Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at Community level of

hexabromocyclododecane (HBCDD)

ECHA/RAC/ CLH-O-0000001050-94-03/A2

Adopted

8 December 2010

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPSAL ON HEXABROMOCYCLODODECANE (HBCDD)

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments that refer to several hazard classes are entered under each of the relevant categories/headings

Substance name: Hexabromocyclododecane (HBCDD)
CAS number: 25637-99-4 and 3194-55-6
EC number: 247-148-4 and 221-695-9

General comments

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
22/12/2009	**Netherlands / Rockwool Benelux**	Instead of HBCDD containing insulation materials, alternative materials do exist with effective thermal and fireproof properties, such as mineral wool and cellular glass	Thank you for the information	Information is noted.
19/12/2009	**France / Individual**	Polystyrene manufacturing is already known for the use of chemicals which have been proved not so safe such as pentane or styrene. Styrene has already been classified as a potential carcinogenic substance. When using flame retardants which is generally the case in constructions, EU citizens are now facing HBCDD, a PBT substance potentially dangerous for unborn children. It is a huge preoccupation for parents. How come just living in their own house, and just because of a construction material, cannot be safe even for an unborn baby. We all know that when polystyrene is used for insulation, safe alternatives do	Thank you for the information and your support.	Information is noted.

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		exist such as stone wool which does not even contain flame retardants but with irreprochable fire safety properties in contrary to fire-retarded polystyrene. It is well-known that such chemicals are only used for economic reasons and it is really worrying that human life is badly exposed to such a consideration. How can they still be used? A fire hazard involving a polystyrene manufacture has happened in France in June 2006 (one polystyrene manufacture fire hazard among others). A huge dioxine pollution has been discovered afterwards in the area (milk, meat...). The direct link cannot be proved. French authorities have also admitted a lack of knowledges in the brominated substances. More than the economic aspect, there is also an environmental aspect which cannot be neglected in the actual context.		
18/12/2009	**Norway / AS Rockwool**	EPS and XPS insulation with HBCDD is not the only type of insulation and viable, safe alternatives do exist with effective thermal and fireproof properties i.e. glass wool or stone wool.	Thank you for the information	Information is noted.
18/12/2009	**Slovakia / Associaiton EPS Slovak republic**	Association of EPS Slovak Republic do not agree with classification of HBCDD as Toxic for Reproduction Cat.3. EPS with HBCDD content is used for the purposes of termal insulation in the building and construction industry. HBCDD is physically bonded in to the	Thank you for the information. However, classification and labelling is solely based on inherent properties, and use pattern should not be considered in this context.	Information is noted. Socio-economic analysis and risk assessment are not a part of CLH process.

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		matrix of EPS and it is not released in to the environment. Its use doesn´t pose an unacceptable risk to human healt and environment. On the other side, the content of HBCDD in EPS is very low, less than 0,5 %. Classification of HBCDD as Toxic for Reproduction Cat.3 wil open further problems by aplication of this substance especialy in building construction as flame retardad in EPS construction products. This fact may cause negative impact on acceleration of thermal insulation programmes and potentionaly on climat changes.		
17/12/2009	**Norway / IPF - Association of Insulation Manufacturers**	- There is no need for using HBCDD in EPS and XPS insulation. This can be solved by using fireprotecting boards or in applications where fire is not a problem. - Norwegian manufacturers of insulation have stopped using HBCDD in foam insulations.	Thank you for the information	Information is noted.
15/12/2009	**Germany / Mark Schwägler / MSCA**	German CA: Hexabromocyclododecane is not included in Annex VI of EC Regulation No 1272/2008. But a classification with N; R50/53 was decided at the Technical Committee for Classification & Labelling (see section 3.1). The now proposed classification is only for selected endpoints. Hence for transparency, note H should be included in section ´proposal for harmonised classification and labelling – proposed notes (if any) ´ (page 5).	We will add Note H, but also note that COM still have to decide on how to use Note H in Annex VI.	Note H is not needed in the current ATP of CLP Regulation, because its requirements applies to all entries .

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		Available data from studies with repeat administration of HBCDD indicate effects on the thyroid gland and on the thyroid hormone system, thus raising concern not just for endocrine modulating properties of the compound, but raising concern for endocrine toxicity of HBCDD, which is relevant for humans. Although the effects observed on the thyroid gland and the thyroid hormone axis/thyroid hormone levels (as observed in studies of Ema et al., 2008 and of Saegusa et al., 2009; as well as reported from studies with repeat administration for 28 days [van der Ven et al., 2006] and for 90 days [Chengelis, 2001]), may partly arise secondary to enzyme induction in the liver – as outlined in the CLH report - , we suggest considering, whether or not the effects observed for the thyroid gland and on the thyroid system hormones should be evaluated as an adverse effect on this (hormonal) organ system, probably resulting in endocrine toxicity. It may well be, that the effects of HBCDD on the thyroid gland become obvious with the experimental settings applied and respective endpoints measured at the higher dose levels only, whereas the condition of subclinical hypothyroidism, which may be relevant for the impairment of ovarian and brain/behavioural development may have been missed by		

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		conducting standard tests only. HBCDD then might be considered relevant for classification because of specific target organ toxicity (thyroid organ/hormone system) in addition to reproductive toxicity, e.g. with H373. Note that regulation (EC) No 1272/2008 says: "Conversely, a specific profile of toxicity may be seen in animal studies occurring above a guidance value, such as > 100 mg/kg/day by the oral route, and in addition there is supplementary information from other sources, such as other long-term administration studies,…., which supports a conclusion that, in view of the weight of evidence, classification is the prudent action to take." References: van der Ven et al. A 28-day oral dose toxicity study enhanced to detect endocrine effects of hexabromocyclododecane in Wistar rats. Tox Sci, 2006; 94:281-292 Chengelis CP. A 90-day oral (gavage) toxicity study of HBCD in rats. WIL-186012. Arlington, VA: Brominated Flame Retardant Industry Panel. Chemical manufacturers association; 2001	We have considered the proposal, and we agree the thyroid hormone system is a target organ for HBCDD. However, as the effects on the thyroid hormone system may be manifested as developmental toxicity (e.g., effects on behaviour and hearing), we feel that a classification for developmental toxicity also will cover thyroid effects, and classification for specific organ toxicity is therefore not needed.	STOT classification was not proposed by dossier submitter and is outside of harmonization of classification of chemicals at EU level. HBCDD do not exert the toxic action on thyroid directly, it acts most probably through liver enzyme induction at the levels higher than 50 mg/kg bw/day to justify the classification. However, the STOT may be reconsidered when proposed by the MSCA.
09/12/2009	**Lithuania / Individual**	Alternatives do exist: EPS and XPS insulation is not the only type of insulation around and viable, safe	Thank you for the information	Information is noted.

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		alternatives do exist with effective thermal and fireproof properties i.e. 'stone' wool.		
09/12/2009	**Lithuania / Rockwool UAB**	HBCDD and XPS insulation is not the only type of insulation around and viable, safe alternatives do exist with effective thermal and fireproof properties i.e. mineral or 'stone' wool.	Thank you for the information	Information is noted.
04/12/2009	**Netherlands / Bureau REACH / RIVM**	Please update Chapter 3 by referring to Annex VI of EC 1272/2008. Include classification according to Regulation EC 1272/2008 in paragraph 5.9.5 using the criteria of that regulation. Identity: Page 4: Purity: change 'the content of the different stereoisomers…' in 'the total content of the different stereoisomers…' HBCDD is put on the market in different forms (high and low melting) with different concentrations of the alpha, beta and gamma isomer. The available data on toxicokinetics show that there are differences in bio-accumulation between these isomers. These differences in kinetics could result in differences in toxic effects especially for effects after prolonged exposure and where transport through milkfat is important. Please explain why the results with the tested substances containing a mixture of the available substances on the market are relevant for all substances on the market including the substance with mainly the	The text has been amended accordingly The text has been amended accordingly The text has been amended accordingly. When testing of HBCDD was conducted, as required under the ESR, industry tested a mixture of three commercial products (each containing the three diastereomers at different ratios) based on the reasonable assumption that this mixture would be representative for all HBCDD products and all diastereomers. Much later, it has (unexpectedly) been discovered that there are differences between the diastereomers, most notably concerning water solubility. There are also differences with regard to bioaccumulative properties, most likely related to different susceptibility to metabolism. The different diastereomers	Thank you for suggestions The issue raised is important and should be followed when data on toxicity of various isomers will be produced. In the current process the proposed classification refers to mixture of isomers.

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		gamma isomer.	have not been tested in any toxicity assays, so there is no way of knowing whether the different diastereomers may have different toxicological properties. Thus, we do not know for sure to what extent the tested mixture represent all products on the market. Although it is possible that there may be some differences between different commercial products, it is now recognised that there is transformation between the different diastereomers (so that a product containing mainly gamma-HBCDD after exposure to heat or enzymes will contain also alpha-HBCDD). Therefore, based on the present knowledge, we don't think there are any qualitative differences in toxicity profiles of the different products that would affect the classification and labelling of HBCDD. In contrast, there is considerable uncertainty when assessing the risk from human exposure to almost exclusively alpha-HBCDD using toxicity data from a mixture containing only some 10% alpha-HBCDD, but this risk assessment consideration should not affect the C&L.	
28/11/2009	**Czech Republic / Individual**	As parents of two adolescent sons, who will soon set up families, my husband and myself look very much forward to our grandchildren and we expect them to be healthy. Information we got about some chemical products like HBCDD, which could very	We hope that classification for reproductive toxicity will inform about the health risks posed by HBCDD.	The opinion is noted. However, in this CLH process RAC does not assess risk posed by HBCDD or alternatives.

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		seriously harm children even before the childbearing, make us to express our strongest protests against using of such products. Use safe alternatives as mineral wool.		
28/11/2009	**Czech Republic / Rockwool**	By the tests has been proved, that polystyrene (EPS) with HBCDD fire retardant does not improve fire safety of external thermal insulation systems used commonly for refurbishment as well as for new buildings. HBCDD treated EPS allows fire to spread through the facade. Therefore mandatory fire belts made from traditional thermal insulating product – stone wool – were incorporated into the Czech building code. This proves, that EPS with HBCDD fire retardants or XPS can be replaced by safe alternative with effective thermal and fireproof properties i.e. mineral or 'stone' wool.	Thank you for your information	Information is noted.
13/11/2009	**United Kingdom / Rockwool Limited**	There are many types of thermal insulation that are extensively used in the UK and elsewhere in Europe, which do not contain HBCDD. These alternative, safe insulation products are used in the same applications as the EPS and XPS insulation products that contain HBCDD. Examples of these alternative insulation materials include other types of plastic foam (such as PUR, PIR, PF and PS that does not contain HBCDD), mineral wool and others. There is therefore no reason	Thank you for the information	Information is noted.

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		to retain and authorise HBCDD for use in thermal insulation products.		
05/11/2009	**China / cserc ltd.**	There is no information about acute toxicity for this substance, so I am doubt that there are insufficient indications for crisis management if an accident happened during utilization or transportation.	The substance does not exhibit acute toxicity, and the substance should therefore not be classified for acute toxicity.	Acute toxicity of HBCDD is so low that it is not posing any danger, in contrary chronic exposure may pose a danger, when sufficiently high.

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
18/12/2009	**Belgium / Denauw Frédéric / Federal Public Service Health, Food Chain Safety and Environment**	Fertility: Since the low effects on the fertility endpoint, the fact that this effect could only be demonstrated by a specific statistical analysis (not completely explained by the authors of the dossier) and not demonstrated by the classic analysis performed by the authors of the study, that this statistically significant effect was showed in F0 but not in F1 where the pool of primordial follicles was significantly decreased, the fact that if there is effectively a relation between the diminution of the pool of primordial follicles and the decrease in fertility, as suggested by the authors of the dossier, this relation could only be demonstrated in F1-females as this endpoint was not studied in the other generations, the current database does not allow to clearly distinguish these effects on fertility from developmental effects. In male, the	It is correct that the statistical analyses performed by us didn't follow the standard approach, but the report clearly includes the fertility index as such. The copulation index has also been added. It appears that HBCDD slightly affects both male and female copulation success and fertility in F0, although none being statistically significant. If assuming that both these effects are substance-related, this statistical exercise indicates that the trend for the total effect is statistically significant. Since it is not known when the primordial follicles have been affected by HBCD, the effect can be attributed to either	As it was pointed out in the background document existing data do not allow classification of HBCDD for fertility effects, although such effects cannot be excluded This was taken into account in classification.

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		effects observed on the weight of seminal vesicles were not confirmed by histological changes. For all these reasons, we can not conclude that the substance warrants a classification for fertility. Development: Even if some studies didn't show a clear evidence for developmental toxicity, the potential for developmental effect cannot be excluded. Some recent studies (Van der Ven et al, 2009 and Lilienthal et al, 2009) have shown that HBCDD could exert some effects on offspring at relatively low doses. These effects could justify a classification in Repr Cat 3, R63. Effect via lactation: As there is strong evidence that HBCDD is found in Human breast milk, that the substance has an high capacity to bioaccumulate, that this bioaccumulation could explain the severe effects observed in F2 pups, already on PND4, effects not observed in F1pups and that effects were observed in rats in recent studies (Van der Ven et al, 2009 and Lilienthal et al, 2009) at relatively low doses, there is sufficient concern to support the classification R64.	(affecting) fertility or (being casued by) developmental toxicity, or both. The effect is clear, but we agree that it is not clear which endpoint it should be referred to under the DSD. However, for classification of reproductive toxicity according to CLP, the effect is attributed to reproductive toxicity irrespective of when it has occurred. Thanks for the support. Thanks for the support.	Effects of HBCDD on development have been found in several studies and justify classification R63. Agree Thank you for support
18/12/2009	**France / MSCA**	Fertility: A dose related decrease in fertility index	Thanks for the support.	Thank you for this observation. When analysing original data of Ema *et*

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		in both generations was observed in the two-generation reproductive study. The author concluded that this decrease was only significant in the F0 generation but there was an error of calculation of fertility index for F0 at high dose. Indeed, if the definition of fertility index was No. of pregnant female divided by No. of mated female/male, fertility index were 86.9% for female and 90.9% for male. In this way the decrease may not be significant. A significantly reduced number of primordial follicles, within the limits of historical control data, in the mid and high dose were observed and could explain decrease of fertility index in F1 generation. This decrease could decrease the period of fertility of female later in their life, but we had no information about it. Moreover in cell cultures, HBCDD was found to exert antagonistic effects at the progesterone receptor, androgen receptor and oestrogen receptor. But it is not clear whether and how these effects are expressed in vivo. However, this could explain delayed vaginal opening and decrease weight of the testis seen in the one generation reproductive study, although no alteration of testicular histology or sperm count was reported.		*al.* study it was found that HBCDD has significantly reduced the proportion of F0 mated females in the 15,000 ppm group, which became pregnant or delivered live pups (p=0.05 or less than 0.05 in Fisher exact probability respectively). As it was pointed out in the background document existing data do not allow classification of HBCDD for fertility effects, although such effects cannot be excluded This was taken into account in classification. The effect on number of primordial follicles might be accidental, as they were within historical control. This is not a main criterion showing reduced fertility – see above. The level of sex hormones, except for FSH and dihydtestoterone, (testosterone, estradiol, progesterone and LH) was not altered *in vivo* in the Ema study. Agree; the data do not provide evidence

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		Therefore, some effects (fertility index, reduced number of primordial follicles) were observed but there were lack of information (no information on the number of primordial follicles in F0 females, historical control data to interpret the magnitude of the decrease in the fertility index really significant decrease of fertility index?,) to establish relationship between the effects. Moreover, single specie (rat) was studied and no information in humans was available. Consequently, France agrees with a classification in category 3 (possible risk of impaired fertility). Developmental toxicity: In the two-generation reproductive study, no signs of toxicity in dams were observed but high and dose-dependent pup mortality during lactation was observed in the F2 generation and this was statistically significant in the high dose group (1724-2200 mg/kg/d). However, no information about causes of death was noted (no information about necropsy or histopathology) in order to determine if malformation could explain it and high dose was really high. Moreover, unscheduled death and euthanasia due to moribund condition were noted in some F0/F1 adults although cause of death is not reported.	We agree that historical control data on the fertility index would have been helpful. Although the effect was weak, it was observed as trends in both generations. Thanks for the support. There were only few such cases death, and they were not related to HBCDD exposure.	to classify HBCCD to other than DSD category 3 for reproductive toxicity or category 2 in CLP regulation . In fact the F0 and F1 dams were poisoned by HBCDD causing such effects as e.g. significantly increased absolute and relative weights of the liver at 1500 ppm and 15,000 ppm and of the thyroid in F0 males exposed at 15,000 ppm, decrease of relative weight of the brain of F0 males at 1500 ppm, significant increases in the absolute weight of the thyroid, liver and adrenal, and relative weight of the liver in F0 females at 15,000 ppm, more data in the modified report.

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		In the one-generation reproductive study, decreased weight of the testis and prostate in males was thought to be treatment related and delayed vaginal opening was seen in females. Some neurotoxicity developmental studies were realised and showed effect of neurotoxicity but they had some deficiencies which question reliability of the studies. For example, in the study of Lilienthal we didn't know if the last exposure to HBCDD was just before injection of haloperidol (at the age of 110 days) or if it was 20 days before (at the age of 90 days). So in function of the last exposure, the mechanism which explains effect could be different. Moreover, the author supposed that the outcome may be due to HBCDD-related hepatic enzyme induction, resulting in enhanced metabolism of haloperidol but this effect could be classify as an other effect than a reproductive effect. In the study of Saegusa and al. rats were exposed through diet from gestation day 10 instead of gestation day 5 (as recommended in the guideline) consequently, some malformations may not be observed (e.g. brain development). In the study of Eriksson and the human study, no information about the period of exposure of offspring was given, therefore it is difficult to determine relevance of	Our understanding of the publication is that the animals were exposed throughout life, i.e., until being tested. In the Eriksson study, the pups were administered HBCDD once on day 10. The human study (Meijer et al, 2008, extended abstract) should reflect the current exposure levels. It is noted that the data just has been properly published, and that no adverse effects were correlated with exposure to HBCDD (Roze E el at, 2009)	Postnatal exposure of rats studied in Liliental lasted till 90 days post partum just before transfer to another laboratory. Not only Lilienthal study but also other studies provide evidences of developmental neurotoxicity of HBCDD such as Ema *et al*. 2008 found that: The development of basic reflexes during rats development was also affected by the HBCDD at the highest dose level leading to: -shorter time response in the surface righting reflex in F1 male pups on PDN 5 at 15,000 ppm - significantly lower incidence of females completed mid-air righting (76.9% vs. 100% in controls) at 15,000 ppm - a significantly shorter elapsed time at 1500 and 15,000 ppm and fewer number of errors at 15,000 ppm on day 3 of the T-maze test in F1 males in the age of 6

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		observation, for example if exposure was realised or not during brain development. In the one-generation developmental toxicity study, serum levels of thyroid-related hormones were examined only in male offspring. The level of T3 was decreased and the level of TSH increased at post natal day 20 in the high group. At 11 weeks, T3 was decreased in the mid and high dose groups, but there were no effects on TSH. The relative thyroid weight was dose-dependently increased in males, with the increases being statistically significant in the mid and high dose groups. Brain morphometry showed effect on the oligodendroglial development significant at the high dose and supported by a dose-dependent trend. Therefore, some effects (viability, thyroid, neurology) were observed but there were lack of information and some deficiencies (high dose very high in the 2-generation study, exposition with regard to brain development) to class substance with certainty in category 2. Consequently, France agrees with a classification in category 3. Lactation: France agrees with argumentation and classification	Thanks for the support. Thanks for the support.	weeks. No structural malformations of foetuses were observed when female rats were exposed (Murai *et al*., Stump, 1999 in EU RAR). Thanks for support. No structural malformations of foetuses were observed when female rats were exposed (Murai *et al*., Stump, 1999 in EU RAR). Thank you for support Thank you for support
18/12/2009	**Ireland / Health & Safety Authority**	The Irish CA is in agreement with the proposed classification of Repr Cat 3;	Thank you for your support	Support is noted.

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		R62; Repr Cat 3, R63; R64 [Repr. 2 H361fd, Lact. H362].		
17/12/2009	**United Kingdom / MSCA**	Pages 32-33 The high F2 pup mortality observed in the two-generation study (Ema et al, 2008) is likely to be due to transfer of HBCDD in the milk and we therefore agree with the proposal for R64 (H362). However, we do not believe that these represent a specific developmental effect and therefore should not be used to support classification for developmental toxicity. It could be considered whether R33 is also appropriate, given that the substance may accumulate in the body and is released into milk. Pages 33-34 We consider that the decrease in testes weight (by ~14 %) in the F1 generation males is likely to be secondary to the lower bodyweight (by ~12 %) and therefore not relevant for classification (van der Ven et al, 2009; see the supplementary content of the e-publication, Table 8). Furthermore, this finding is not corroborated in the two-generation study, which included testing at a higher dose level. There is a possibility that the F1 reduction in prostate weight (by 36%) was not secondary to the lower bodyweight, but again this finding was not corroborated in the two-generation study (Ema et al,	Thank you for your support for R64 (H362). In F2 pups, there was both mortality and decreased body weights of live pups already at day 4, indicating that lactational exposure, and perhaps also prenatal exposure, could have affected the pups. The pups are also much more sensitive than the adults, as no mortality was observed in adult animals. We therefore think that classification for developmental toxicity is relevant. R33 seems not to be used anymore (ECBI/129/06 Rev. 2, Ispra, 24 July 2007), and there is no equivalent classification under GHS, so although we agree in principle that the DSD criteria are met for R33, we have not included this risk phrase. A relation to the decreased body weight can not be ruled out. A specific effect on the prostate was indicated in the 90 days study by Chengelis (2001), who observed an increased prostrate weight in rats exposure during adulthood. We therefore find it likely that the prostrate was directly affected in F1 animals exposed both pre- and postnatally.	Developmental toxicity has also been seen in other studies and other developmental effects were seen in Ema study, besides increase mortality. R33 was not proposed by the dossier submitter and seems to be outside of harmonised classification. The effects on testes weight or prostate have a character of supplementary evidence and do not justify by themselves classification as they did not appear in all the studies.

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		2008). Pages 35-36 We are unfamiliar with the techniques used in the BAEP study (Lilienthal, 2009) and share Swedish reservations about the robustness of the assays. Nevertheless, we regard the possible hearing loss, observed in males, to be of potential concern and we accept that there is a plausible, albeit not proven, mode of action for developmental toxicity. However, these animals were dosed through to adulthood and consequently it is unclear whether the observed effects are due to direct toxicity on the fully developed auditory system or a specific developmental effect. Given our doubts about the relevance of both the F1 testes/prostate weight differences, the F2 pup mortality data and reservations regarding the effects on the auditory system, we do not consider that there is sufficient strength of evidence to justify a proposal for a developmental toxicity classification. Pages 23-24 Although there are indications that fertility was decreased in rats in the two-generation study (Ema et al, 2008), only a small number of animals were affected, the changes were not statistically significant when individual test groups were compared with the controls and this	We agree that it is not proven whether it is direct toxicity to adult animals or developmental toxicity, but note that developing organ systems generally are more sensitive that the adult fully developed system. Furthermore, these effects have been demonstrated in developing animals, but not so far in animals only exposed in adulthood. In spite of some uncertainties, we think a weight of evidence assessment supports classification for developmental toxicity in category 3, but not in category 2.	We share also Swedish reservation concerning robustness of this design. This study provides supplementary evidence in addition to results of other studies indicating HBCDD effects on rat development. Thank you for support. Classification into category 3 (DSD) and 2 (CLP) is proposed.

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		effect was not clearly maintained across generations. Additionally, the decease in fertility was not corroborated at the higher dose levels in the one-generation study (van der Ven et al, 2009), which employed similar dose levels to the low and middle doses of the two-generation study. Furthermore, the data presented as 'fertility index' in table 5.4 could be a little misleading as it includes both animals that did not mate and those that did mate but did not achieve pregnancy, which are different effects. For clarity, the observations could be presented separately as copulation (% of paired animals mating) and fertility indices (% of matings resulting in a pregnancy). Overall, there is a possibility that the differences in fertility could be due to chance. Pages 24-25 As a final point, we do not consider the reduction in primordial follicles observed in the F1 generation in the two-generation study (Ema et al, 2008) to be of concern as the values were within the historical control range and were not dose-related. When the above factors are taken into consideration, an equally valid conclusion would be that classification with respect to fertility is not warranted.	We are hesitant to compare dose levels between the different studies, as only the van der Ven study is studying the inherent toxicity of (dissolved) HBCDD. The others are studying the toxicity of HBCDD-particles of unknown bioavailability, where bioavailability is likely to be dose-dependent (lower at higher doses). The copulation index has been added to table 5.4. It is noted that the calculations are described in a transparent manner in the text. We believe the comparison with the present controls is the most valid comparison.	Agree with consideration concerning calculation of "fertility indexes. As it was pointed out in the background document existing data do not allow classification of HBCDD for fertility effects, although such effects cannot be excluded This was taken into account in classification. The presentation of data was modified accordingly. The reduced number of primordial follicles is a supportive, but not main evidence of reduced fertility
16/12/2009	**Belgium / CEFIC**	p.4 : The number of primordial follicles is a very varying parameter, which can also be seen in the values obtained in historical	We believe the comparison with the present controls is the most valid	The reduced number of primordial follicles is a supportive, but not main

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	milk	controls. The numbers in all dose groups are within the historical control variation (189.5 to 353.4) and the findings also do not show a clear dose response as stated correctly in the EU-risk assessment. For reasons commented below, the effects on the follicles are rather unspecific and the study itself did not report a decrease in fertility index. The conclusion in this dossier of an effect on the fertility index was drawn only after combining the data in a very non-traditional manner that does not provide any biological significance to observations, as ability to copulate, implant fertilized embryos, and maintain a pregnancy are separate and discrete events. This novel approach to data analysis is justified with the comment "It should be noted that fertility index is affected by both copulation ability and impregnation ability." Nevertheless, there is a good reason why these two parameters are calculated independently of one another, that being, a lack of producing offspring in an animal that did not copulate and/or is not pregnant is not only self fulfilling, it provides no ability to determine if the lack of offspring was the result of any treatment-related effects. The correct measure for determining if a chemical affected pregnancy rates is to determine if there was a presence of implantation scars in females seemingly non-pregnant due to lack of a copulatory	comparison. The copulation index has been added to table 5.4. It is noted that the calculations are described in a transparent manner in the text.	evidence of reduced fertility. The data are presented in modified report; As it was pointed out in the background document existing data do not allow classification of HBCDD for fertility effects, although such effects cannot be excluded This was taken into account in classification.. As it was pointed out in the background document existing data do not allow classification of HBCDD for fertility

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		plug. Based on such an analysis the study report concluded that no HBCDD treatment-related effects were observed in the fertility index. From the available studies there is no clear evidence that HBCDD adversely affects fertility. p.5 : The classification is not justified because the quoted effects are in our opinion not due to developmental toxicity, but rather likely to reflect direct high dose toxicity to the pups during lactation and were observed at a dose level exceeding the limit dose. (For detailed comments, see attached document). In accordance with Annex VI of 2001/59/EC 4.2.3.3 last paragraph: "Annex V to the directive specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may not be considered necessary. If data are available from studies carried out with doses higher than the above limit dose, this data must be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at doses in excess of the limit dose would not necessarily lead to classification as Toxic to Reproduction", those effects should not lead to a classification. The reported effects in the 1-generation	In F2 pups, there was both mortality and decreased body weights of live pups already at day 4, indicating that prenatal exposure could have affected the pups. The effect was then worsened by the lactational exposure. Regarding the doses used in the Ema study, it should be noted that dose-dependent pup mortality also was observed in the mid dose, supposed to be 100-140 mg/kg/day. However, this is the dose of HBCDD-particles of unknown bioavailability, where bioavailability is likely to be dose-dependent (lower at higher doses). In other studies, developmental effects were indicated at even lower exposure levels.	effects, although such effects cannot be excluded This was taken into account in classification. Developmental toxicity has also been seen in other studies and other developmental effects were seen in Ema study, besides increased mortality.

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		study are difficult to interpret from the publication, as stated already in the conclusions section. A number of issues indicate that this study should not be used as a basis for a conclusion on developmental effects. (For detailed comments, see attached document). The classification criteria for R64 state "that the risk phrase should only be used for substances and preparations which are absorbed by women and may interfere with lactation or which may be present in breast milk in amounts sufficient to cause concern for the health of a breastfed child", From the available monitoring data and No effect levels it can be concluded that levels observed in mothers milk are unlikely to cause concern for a breastfed child. This was also concluded in the EU risk assessment on HBCDD (*) (For detailed comments, see attached document). (*)European Communities, 2008, Risk assessment Hexabromocyclododecan, CAS-No. 25637-99-4, EINECS No. 247-148-4, May 2008	The classification with R64 is not based on a risk assessment. As compared with the EU RAR, the classification report contains data showing higher breast milk concentrations of HBCDD than in those studies cited in the RAR.	The study of Rose *et al.*2009 provides data which suggest that HBCDD may affect postnatal development of humans. According to Rose *et al.* the concentration of HBCDD in maternal blood was positively correlated with motor coordination (p less than 0.05), total intelligence (p less than 0.05) and verbal intelligence (p less than 0.01). These findings on humans corresponds well with the results of animal study (Ema *et al*. 2008), which revealed better motor and memory performance of F1 male rats exposed to HBCDD, which had a significantly shorter elapsed time and fewer number of errors on day 3 of the T-maze (Ema *et al*. 2008). Although the Rose study was rather exploratory, with limited number of investigated children, but support the classification of HBCDD into R64.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
15/12/2009	**Germany / Mark Schwägler / MSCA**	German CA: Based on the data and information of the study of Ema et al., (2008), which is considered to represent the key study, the proposal to classify and label HBCDD due to developmental toxicity and lactational effects in our opinion is well justified and thus a proposal for Repr. Cat 2 with hazard statement H361d and H362 is supported. Developmental toxicity: It is suggested that, in addition to the effects listed under the summary section 5.9.5 Development, also postnatal growth retardation [as observed in the surving F2 weanlings of the two-generation study (Ema et al., 2008)] as well as the consistently observed adverse effects on the thyroid organ system [in weanlings (Saegusa et al., 2009) and in F1 animals (Ema et al., 2008)] should be listed as further developmentally toxic effects that had been observed after treatment with HBCDD. Consideration of postnatal growth retardation as a further developmentally toxic effect also applies to the list of effects in table 5-6. Concerning the effects of HBCDD	Thank you for the support. The report is amended as suggested.	Support is noted. The report has been amended as suggested.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		treatment on the number of primordial follicles in the F1 generation as observed in the study of Ema et al. (2008) we consider this clearly as a toxic effect on (ovarian) development, since it results from impairment of neonatal ovarian primordial follicle assembly and development. This process goes from immediately after birth through postnatal day 4 in rodents (Kezele and Skinner, 2003). Besides and concerning mode of action considerations, there is information available that impairment of ovarian follicles development in newborn mice for instance resulted from experimentally induced hypothyroidism, however, not necessarily affecting reproduction after puberty (Chan and NG, 1995). Similar to the findings in mice, also for the F1 rats in the Ema et al. (2008) study there is no clear indication that the effects observed on ovarian follicles development in the F1 resulted in a reduction of fertility of the F1 generation. There are, however, some questions concerning the classification of HBCDD based on regulation (EC) No. 1272/2008 in category 2 as a substance which is suspected of damaging fertility or the unborn child with the hazard statement H361d. The two studies which are mainly used to justify classification concerning developmental toxicity are not matching. In the study of van der Ven et al. 2009		Thank you for support

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		decreases in testis and prostate weight are observed. Although applying higher doses Ema et al. 2008 do not identify a decrease in relative weights of male reproductive organs. For this endpoint it would be very helpful if the changes in weight are shown quantitatively in the report. Listing these data would facilitate the determination of dose-response relationships. The absence of histopathological changes in the testes of the F1 males in the study of van der Ven et al. 2009 do not match the decreased weight observed in the same dose group.	More information has been added.	More information has been added
		What means a 12 % delay in vaginal opening in females? The naming of absolute entities and the historical control data would be necessary to assess the impact of this effect on developmental toxicity.	Time of vaginal opening were 39.9±2.6 days in the high dose vs. 35.4 ±2.3 days in controls; the corresponding body weights at 5 weeks of age were 107±20 vs. 125±25 g in controls. This information has been added. There are no historical control data available for vaginal opening in the study reports.	
		The aspect that no effects on developmental toxicity in studies with prenatal exposure are observed should be considered regarding classification of the substance in category 2 based on regulation (EC) No. 1272/2008 as suspected human reproductive toxicant. It is possible that the postnatal exposure of the pups triggers the changes in reproductive organ weights, delay in vaginal opening and brain development in the pups. References: Kezele and Skinner. Regulation of	The absence of malformations in the standard TG414 developmental toxicity studies may not contradict other more subtle effects on development. In addition, it is noted that these studies are based on dosing HBCDD-particles rather than dissolved HBCDD, and that this likely would lead to low absorption. Liver weight increases could be a marker for exposure, and this was studied in the Murai study (1985), but only observed in dams of the highest dose (at the nominal	Lack of teratogenicity does not exluded occurrence of alterations in the postnatal development as observed in several studies (Ema *et al*; van der Ven *et al.* Saegusa *et al*.).

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Ovarian Primordial Follicle Assembly and Development by Estrogen and Progesterone: Endocrine Model of Follicle Assembly. Endocrinology,2003, 144(6): 3329-3337 Chan and NG. Effect of Hypothyroidism Induced by Propylthiouracil and Thiourea on Male and Female Reproductive Systems of Neonatal Mice. The Journal of Experimental Zoology, 1995, 273:160-169. Fertility: From the Ema et al. (2008) study it is not clear, whether HBCDD performs toxic also to the mature ovary in the adult and thus presumably leading to effects on fertility in the F0. If this was the case, a more pronounced effect on fertility would have been expected in the two-generation study on the fertility index of the F1, since due to its lipophilicity and relatively long elimination half-life (in the order of weeks and months) an even higher HBCDD body burden at the time of mating should be assumed for the F1 in comparison to the F0. However, a trend for a decrease in fertility index was observed if at all, for the F0 generation only. As the fertility index is no specific effect the historical control data have to be mentioned to justify classification.	dose of 750 mg/kg/day, but not at 75 mg/kg/day). This indicates that there was exposure, but may question the appropriateness of the dosing. Although it would in theory be possible that the fetus cannot be affected by any exposure to HBCDD, and that all effects are caused by postnatal exposure, it doesn't feel very likely. In addition, there was both mortality and a decreased body weight of live F2 pups already at day 4, indicating that prenatal exposure could indeed have affected the pups. It should be noted that the relative ovary weight was significantly increased at 150 and 15,000 ppm in F2 weanlings, and non-significant tendencies of increased relative	Support to the explanation provided in the dossier submitter response Most probably HBCDD do not act directly on the ovary, but lead to alterations of the hormonal system, mostly function of thyroid due to faster elimination of the T4 or T3 from blood by liver enzymes activated by HBCDD. So the effects in ovary are rather of secondary nature, but they should not be taken as non-specific. Nevertheless, this hypothesis may at least partially explain why the effects on fertility and ovary was not pronounced, and was not reflected in oestrous cycle alterations.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Furthermore the given data show no clear dose-response relationship. The fertility index in the F1 parents is 95.8 %, 87.5 %, and 87.5 % in the controls, the mid dose (1,500 ppm), and the highest dose group (15,000 ppm) respectively. Effects on lactation: The argumentation to warrant the classification of the substance HBCDD based on regulation (EC) No. 1272/2008 in the additional category for effects on or via lactation as a substance that may cause harm to breast-fed children with the hazard statement H362 is comprehensive. The viability of the F2 offspring in the highest dose group (15,000 ppm) on post natal day (PND) 4 is decreased compared to the controls, 68.4 vs. 86.9 % respectively. The reduction in postnatal viability is attributable to death of total litters by days 4, 5, 7, 9, 11, 13 or 18 of lactation. Thus, on PND 21 the viability of the F2 offspring is further decreased to 49.7 %. For the increased pup mortality on PND 21 a direct toxic effect of the substance can not be excluded for pups that died later than about lactation day 14, as exposure to hexabromocyclododecane through the diet has to be taken into account.	ovary weight were observed in F1 weanlings and adults. These effects could indicate direct effects on the ovary, but the lack of statistical significance hampers drawing firm conclusions. Thanks for the support. We agree that cases of very late deaths can be affected by late exposure directly via the feed.	The effect on or through lactation is rather suspected and not as an effect that can by proved or characterized with existing data. Please note additional supportive evidence provided in the study of Rose *et al.* (2009) on children.
15/12/2009	**Norway / Norwegian Pollution Control Authority**	Page 42, Summary and discussion of reproductive toxicity.		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Fertility: The results reported in the 1- and 2-generation studies indicates that HBCDD have endocrine disrupting effects. A decreased fertility index as well as a reduced number of primordial follicles in the mid- and high dose groups which are in accordance with the EU criteria for classification for reproductive toxicity and justifies the classification proposed by Sweden. Development: Pup mortality during lactation in a 2-generation study as well as decreased weight of testis and prostate in male weanlings and delayed vaginal opening in female weanlings in a 1-generation study extended with endocrine endpoints. These effects are in accordance with the EU criteria for classification for reproductive toxicity and justifies the classification proposed by Sweden. Lactation: Increased mortality during lactation in a 2-generation study indicates that exposure via lactation is important. This effect is in accordance with the EU criteria for lactation and justifies the classification proposed by Sweden. HBCDD is also found in human breast milk.	Thanks for the support. Thanks for the support. Thanks for the support.	As it is analyzed in the background document existing data do not allow classification of HBCDD for fertility effects, although such effects cannot be excluded This was taken into account in classification. Thank you for support Thank you for support
09/12/2009	**Lithuania / Individual**	Persistent and bioaccumaltive substance which can potentially harm unborn children in our walls and ceilings is a	We hope that classification for reproductive toxicity will inform about the health risks posed by HBCDD.	Probability of harmful effect has been not assessed yet.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		frightening prospect for parents.		
04/12/2009	**Netherlands / Bureau REACH / RIVM**	Reproductive toxicity: Fertility: We agree with the proposed classification according to Directive 67/548/EEC, based on the significant decrease in number of primordial follicles together with the decrease in fertility index. Please explain in the discussion why the effect on primordial follicles is an effect that results in classification for fertility and not for development taking into account the criteria of both directive 67/548/EEC and regulation EC 1272/2008. Please add an argumentation why Cat 3 (CLP Cat 2) is proposed and not Cat 2 (CLP Cat 1b). Please also include classification according to Regulation EC 1272/2008 Development: We agree with the proposed classification according to Directive 67/548/EEC, based on the endocrine disrupting properties and pup mortality during lactation. However, probably related to the pup mortality, also a reduction in body weight is observed in F2 pups in the study of Ema et al. This should also be mentioned in the summary section on development.	Since it is not known when the primordial follicles have been affected by HBCD, the effect can be attributed to either fertility or developmental toxicity, or both. The effect is clear, and can be used to support either of the endpoints under the DSD. However, for classification of reproductive toxicity according to CLP, the effect is attributed to reproductive toxicity irrespective of when it has occurred. Classification according to Regulation EC 1272/2008 is added. Classification in other categories is not relevant as there is only data from one species and the data is not sufficiently convincing to place the substance in category 2 (DSD) or category 1b (CLP). The text is amended.	Support is noted. The reduction in number of primordial follicles can be taken as evidence of developmental toxicity, however, they can also result from high biological variability of this parameter

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Some effects such as the neurotoxicity were observed in developing animals and were therefore considered developmental effects. However, it is not known whether exposure of adult animals to the same dose levels would result in the same effects. If the same effects are present in developing and adult animals after exposure to the same dose it can be questioned whether these effects are developmental effects. Please include information on the relative testis and prostate weights as also an effect on body weight was found. Also for other parameters like delayed vaginal opening indicate whether this effect could be secondary to the effect on the body weight. Please also include classification according to Regulation EC 1272/2008 (Rep Cat 2; H361). This should take into account the definition of developmental effects as described in paragraph 3.7.1.4 where it is stated that "for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure". Please also discus the human relevance of the effects on the thyroid in chapter 5.9.5 or give a reference to chapter 5.6.	We agree that it is not proven that these effects can not affect adult animals, but note that developing organ systems generally are more sensitive that the adult fully developed system. Furthermore, these effects have been demonstrated in developing animals, but not so far in animals only exposed in adulthood. It is therefore prudent to assume these are developmental effects. The relative organ weights are not given in the publication. If comparing body weights and organ weights between the control and the highest dose, one has to acknowledge that there are only 5 animals per group (because of the benchmark dose testing design) and that the comparison has little statistical value. However, except for the large decrease in the prostrate weight (-36%), it otherwise appears that organ weights and body weights are decreased to a similar magnitude (10-15%). A relation to the decreased body weight can not be totally ruled out, although the effect on the prostrate indicates direct effects not only caused by the reduced body weight. The text in amended. A reference is introduced. Although the rodent thyroid system is generally believed to be more sensitive to perturbations that the human system, the	Text of the report has been amended The possibility of neurotoxicity HBCDD only in adults was in fact not a part of experimental design in the two- or one-generation studies, so it is in fact it is possible that HBCDD induce neurotoxicity both in adults and developing animals, however, the latter ones are more sensitive. The increased mortality of pups was seen before the pups could start eat feed, before the age of 14 days.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Lactation: With regard to mortality during lactation it should be better argued whether this is an effect due to prenatal exposure, exposure via lactation or due to exposure via food. From postnatal week 2 pups start eating food next to drinking milk. Since HBCDD is administered via the diet of the dams, this means that the pups will be exposed, from postnatal week 2, via milk as well as via food. However, data from Ema et al. show that the viability index and pup body weight are already decreased at postnatal day 4, a time point when pups are only exposed via milk. Since HBCDD is found in human breast milk and the viability index is already decreased at postnatal day 4, together with the decreased pup body weight from day 4, we agree that it is likely that the mortality is caused by the exposure through lactation. Therefore, we agree with the proposed classification according to Directive 67/548/EEC, however, we propose to include above mentioned argumentation in the summary section on lactation.	thyroid hormone system is also crucial in humans for successful reproduction. Thank you for your support for R64 (H362). The text is amended as suggested. In F2 pups, the mortality was increased and there were decreased body weights already at day 4, indicating that lactational exposure had affected the pups, and that the prenatal exposure also could have been involved. The effect was then clearly worsened with time, most likely as a result of the lactational exposure as additional exposure via food doesn't start until much later.	Thank you for support, additional argumentation has been included into Background document.
		Do you have an explanation why no mortality during lactation was observed in the F1 generation? Could the difference in exposure duration between the P and F1 result in different exposure through the milk in the F1 and the F2? The difference may be the amount but also a difference	We can only speculate regarding the reasons for no mortality in F1. We agree that it could be both a matter of time and extent of exposure, but also that the relative exposure to alpha-HBCDD will increase over time. However, nothing is known about the relative toxicity of the	Probably the difference was due to fact

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		in isomers. Please also include classification according to Regulation EC 1272/2008 (H362).	three diastereomers. Agreed.	that F1 generation were exposed longer than F0 generation, including their earlier development, also during lactation.
17/12/2009	**United Kingdom / MSCA**	Due to the high F2 pup mortality observed in the two-generation study (Ema et al, 2008), we agree with the proposal for R64 (H362). However, based on the information presented in the proposal, we do not consider that there is sufficient evidence to support classification of HBCDD for the other reproductive toxicity endpoints (Repr. Cat 3; R62 and R63).	In our opinion, a weight of evidence assessment indicates that HBCDD can cause reproductive toxicity, with findings of toxicity in most studies. However, the evidence is not as strong as required for cat 2 classification (DSD), and cat 3 therefore seems relevant.	Classification R62 is not supported but R63 is considered justify as there is evidence of developmental toxicity
16/12/2009	**Belgium / CEFIC**	The proposed classifications are in our opinion not justified and the findings do not meet the classification criteria for toxicity to reproduction. This is the case for all endpoints addressed in this Annex XV dossier.	We disagree.	Opinions are noted, and arguments are provided in the Background document.
15/12/2009	**Norway / Norwegian Pollution Control Authority**	We support the Swedish proposal to classify HBCDD for reproductive toxicity and lactation with Repr Cat 3; R62, Repr Cat 3; R63 and R64 according to Directive 67/548/EEC and Repr. 2 H361fd and Lact. Effects H362 according to Regulation 1272/2008.	Thanks for the support.	Support is noted.

Other hazards and endpoints

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
04/12/2009	**Netherlands / Bureau**	Repeated dose toxicity:	The text will be amended by adding these	Thank you for suggestion, the text of

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
	REACH / RIVM	Page 16: Several clinical signs reported in the RAR are not mentioned in the summary of repeated dose tox (i.e. hair loss, uncertain gait, reduced body weight gain). In addition, in one 90 day study in rats (Chengelis, 2001), minimal to mild hepatocellular vacuolisation was observed in both sexes at all dose groups, as well as minimal to mild hepatocellular hypertrophy in females in the high dose group. In addition, in the other 90 day study in rats (Zeller and Kirsch, 1970), hepatic lipoid phanerosis was observed in many animals. Also in a lifetime study (Kurokawa et al., 1984) in mice, liver lesions, such as hepatocytic swelling, degeneration, necrosis, vacuole formation and fatty infiltration were observed, although the dose-response relationships were not clear-cut. Although some questions regarding some of these studies remain, it cannot be stated that no clear pathological signs were observed in the liver.	effects, i.e., "other effects noted after long-term high exposure to HBCDD are hair loss, uncertain gait, and reduced body weight gain". Agreed. This text will be added; When it comes to effects on the liver, enzyme induction clearly occurs. In addition, histological effects have been described in some studies, including hepatocellular vacuolisation, hepatocellular hypertrophy, lipoid phanerosis, hepatocytic swelling, degeneration, necrosis, and fatty infiltration.	section 5.6 of the background document has been amended as suggested.

Reference referred to by MSCA

ECBI/129/06 Rev. 2, Ispra, 24 July 2007, Background Document for Translation of the Classification and Labelling of Substances listed in Annex I to Directive 67/548/EEC into the corresponding Classification and Labelling according to the new Regulation based on the Globally Harmonised System (GHS) to be included in Annex VI.

Page 20-21 “70 Annex I entries are assigned R33. R33 should be deleted for those four substances which are already classified with R48, as the R33 classification does not give any additional information in these cases. The remaining substances should be regarded as R48/(20/21/22) and then be translated into **Specific Target Organ Toxicity – Repeated** 21 **exposure, Category 2** (see R48 below). The reasoning is that during recent years no substances have been assigned the R33 phrase, but in case of sufficient evidence classified with R48 in the harmful range. Some substances in Annex I that were reclassified were updated with R48 and the R33 was deleted. Some of the current R33 substances might not fulfil the R48 criteria but as the Guidance Value Ranges under the GHS criteria are lowering the cut off values for classification considerable at least for oral and dermal route (see below under R48) it is considered that most of the substances classified with R33 today would be included in the new hazard category. In the current translation it is therefore suggested that R33 would be translated into **Specific Target Organ Toxicity - Repeated exposure, Category 2**. In the future it could be re-evaluated on request on a case-by-case basis.”

Roze E el at, 2009, Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioural performance at school age. Environmental Health Perspectives, 117(12), 1953-1958.