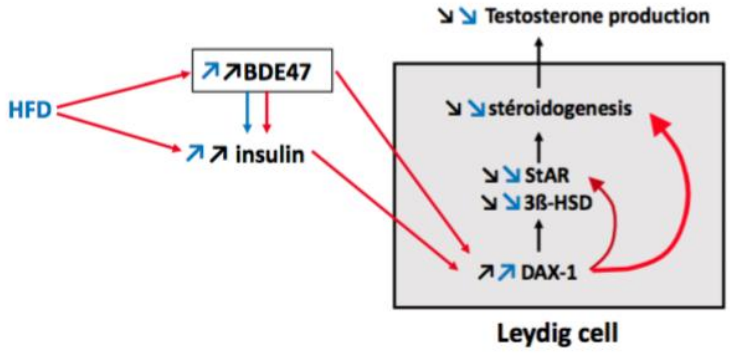
Metabolic effects

BDE47 induced increase retroperitoneal and gonadal adipose tissue, increase plasma TG, no change in plasma cholesterol levels, increase plasma insulin level, increase fast glucose. All these effects are increased in HFD animals as compared with normal diet ones.

In vitro effect of BDE-47 in primary Leydig cells cultures.

BDE-47 induced a dose-dependent reduction in testosterone production from 10 µM onwards. Using immunoblotting, StAR and 3-HSD expression were reduced from 10 µM and 5 µM onwards respectively, whereas DAX-1 expression was increased from 5 µM onwards. Importantly, DAX-1 siRNA totally reversed negative effect of both BDE-47 and insulin on testosterone production.

In conclusion, this study evidenced an ED MoA of BDE-47 and how insulin and High Fat Diet interact with this MoA.



1) **BDE47 directly acts on Leydig cells function** by increasing the expression of DAX-1, an orphan nuclear receptor which induces the repression of several of steroidogenic genes resulting in a reduction of testosterone production.

2) **BDE47 increases insulin secretion** which inhibits testosterone production in the Leydig cells via the same pathway.

3) In **HFD animals, the antiandrogenic BDE effect is enhanced** via 3 processes:
- HFD increases BDE47 concentration in the testis,
- HFD increases insulin secretion,
- BDE further increases insulin secretion.

- **Nervous system**

Fourteen studies addressed the potential effects of BDE-47 exposure on neural functions and behaviors.

Seven studies analyzing the effects of perinatal / postnatal exposure to BDE-47 and two dedicated to adult exposure did not investigate a potential link between neural effects, when observed, and an endocrine disruption mode of action.

Haave *et al*. (2011) have studied the effects high-doses and low-dose perinatal exposure to BDE-47 on behavior, brain gene expression and accumulation of BDE-47 in brain of BALB/c mice. Mice were fed with food containing BDE-47 either during gestation or lactation. No overt symptoms of general toxicity were observed and no significant effects were observed on hepatosomatic index (HIS), body weight of dams and pups, and litter size and reproductive success of dams. At the behavioral level, a low development of righting and hind limb grasp reflexes were observed at the high dose of 402 ± 32 µg/kg bw/d in fish. No effects were observed on all other behavioral parameters investigated. Microarray analysis of cerebral RNA expression revealed only a low modulation of genes despite accumulation of BDE-47 in brain, which mainly concerns genes involved in cell signaling and glutamatergic pathways.

Three studies using the same protocol of oral exposure to BDE-47 (4 weeks before mating until weaning at postnatal day PND 21) assessed behaviors in C57BL/6 mice (Ta *et al*. 2011; Koenig *et al*. 2012: 0.03 -0.1 -1 mg/kg/day) or heterozygous animals for methyl-CpG binding protein 2 mutation (Mecp2308/+; Woods *et al.* 2012: 0.03 mg/kg/day). BDE-47 was detected in pregnant, parturient and lactating dams. Ta *et al*. (2011) reported increased levels of BDE-47 after 4 weeks of exposure in dams (blood, brain, liver, fat) with the highest levels in liver and fat. They continue increasing until parturition, then decreased during weaning. BE-47 was also detected in blood and brain of offspring. Similarly, Koenig *et al*. (2012) showed that BDE-47 tended to accumulate in blood, brain, fat and milk of dams and in the blood, brain and whole body of fetus. Comparison with human brain samples showed comparable levels of BDE-47 levels (Woods *et al*. 2012). At the behavioral level, Ta *et al*. (2011) reported longer duration of ultrasonic vocalizations emitted by F1 offspring at PND 9, 11, 13 and 17 for the group exposed to the highest dose (1 mg/kg/d) and reduced locomotor activity of F1 females at PND60 in the open-field test for 0.1- and 1- groups. For the other tested behaviors, no data were shown while no distinction of sex was made in the water maze test. Koenig *et al.* (2012) found no effect on the behavioral parameters investigated, except an increase in escape latency and distance traveled to escape in Barnes Maze, which reveals an impairment of spatial learning and memory. In the work of Woods *et al*. (2012), exposure to BDE-47 exposure lowered pre-weaning weight of female offspring but did not affect sensory development and juvenile tests of motor behaviors. Males showed an Mecp2 genotype effect on sociability, motor activity and barrier social interaction tests, while females were more sensitive to BDE-47 exposure and showed interactions of Mecp2 genotype with BDE-47 in social and learning tests. BDE-47-induced an effect on social novelty not observed in Mecp2308/+ mutants, and associated with increased Dnmt3a levels. In another study, Byun *et al*. (2015) analyzed the effects of perinatal exposure to BDE-47 on DNA methylation in the forebrain of the rat. The authors reported that the doses assessed are far below the doses encountered in human populations. From these observations, the authors state that we cannot derive a significant effect of BDE-47 on DNA methylation in the brain. Gee *et al*. (2011) showed that exposure to a single oral dose of BDE-47 (10 mg/kg/d) at PND10 induced long-term increase in the levels of dopamine (quantified by HPLC) in cortical tissues of adult males. Finally, Rasinger *et al*. (2014) have studied the effects of some persistent organic pollutants (POP), CB-153, BDE-47, HBCD and TCDD, on the neural gene and protein expression in juvenile female mice. Mice orally were exposed to BDE-47 for 28 days, from PND21, at 450 µg/kg bw/d. No effect of BDE-47 was observed on feed intake and body weight. BDE-47 can cross the blood-brain barrier but does not bioaccumulate (BCF = 0.2). Transcriptomic analysis revealed that BDE-47 impairs

expression of genes involved in calcium homeostasis regulation through AHR whereas proteomics revealed that BDE-47 impairs expression of genes involved in excitotoxicity.

Concerning adult exposure, two articles analyzed the effects of oral exposure on memory in male rats and mice (Yan et al. 2012: 0.1, 0.5 et 1 mg/kg/day for 4 weeks; Zhuang et al. 2017: 20 mg/kg/day for 8 weeks). Yan et al. (2012) reported learning and memory deficits assessed by the Morris water maze in male rats of the three exposed groups. The data presented for NMDA receptors by IHC and RT-PCR are not convincing. Zhuang et al. (2017) showed that exposure of male mice to BDE-47 for 8 weeks induced a cognitive deficit in the Morris water maze, which was associated with an up-regulation of TAR-DNA binding protein-43 (TDP-43). Knockdown of TDP-43 in the hippocampus attenuated apoptosis, rescued synaptic protein levels (synapsin I, PSD-95), increased expression of Parkin (E3 ubiquitin ligase) and restored the cognitive impairment. TDP-43 down-regulation was also achieved by hippocampal knockdown of the NLRP3 inflammasome. **Together, these data show that neurotoxicity and cognitive deficit induced by BDE-47 may involve TDP-43 up-regulation mediated by NLRP3 inflammasome activation, via Parkin down-regulation.**

Five studies investigated the effects of perinatal/postnatal exposure to BDE-47 on endocrine systems, in particular the thyroid axis. He *et al*. (2011) assessed the effects of exposure to BDE-47 at PND10 on organ to body weight ratios, learning and memory at two months. The authors reported increased ovaries to body weight ratio and reduced uterus and thyroid to body weight ratios. They also described decreased serum level of T4 thyroid hormone without any significant changes in the levels of T3 and TSH in the group treated with a medium dose of BDE-47. This decreased T4 level in the serum was not observed at lower or higher dose and the effect seemed weak. In a second set of experiments, the authors assessed the effects of the treatment on spatial learning and memory. **This study does not show any clue on an endocrine disruptor mode of action of BDE-47. There are some concerns about the statistics and the methods, which impair the overall value of the paper.**

Exposure to BDE-47 at PND10 (10 mg/kg) was also associated to increased expression of apoptotic and oxidative stress biomarkers both in vitro (cerebellar granular neurons and astrocytes coculture) and in vivo in male mice (high dose 10 mg/kg) in the cerebellum (Costa *et al.* 2015). In vivo, no modification of circulating free and total thyroid hormone concentrations could be evidenced. The design of this study does not allow a proper evaluation of the thyroid function at this particular physiological stage (very low number of animals). **Thus, this study remains inconclusive regarding a potential endocrine (thyroid) mode of action on BDE-47-related neurotoxicity.**

In the study of Suvorov *et al.* (2011), exposure to BDE-47 did not show THRbeta 1 binding capacities in vitro and the exposure of rats to BDE-47 (0.2 mg/kg/d) from GD15 to PND20 was not associated to modification of the expression of TH-putative targets genes in the cortex at PND41. The only conclusive result is that BDE-47 itself does not bind the THRbeta receptor. No conclusion whether positive or negative can be drawn from this study regarding a thyroid mode of action of BDE-47 on neurotoxicity. The same group (Suvorov and Takser, 2011) assessed the effects of perinatal exposure to BDE-47 on gene expression in the total rat brain or the frontal lobe at post-natal day 10 and 41, respectively. The gene enrichment analyses did not bring any information on the endocrine disrupting properties of BDE-47. Nevertheless, the authors reported an overexpression of three genes involved in insulin signaling (IGF2, IGFBP2, Igfbpl1) as well as an overexpression of pro-opiomelanocortin a precursor of many biologically active peptide. This result suggests an effect of BDE-47 exposure on endocrine signaling but without any phenotypic analysis it is impossible to conclude on the biological significance of

such differences in gene expression levels. It is hard to derive a putative endocrine disruptor mode of action of BDE-47 from the present paper. Nevertheless, it suggests that more experiments are needed to assess the effects of an exposure to BDE-47 on hypothalamic pituitary adrenal axis and insulin signaling.

The last study (Wang *et al*. 2011) aimed at determining the effect of exposure to BDE-47, PFOS, or a combination of both from GD1 to PND14 on blood TH concentrations during neo-natal development in Dams and pups and on the expression of T3-regulated genes in the cortex and hippocampus. As for BDE-47 alone exposure, pregnant/ lactating Wistar rats received a powered diet containing the BDE-47 at two different doses (3.2 and 32 mg/kg/d) or vehicle from GD1 to PND14. BDE-47 concentrations in blood in dams, blood and different cerebral structures in pups were evaluated jointly to blood TH concentrations at PND1, 7 and 14 along with the expression of TH-dependent genes and proteins in the cortex and hippocampus. Global analysis revealed a negative correlation between serum concentrations of BDE-47 and TT3, TT4 in dams but not in pups, no correlation between BDE-47 brain exposure and gene expression in neonates could be observed. TH blood concentrations appeared to be altered in both the mothers and the offspring although with a different pattern. TT4 was decreased by approximately 30% in dams at PND1-7 and 14 for both doses and TT3 was lower at high dose as compared to the low dose. In pups, TT4 was decreased at both doses starting only at PND7, and TT3 was decreased at PND14 for the high dose only. Region and/or exposure and time- dependent effects of PBDE on TH-regulated genes could be evidenced at the level of mRNA as well as protein expressions. The authors concluded that there is a complex response of TH-target genes and proteins to PBDE and that this response seems little related to TH homeostasis. Although no functional investigation on behavior and/or neurocognitive markers has been performed in this study, it appears to be an interesting one showing at the same time modifications of materno-fetal blood TH jointly to neonate brain TH-target genes expression. In addition, the studied period is of critical importance since it corresponds to the final maturation stage of thyroid function and is a period of tremendous modeling of the central nervous system (CNS) in rodents. **At this stage, the hypothesis that the modifications observed in cerebral structure are related to disruption of thyroid homeostasis is as likely as unlikely. Overall, although those results cannot be considered as a formal proof of the action of BDE-47 on the development of the central nervous system via thyroid-regulated pathways, they are not in discrepancy with the hypothesis of a thyroid -mediated effect of BDE-47 on neural development.**

In conclusion, none of the analyzed studies provides direct evidence linking neurobehavioral/neural alterations to TH-mediated disruption at the level of neural development in rodents. However, the last study targeting a critical period in terms of both thyroid maturation and neural neonatal development in rodents provides few elements of proof that could be consistent with potential thyroid-related mode of action mediating the effects of BDE-47 on neural development in rats. One has to bear in mind that although the evaluated genes are considered as TH-regulated in the central nervous system, their expression can be modulated by many other pathways. At this stage, it is neither possible to formally conclude that BDE-47 induced alterations on the CNS development proceeds more or less from thyroid disruption, nor it is possible to reject this hypothesis.

Environmental effects

Environmental hazards properties presented are based on available data from the scientific public literature. Indeed, as this substance is not anymore produced and imported inside the UE, there is no registred data nor CSR.

- **E-fate and Ecotoxicity of BDE-47**

BDE-47 is, in its pure form, a viscous liquid with a molar mass of 485.8 g/mol and a melting point comprised between 79°C to 82°C. According to data, BDE-47 exhibits a water solubility of 11 to 70 µg/L (ANSES, 2017), and has a low vapour pressure of $1.8x10^{-5}$ Pa to $2.9x10^{-4}$ Pa at 25°C. The BDE-47 log Kow is comprised between 5.87 to 6.81 and exhibit an estimated log Koc comprised between 4.12 and 4.73 ((EPIsuite v4.1), MCI method and Kow method) and a Koc value of 13230 (US EPA, 2011). BDE-47 is not expected to undergo hydrolysis.

Concerning biodegradation, screening tests and OECD guidelines data are not available for BDE-47 in its pure form. An OECD 301B ready biodegradability assay with pentaBDE give a no degradability result (Schaefer and Haberlein, 1997). According to the modelisation program EPIsuite, BDE-47 is not biodegradable (EPIsuite v4.1). The estimated half-life of BDE-47 is estimated of being 180 days in water, 360 days in soil, 1600 days in sediment according to PBT profiler. An other estimation gave an estimated half-life for BDE-47 of 1.1 year in water to up to 3.4 year and even longer time in sediment (Gouin and Harner, 2003). In Fish, the estimated half-life of BDE-47 is estimated to be 11 days in Japanese medaka (*Oryzias latipes*), 30 days in carp (*Cyprinus carpio*) and from 39 to 346 days in lake trout (*Salvelinus namaycush*) (Muirhead et al., 2006; Stapleton et al., 2004; Tomy et al., 2004). In Leopard frog (*Lithobates pipiens*), the half-life of BDE-47 is estimated to be 5.29 days in tadpole stage and 17.3 days in juvenile stage (Cary et al., 2013).

According to these data, the BDE-47 could be classified as persistent and very persistent.

The BDE-47 log Kow is comprised between 5.87 to 6.81, indicating that it could bioaccumulate in organisms. Regarding bioaccumulation, a BCF value of 4134 L/kg was calculated (EPIsuite v4.1) and a value as high as 14 000 was estimated according to the PBTprofiler. In literature, different BCF values were measured. Thus, a BCF of 10 900 L/kg in mussels (Vidal-Liñán et al., 2015), a BCF of 2430 L/kg at 120 hpf in zebrafish (Liu et al., 2015) and a BCF of 24 000 L/kg in turbot (Mahdbi, 2012) were measured. It was also highlighted that the preferential accumulation of BDE-47 would be in the brain for fish and frog (Zhao et al., 2016).

In literature, it was highlited that more than half of fish analyzed in freshwater sites in Virginia US had concentrations greater than 1 µg/g lipid weight (Hale et al., 2001), and concentrations as high as 864 ng/g in artic whales (de Boer et al., 1998) and even 13 µg/g in bat, *Myotis lucifugus* (Kannan *et al*., 2010) where measured. The BDE-47 has a very wide repartition and was even measured in polar bear (Ursus maritimus) in Greenland and Svalbard (Gustavson *et al*, 2015; Villanger *et al*, 2011).
In France, the measured concentration of BDE-47 in differents fishes species in the Seine river were found to be hundred times higher than the Environmental Quality Standards (EQS) applicable to surface water (Abarnou, 2008) and was even ten time higher in fishes of the Saint-Laurent in Canada (Law *et al*., 2003).

According to these data, the BDE-47 could be classified as bioaccumulable and very bioaccumulable.

For ecotoxicity assessment, long term toxicity data are lacking in literature. For the short term toxicity test, the ecotoxicity values were comprised between 7.9 µg/L LC_{50} in a *Daphnia magna* 48 h toxicity test to 20.30 mg/L in a fish embryos*, Danio rerio,* 96h EC_{50} toxicity test based on hatching success (Davies and Zou, 2012; Chan and Chan, 2012). These data allow to classify the BDE-47 as Aquatic acute 1 toxic H400.

Regarding long-term data an alert exist on the toxicity of BDE-47 with a fish ChV[2] of 0.003 mg/L according to PBT profiler. This chronic toxicity value could be achievable especially when looking at the solubility value comprised between 11 to 70 µg/L (Anses, 2017). A subchronic toxicity test result is available with the copepod *Arcatia tonsa*, giving a 5 days EC_{50} of 13 µg/L in larval development test for BDE-47 (Breitholtz et al., 2001).

The lack of chronic toxicity data do not allow to propose an harmonized classification. Nevertheless, it is possible to use the subchronic toxicity test to propose a classification for substance with lacking of appropriate chronic toxicity data. BDE-47, as being of low solubility and presenting a BCF value > 500, can be classified as aquatic chronic 1 H410.

In conclusion, BDE-47 can be classified as aquatic acute 1 H400 and aquatic chronic 1 H410.

- **Endocrine disruptor characteristic of BDE-47 for the environment**

BDE-47 is listed in the TEDX list as potential endocrine disruptor based on *in vitro* profiling

Unexhaustive literature review on the potential of the BDE-47 as endocrine disruptor is reported in Annex 1.

As indicated by this unexhaustive review of scientific literature, there is some evidence that BDE-47 could interfere with endocrine systeme *in vitro* and *in vivo*. The screening of the BDE-47 disrupting endocrine potential was assess according to the conceptual framework of OECD guidance n°150 for evaluating chemicals for endocrine disruption (OECD, 2012). According to this guidance document, the evidences available reach the level 3 of the conceptual framework. Assays of this level provide *in vivo* screening for possible endocrine disruption activity. They are designed to provide a qualitative answer about the ability to interact with estrogen, androgen and thyroid hormone receptor mediated modalities, or interfere with steroidogenesis.

The amphibian metamorphosis assay OECD 231 realized by Yost and collaborators (Yost et al., 2016) indicate that BDE-47 had an impact on growth and development (5000µg/g food), decrease thyroid-hormone associated gene expression in the brain (*dio2* (50 to 5000 µg/g), *tra*, *trβ*, *bteb*, *mct8*, *oapt1c1*, *tshβ* (500, 5000

[2] Estimated chronic value according to ECOSAR/EPI (EPIWIN/EPISUITE) Estimations Programs Interface for Windows, Version 1.11.

µg/g)), decreased snout to vent length, weight, hind limb length and stage development. It was concluded that BDE-47 disrupts thyroid hormone signaling at the molecular and whole-organism levels. The other data available are based on tests with fishes and invertebrates. In fishes, tests with acute to chronic exposition times were available, ranging from few hours post fertilization to one generation (180 days). BDE-47 led to a female biased sex ratio and a decrease in male condition factor, impact the spermatogenesis and tubercules quantity (Thornton et al., 2016). An negative effect was also recorded on egg production, clutch size, spawning and hatching (Zhao et al., 2016; Muirhead et al., 2006; Lema et al., 2007; Mhadhbi et al., 2012). The fecundity, the the total body weight, the post-hatching size and the survival were also decreased in fishes after exposition to BDE-47 (Zhao et al., 2016; Thornton et al., 2016; Muirhead et al., 2006; Kang et al., 2017; Lema et al., 2007; Mhadhbi et al., 2012; Liu et al., 2015; Noyes et al., 2015). Proteins were up and down regulated in ovaries and testis, possibly impacting spermatogenesis, oogenesis, and develpment of fishes (Fong et al., 2014). Regarding spermatogenesis, BDE-47 fewer mature spermatozoa and more primary spermatocytes were observed when fathead minnows were dietary exposed to BDE-47 (high dose 12.30 µg/pair/day) (Lema et al., 2008). A large amount of genes involved in hormones synthesis were also impacted by BDE-47 exposure with concentration as low as 0.1 µg/L (Kang et al., 2017). In those fish species, thyroid hormones were impacted, with variation depending on species (Zhao et al., 2016; Lema et al., 2008; Kang et al., 2017).

BDE-47 exposure led to increase malformations for several body parts in fishes and differents invertebrates (spinal curvature, bone, eye, gill injuries (lamellar fusion, blood congestion, hyperplasia and hypertrophy of mucous epithelium cells and goblet cells), intestine injuries (hyperplasia and hypertrophy of mucous epithelium cells), hepatic lesions (circulatory disturbances, irregular morphology of hepatocytes, cellular and nuclear hypertrophy, nuclear vacuolation and pyknosis), pericardial edema, tachycardia, arrhythmias, swim bladder defect) (Barsiene et al., 2006; Jiang et al., 2017; Zhao et al., 2016; Kang et al., 2017; Zhao et al., 2013; Lema et al., 2007; Mhadhbi et al., 2012; Usenko et al., 2011; Barja-Fernández et al., 2013; Liu et al., 2015; Song et al., 2016; Xu et al., 2015)

For invertebrates, BDE-47 act as an ecdysteroid antagonist, by inhibiting gene expression and hormone synthesis enzymes in copepod *Tigriopus japonicas* (50 µg/L) (Hwang et al., 2016). It also impact the ratio of ovigerous female/non-ovigerous female and mictic/amictic females (6 mg/L) of *Brachionus plicatilis,* decreased fecundity and reproduction, damage ovary ultrastructure, led to developmental retardation and in an other species, decreased heterozygosity (Wang et al., 2015; Han et al., 2015; Garderström et al., 2006; Sha et al., 2015). The effects of BDE-47 were also measured on metamorphosis, especially against the molting process in cladocera and phyllopoda (*Tigriopus japonicas, Daphnia magna, Gammarus pulex*) with concentration as low as 0.1 µg/L (Gismondi and Thomé, 2014; Hwang et al., 2016; Davies and Zou, 2012).

- **Neurotoxicity, heart effect and metabolism toxicity**

Table 3: Effects of BDE-47 on heart, metabolism and nervous system

Methodology	Results	Reference
Zebrafish embryos 6-96 hpf (*Danio rerio*)	↑ spontaneous movement (20 µM) ↓ Touch response (concentration-dependent 5-20 µM) and free swimming	Chen et al., 2012

waterborne exposure	(concentration-dependent 20 µM), behavior in response to light (5-20 µM) Inhibition of axonal growth of primary and secondary motor neurons (1.25 to 20 µM), reduction of the number, size and distribution of nAChR (20 µM),	
Zebrafish larvaes (*Danio rerio*) 6 dpf	Alteration of retinal metabolism (eye morphogenesis, visual perception) , disruption of bone development consistent with body curvature (500 µg/L)	Xu et al., 2015
Zebrafish larvaes (*Danio rerio*) 6 dpf	Locomotion hypoactivity at 5 dpf in response to dark/light cycle (continuous and discontinuous exposure at 500 µg/L)	Zhao et al., 2014
Mussels (*Mytillus galloprovinciallus*) 30 d exposure	↓ In AChE and GST activity (2 to 15 µg/L)	Vidal-Liñán et al., 2015
3 month Marine medaka (*Oryzias melastigma*) Liver transcription profile	Male have stronger modification on liver genes transcription profile than females at low (290 ng/day) and high dose (581 ng/day) at 5 and 21 days. In male only, exposure activate phosphoionositide-3-kinase, mitogen activated protein kinase (cell growth, proliferation and survival)	Yu et al., 2013
Marine Copepod (*Paracyclopina nana*)	↑ in ROS, GST and GPx (1 µg/L), activation of extra-cellular signal-regulated kinase (ERK) and c-jun-N-terminal kinase (JNK) in MAPK pathway, promoting ligation to lipogenesis EcR, SREBP, ChREBP promoters. BDE-47 exposure promotes the conversion of fatty acids SFAs in PUFAs linked to the delay in early post-embryonic development (10 µg/L)	Lee et al., 2016
Marine Copepod (*Paracyclopina nana*)	↑ in *De novo* lipogenesis transcription genes (2.5 µg/L for 24h) and lipid droplet area ↑ in palmitic acid, fatty acid synthesis related genes (day 1 and 4), fatty acid content ↓ in docosahexanoic acid and arachidonic acid (day 1 and 4)	Lee et al., 2016
Diptere (*Chironomus sancticaroli*)	↓ AChE activity from 18 to 72 % (0.5 to 2.0 µg/L) ↓ EST-*α* of 21 to 52 % (0.5 to 2.0 µg/L) and EST-*β* of 20 to 35 % (0.5 to 3.0 µg/L) ↑ GST of 346 % (1.0 µg/L)	Palacio-Cortés et al., 2017
Frog (*Xenopus tropicalis*) 14 days exposure, 1 mg/g food	↓ hind lamb length in tadpoles, SV length body weight and body length	Carlsson et al., 2007

Exposure to BDE-47 led to decrease the AChE activity (Palacio-Cortés *et al*., 2017; Vidal-Liñán *et al*., 2015), inhibit the axonal growth of primary and secondary motor

neurons and to the reduction of the number, size and distribution of nAChR in zebrafish (Chen *et al*., 2012). Impact on locomotion and dark/light adaptation was also recorded (Chen *et al*., 2012; Zhao *et al*., 2014; Muirhead *et al*., 2006; Lema *et al*., 2007; Usenko *et al*., 2011). Moreover, the BDE-47 impact the hepatic metabolism seen through the impairement of the fatty acids metabolism (Lee *et al*., 2016 a, b) and the liver (Barja-Fernández *et al*., 2013; Yu *et al.,* 2013).

General conclusion

Regarding the effects on the human health, *in vivo* data on reprotoxicity in rat indicates that there is some possibility that BDE-47 directly acts on Leydig cells function by increasing the expression of DAX-1, an orphan nuclear receptor inducing the repression of several of steroidogenic enzymes. Moreover, BDE-47 increases insulin secretion which inhibits testosterone production via the same pathway.

Adult exposure to BDE-47 in rat indicates that BDE-47 can alter hypothalamic and liver gene expression and impact food intake and glucose homeostasis in a sex-dependent manner. These effects involve at least partly the ERα.

In vivo data on metabolism shows that BDE-47-induced alterations on metabolism are linked to an endocrine disrupting mode of action. However, the direct link between thyroid hormone receptor mode of action and BDE mode of action can only be suggested and will need to be further assessed.

In vivo data indicates that at this stage, it is neither possible to formally conclude that BDE-47 induced alterations on the CNS development proceeds more or less from thyroid disruption, nor it is possible to reject this hypothesis. Moreover, it is important to note that an adverse outcome pathway n°152 entitled "Interference with thyroid serum binding protein transthyretin and subsequent adverse human neurodevelopmental toxicity" is described for PBDE with high evidence.

In summary, the data available indicate a trend for effects through an ED mode of action on:

- Male reproduction in rats,

- Metabolism in rats and mice,

Regarding the effects on the environment, data indicate that there is a concern that BDE-47 can be bioaccumulable / very bioaccumulable and persistent / very persistent according to modelisation and environmental measurements.

Nevertheless, BDE-47 is not identified as a PBT because available experimental data for chronic aquatic toxicity are lacking (for the T criteria and properly evaluating the chronic toxicity). Experimental data allow to classify the BDE-47 as Aquatic acute tox cat. 1 H400 and Aquatic chronic 1 H410 when based on assessment with lacking information on chronic toxicity.

There is some possibility that BDE-47 engender some neurotoxicity. Indeed, recent studies performed in different fish species indicate a potent toxicity for the brain reflected by modification of the locomotion and dark/light adaptation *in vivo*.

In vivo data on reprotoxicity in fishes indicates an impact of BDE-47 on spawning events, egg production and their hatchability. Developmental impact of BDE-47 was recorded, leading to cardiac, bone and eye malformations, edemas and embryos malformations, also reflected by modifications on the expression of some of the related genes and proteins on fishes.

There is some informations on a possible effects of BDE-47 on thyroid hormones also reflected by modifications on the expression of some of the related genes and proteins on fishes.

In summary, the data available support:

- toxicity to environment that enables classifying BDE-47 as aquatic acute and chronic toxic category 1; P/vP and B/vB
- effects on reproduction and development in fishes;
- possible toxicity on circulating thyroid hormones;
- metabolic disturbance.

Environmental data show endocrine disruptor potential of BDE-47. There is evidence that BDE-47 can interfere with endocrine system, impaired reproduction and could be considered as being an ED for environment.

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

3.1.2 Self classification

- In the registration: Not classified

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

No proposal identified.

3.1.4 CLP Notification Status

Table 4: CLP Notifications

	CLP Notifications[3]
Number of aggregated notifications	0
Total number of notifiers	0

[3] C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 16 February 2018)

3.2 Additional hazard information

No registration data.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[4]

The substance is not registered.

4.1 Tonnage and registration status

Table 5: Tonnage and registration status

From ECHA dissemination site	
Registrations	☐ Full registration(s) (Art. 10) ☐ Intermediate registration(s) (Art. 17 and/or 18)
Total tonnage band for substance (excluding volume registered under Art 17 or Art 18, or directly exported)	Choose the appropriate option from this dropdown menu.

4.2 Overview of uses

The substance is not registered.

BDE-47 takes part of the polybrominated diphenyl ethers group (PBDEs). PBDEs have been used in the past as flame retardant (FR) - term given to any compound or mixture added to a consumer product or building material to reduce the flammability and thus improve product safety.

4.3 Additional information

The substance is not registered.

[4] *Please provide here the date when the dissemination site was accessed.*

5 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

5.1 Need for (further) risk management

The substance has vPvB properties but is not registered.

Table 6: SVHC Roadmap 2020 criteria

	Yes	No
a) Art 57 criteria fulfilled?	x	
b) Registrations in accordance with Article 10?		x
c) Registrations include uses within scope of authorisation?		x
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?		x

5.2 Identification and assessment of risk management options

Article 58(7) of REACH states that "substances for which all uses have been prohibited under Title VIII or by other Union legislation shall not be included in Annex XIV". Although the POP Convention and the POP Regulation do not necessarily prohibit "all uses" (since there can be exemptions for certain specified uses), it is clear that REACH should neither depart from nor duplicate the rules fixed by the POP Regulation. Therefore, if a substance that is already regulated under the POP Regulation (EC) is included in Annex XIV to REACH, authorisations may only be granted under REACH in relation to uses exempted under the POP Regulation.

According to the European Commission[5], in principle, any risks related to the exempted uses of that substance should be addressed though adaptation to technical progress under the POP Regulation and, therefore, the REACH authorisation requirement should only be superimposed on the provisions of the POP Regulation if there are good reasons for doing so. For BDE-47, exempted uses relate to recycled materials (concentration up to 0.1%) and uses in electrical and electronic equipment that are managed by Directive 2011/65/EU.

Regarding the Environment, the water framework directive 2000/60/EC is an EU directive which commits EU Member States to achieve good qualitative and quantitative status of all water bodies. In this framework the EQS (Environmental quality standards) in water for the PBDE is extremely low, with a maximum of 0.5 ng/L for the sum of the 6 most identified PBDE (BDE 28, 47, 99, 100, 153 et 154). These EQS implies that management options has to be taken up to avoid the occurrence of these PBDE in water.

[5] Common understanding paper. Ref. Ares(2014)2334658 - 14/07/2014.

5.3 Conclusions on the most appropriate (combination of) risk management options

As the substance is not registered and already regulated in the POP Convention, no further action is recommended in the framework of REACH Regulation.

Some uses are however exempted of the POP regulation, such as recycled materials (concentration up to 0.1%) and uses of BDE-47 in electrical and electronic equipment (that are managed by Directive 2011/65/EU).

In order to have information on the exposure levels of European population, BDE-47 was included in the European program for biomonitoring HBM4U as part of the 1st priority list[6]. One objective for that chemical group is a meta-analysis of existing HBM data to identify time trends in exposure and possible regional differences, and also to inform on whether current regulatory structure can effectively lead to decreases in human exposure. Depending on the outome of this program, further action may be considered (including exempted uses of the POP regulation).

As BDE-47 has been identified in some media, eMSCA recommends also the derivation of human reference values (both internal and external) in order to assess health risk of exposed population.

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[6] Prioritized substance group: Flame retardants. Source: https://www.hbm4eu.eu/the-substances/flame-retardants/.

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Annex 1: Endocrine disruptor potential of BDE-47 for the environment

Methodology	Results	Reference
Frog (*Xenopus laevis*) OECD 231 Level 3 Guidance OECD 150	BDE-47 hindered growth and development (5000 µg/g), ↓ thyroid-hormone associated gene expression in the brain *dio2* (50, 500, 5000 µg/g), *tra, trβ, bteb, mct8, oapt1c1, tshβ* (500, 5000 µg/g) ↓ SVL(5000 at 14-21d), wet weight (50 at 21d and 5000 at 7-14-21d), stage (5000 at 7-14-21d) and HLL (5000 at 14-21d) disrupts thyroid hormone signaling at the molecular and whole-organism levels	Yost et al., 2016
Frog (*Xenopus laevis*) for 14 days (stage 58 to 66)	Metamorphosis retardation, Inhibition of tail resorption (a single 100 µg injection)	Balch et al., 2006
Zebrafish (*Danio rerio*) 180 days of exposure for F0 (blastula to adult), F1 follow up	**F0** ↓ survival and ↑ malformation (4 dpf), ↓ whole-body T4 and ↑ T3 (10 µg/L for both sexe) Up-regulation of *tg, pa8, ugt1, tshβ, dio2* and down-regulation of *ttr* ↑ UDP-GT and PEROD activity (5-10 µg/L), EROD and MEROD (10 µg/L) **F1** ↓ T4 and ↑ T3, Up-regulation of *crh*, *tg, pa8, ugt1, tshβ, dio2* (with and without continuous exposure) ↑ malformations and up-regulation *dio1*, ↓ hatching and down-regulation of *ttr* (continuous exposure)	Zhao et al., 2016
Fathead minnows (*Pimephales promelas*) Fertilization to 34 dpf exposure then 184 dpf raised diet free. 21 day breeding study.	↓ In clutch size with breeding pair, fecundity in thrid week (57.68 and 392.59 µg/g Artemia) Female biased sex-ratios, higher proportion of females (low and high dose) Males have fewer tubercules (4.02 µg/g)	Thornton et al., 2016
Fathead Minnows (*Pimephales promelas*) 25 days food exposure, 28 µg/ breeding pair	Egg laying stop after 10 days, ↓ in fecundity ↓ male condition factor, weight loss, erratic swimming behavior, > 50% ↓ of mature sperm (stage 5)	Muirhead et al., 2006

Breeding pairs of adult fathead minnows (*Pimephales promelas*) dietary exposed for 21 days	↓ T4 with ↑ mRNA TSH*β* in the pituitary, ↑ TH*α* (female brain) and ↓ TH*β* (brain of both sex) ↓ BTEB transcript of 53% in male brain Fewer mature spermatozoa and more primary spermatocytes (high dose 12.30 µg/pair/day)	Lema et al., 2008
Marine medaka (*Oryzias melastigma*) Dietary exposed to 0,65 and 1,30 µg/g/day for 21 d iTRAQ analysys	133 (testis) and 144 (ovary) uniques proteins identified with concentration dependant and sex dependant expression, Testis: 42 proteins differentially expressed, with down-regulation of histone variants and parvalbumin (spermiogenesis, testis development) Ovary: 38 proteins differentially expressed, with up-regulation of vitellogenins and apolipoprotein-A-I (oogenesis) indicating that BDE-47 is an estrogen mimicking compound,	Fong et al., 2014
Killifish larvae (*Kryptolebias marmoratus*)	Dorsal malformation, spinal curvature and hemorrhaging, ↓ In body length, weight, ↑ in apoptotic cells, especially in the tail region (1000 µg/L). ↓ In plasma T3 concentration-dependent (10 µg/L) ↑ in plasma T4 concentration-dependent (10 µg/L) ↑ in TRH (100), TRHR (10), TSHβ (0,1), TRα (1), TRβ (0.1) (HPT axis), NIS (1), TG (0.1), TPO (10) (thyroid hormone synthesis), DIO1 (1000), DIO2, DIO3, UGT1 (10) (hormone metabolism) genes expression	Kang et al., 2017
Zebrafish (*Danio rerio*) 20 d exposure in food	Sex difference in accumulation Ratio between eggs/liver of 1.7 suggesting transfer from female to eggs no metabolisation into Me-O-PBDE and OH-PBDE in the liver	Wen et al., 2015
Zebrafish (*Danio rerio*) 6 to 120 hpf	Death (64nM at 24 hpf), Death (6.4nM at 120 hpf), Effect on axis development (64 µM at 120 hpf), hypoactivity in dark starting phase and under dark/light acclimation (6.4µM)	Noyes et al., 2015
Fathead minnows (*Pimephales promelas*)	Female ↓ In hepatic *era* (2.1 fold) and ovarian *arom* (2.9 fold) Male ↑ in brain *dio2* (1.5 fold)	Thornton et al., 2016

	↓ In hepatic *ttr* (1.4 fold), 11-KT when suppressing the outlier	
Zebrafish larvae (*Danio rerio*)	↑ malformations, CHR (1.76 and 2.48 fold), NIS, Nkx2.1 (5 and 10µg/L), TSH*β,* TG protein (1; 5; 10 µg/L),	Zhao et al., 2013
Zebrafish embryos (*Danio rerio*) Waterborne exposure	Delayed hatching, reduced post-hatching size, abnormal dorsal curvature of the trunk (100 % of larvae at 400 µg/L) and tail, failure of swim bladder to inflate, discoloration of liver, abnormal swimming behavior, lethargic movement (400-5000 µg/L) Tachycardia evolving into arrhythmias with increasing concentrations ↓ cerebrospinal fluids movement	Lema et al., 2007
Zebrafish embryos (*Danio rerio*) Waterborne exposure	↑ NIS, TPO, TR*α,* TTR ↓ TG, TR*β,* TSH*β*,	Chan and Chan, 2012
Turbot *(Psetta maxima)* ELS, 6 days, filtered samples	↑ mortality after 48h ↓ hatching success, ↑ malformations, no rupture of the egg membrane, yolk sac alterations, pericardial edema and skeletal malformations, spinal malformations, tail bud malformation at 96 hpf (from 19.23 to 130.2 µg/L)	Mhadhbi et al., 2012
Zebrafish embryos 168 hpf (*Danio rerio*)	↑ Spontaneous movement, malformations, curved body dose-dependent, pericardial edema (2.25 mg/l and up at 120 hpf) ↓ swimming rate after 168 hpf	Usenko et al., 2011
Zebrafish (*Danio rerio*) liver cell line	24h, ↓ deiodinase 1 of 2.7 fold (25% LC50), DioIII and TR*β* of 2.0 fold and UGT1ab of 3.7 fold (50% LC50) 96h, ↑ TTR of 3.2 fold (50% LC50), Sult1-st5 of 1.8 fold (50% LC50),	Yang and Chan, 2015
Turbot (*Psetta maxima*) 0,03 and 0,3 µg/L for 15 d	Gill injuries (lamellar fusion, blood congestion, hyperplasia and hypertrophy of mucous epithelium cells and goblet cells) Intestine injuries (hyperplasia and hypertrophy of mucous epithelium cells) Hepatic lesions (circulatory disturbances, irregular morphology of hepatocytes, cellular and nuclear hypertrophy, nuclear vacuolation and pyknosis)	Barja-Fernández et al., 2013

Zebrafish embryos 120 hpf (*Danio rerio*)	NOEC of spinal curvature and pericardiac edema of 0.5 µM 27.6% of embryos impacted with 2.5 µM and reduction of body length. No transformation into 6-OH-BDE or 6-MeO-BDE ↓ *gr* expression (0.5 µM) ↓ gene expression on AhR and ER pathways, *cyp1a1*, *cyp19a*, *cyp3a65*, *ccnd1* ↑ *ahr1b*, *er2a*, *er2b* (2.5µM)	Liu et al., 2015
Brachionus plicatilis	Reproduction inhibition in a time-dependent manner (8 to 800 µg/L) Prolongation of generation time (800µg/L) ↓ Life expectancy (80 µg/L), net reproduction rate and intrinsic increased rate (80 and 800 µg/L) Damages to ovary ultrastructure (8 to 800 µg/L) ↑ ROS levels (8 to 800 µg/L), GR activity (80 µg/L), induction of GST activity (8 µg/L) and inhibition (800 µg/L) ↓ GPx activity (8 µg/L) and GSH content (8 µg/L)	Wang et al., 2015
Brachionus plicatilis	Swimming inhibition ↓ Population growth rate (6-18 mg/L, LOEC = 405 µg/L), ratio of ovigerous female/non-ovigerous female (6 mg/L), ratio of mictic/amictic female (6 mg/L), ↑ resting egg production (14 mg/L) and mictic rate (14-18 mg/L)	Sha et al., 2015
Brachionus plicatilis	↓ Survival time (0.8-8 mg/L at 48h) ↑ age specific fecundity (0.0008 and 0.8 mg/L at 72h, and 0.08 mg/L at 96h) and ↓ it at 4 and 8 mg/L ↑ Concentration ↓ life expectancy from 166h to 28h, ↓ generation time , life expectancy, population density, population abundance (0.08 mg/L) When concentration > 2 mg/L impossibility to reproduce after 2 weeks ↓ Carrying capacity at 0.008 mg/L and above	Sha et al., 2015
Cladocera (*Gammarus pulex*)	Dose-dependent accumulation, higher in females than males (0.1 and 1 µg/L) ↑ Chitobiase activity 1.5 fold at 48 h in males (0.1 µg/L)	Gismondi and Thomé, 2014

	↑ Chitobiase activity 3.5 and 1.5 fold at 24 and 48 h and ↓ 3.3 fold at 96 in males (1 µg/L) ↓ Chitobiase activity 1.5 and 3.8 fold at 24 and 48 h in females (0.1 µg/L) ↑ Chitobiase activity 9 at 24 h and ↓ 1.6 and 4.5 at 48 h and 96 h in females (1 µg/L) = reflection of molt cycle perturbations	
Copepod (*Tigriopus japonicus*)	Inhibition of developmental rate, delayed in molting and metamorphosis (50 µg/L) Inhibition of molting and metamorphosis-related genes (50 µg/L) Suppression of *NR1*, *NR2* and *NR3* expression gene family and increase of *PNR* gene expression (50 µg/L). BDE-47 act as ecdysteroid antagonist, by inhibiting gene expression and hormone synthesis enzyme.	Hwang et al., 2016
Copepod (*Tigriopus japonicus*)	Developmental retardation (120 µg/L) and reduce fecundity (60 µg/L) ↑ in ROS production in a concentration-dependant manner (24 µg/L) Induction of detoxification genes , *CYP3024A2*, *CYP3027C2*, anti-oxidant, *GST-Σ*, *CAT*, apoptosis *p53*, *Rb*	Han et al., 2015
Copepod (*Nitocra psammophila*) 0,11-1,1 µg/L	Alteration of population structure with a ↓ in nauplii and ↑ in copepodites ↓ RNA content in copepodites linked to growth decrease Alteration of genetic composition and ↓ in heterozygosity	Garderström et al., 2006
Copepod *(N. spinipes)* Full life cycle	↓ Larval development rate (≥13 µg/L for 6 days), population growth rate (40 µg/L)	Breitholtz and Wollenberger, 2003
Cladocera (*Gammarus pulex*)	Difference of 7 proteins expression in sex gender after BDE-47 exposure (among 25 at 0.1 µg/L) 3 involved in energy metabolism, chaperone proteins, transcription/translation All under express in female and all over express in males	Gismondi et al., 2015
Clam (*Ruditapes philippinarium*)	↓ shell length growth for 14 d juvenile (1 and 10 µg/L) ↓ T4 (40%) and T3 (75%) in haemolymphe (1 µg/L)	Song et al., 2016

	Transcription of genes ↑ NIS, Deio and TPO in dose dependent manner (day 5 and 10) ↓ Mct-8 (day 5, 10 and 15)	
Cladocera (*Daphnia magna)* 3 molting for parents and 4 for neonates	Delayed molting in surviving daphnies (20 µg/L from 72 to 132 h)	Davies and Zou, 2012
Nematode (*Caenorhabditis elegans)* Development 48h from L1 to L4 (100% purity)	Impact reproduction at 13 µM (100% effect) Impact larval development at 0.4 µM Impact on MMP inhibition at 12.8 µM without cytotoxicity	Behl et al., 2016