Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

4,4'-sulphonyldiphenol; bisphenol S

EC Number: 201-250-5
CAS Number: 80-09-1

CLH-O-0000006929-56-01/F

Adopted

10 December 2020

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CLH-O-0000006929-56-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **4,4'-sulphonyldiphenol; bisphenol S**

EC Number: **201-250-5**

CAS Number: **80-09-1**

The proposal was submitted by **Belgium** and received by RAC on **10 October 2019.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Belgium has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **9 December 2019**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 February 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Betty Hakkert**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **10 December 2020** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	4,4'-sulphonyldiphenol; bisphenol S	201-250-5	80-09-1	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
RAC opinion	TBD	4,4'-sulphonyldiphenol; bisphenol S	201-250-5	80-09-1	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
Resulting Annex VI entry if agreed by COM	TBD	4,4'-sulphonyldiphenol; bisphenol S	201-250-5	80-09-1	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Bisphenol S is a structural analogue and functional replacement of bisphenol A (Figure 1). In 2014, bisphenol A was classified as **Repr. 1B; H360F** by RAC (ECHA, 2014). Despite the structural and functional similarities between the substances, no comparison to the hazard profile of bisphenol A has been made for the purpose of this opinion on bisphenol S, which relies on its own data and not on read across.

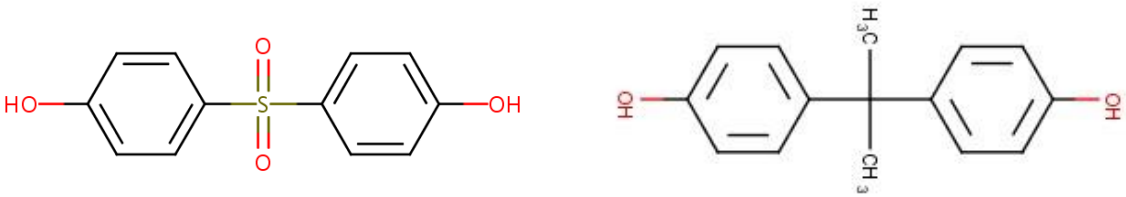

Figure 1. Structural formulas of **bisphenol S (left)** and **bisphenol A (right)** as retrieved from the ECHA dissemination website.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

No human data on reproductive toxicity is included in the CLH dossier.

Animal data

Adverse effects on sexual function and fertility

The potential of bisphenol S to adversely affect sexual function and fertility was investigated in a reproduction/developmental toxicity screening test and an extended-one generation reproductive toxicity study (EOGRTS), including a range-finding study (in the form of a combined repeated-dose toxicity study with the reproduction/developmental screening test) preceding the EOGRTS. Furthermore, relevant parameters related to sexual function and fertility were investigated in three additional repeated-dose toxicity studies with varying duration of exposure. All studies were conducted in rats exposed via the oral route, either via gavage or via diet.

In a 13-day repeated dose toxicity study (no guideline; non-GLP; Anonymous 18, 1973), bisphenol S was administered orally via diet to groups of 5 male rats (strain not specified), dosed at 0, 0.1 and 1% (corresponding to 0, 97 and 810 mg/kg bw/day). No treatment-related mortalities occurred. In the highest dose, toxicity signs included lower terminal body weights, reduced absolute kidney and liver weights, adipose tissue atrophy. Some kidney histopathological effects were also observed.

In a 28-day repeated dose toxicity study (similar to OECD TG 407; GLP; Anonymous 16, 1999), bisphenol S was administered orally via gavage to groups of 6 Sprague/Dawley rats/sex/dose at doses of 0, 40, 200 and 1000 mg/kg bw/day. Furthermore, groups of 6 Sprague/Dawley rats/sex/dose were given doses of 0, 200 and 1000 mg/kg bw/day for 28 days and followed for an additional 2 weeks to observe recovery. Two males in the high-dose group died during treatment. Terminal body weight was decreased in males (m) at the highest dose compared to controls (-20%), but for females (f) the terminal body weight remained unaffected. In the high dose group, weight increases of the liver (m/f; relative to bw), the kidneys (m; relative to bw), the adrenals (m; absolute and relative to bw), and the thymus (absolute to bw (m) and absolute and relative to bw (f)) were observed right after treatment, as well as slight histopathological effects in the cecum (m/f), the liver (m/f), the adrenals (m), the thymus (m/f), and the femur (m/f).

In a 28-day repeated dose toxicity study (similar to OECD TG 407; non-GLP; Anonymous 15, 2017) performed as a range-finding study for the EOGRTS, bisphenol S was administered orally via gavage to groups of 5 Sprague/Dawley rats/sex/dose at doses of 0, 100, 300 and 600 mg/kg bw/day. No treatment-related mortalities occurred. Toxicity at the high dose consisted of salivation (m/f), and slight reductions in terminal body weight (males -12%; females unaffected) as compared to controls. A few weight changes of the kidneys (m/f; relative to bw), adrenals (m; relative to bw), liver (f; relative to bw), prostate, seminal vesicles, and mammary gland (m), and weight decreases of the prostate (relative to bw) and the seminal vesicles (relative to bw), were observed. Some histopathological effects were observed in the kidneys (m), the adrenals (m), the liver (m/f), the cecum (m/f), and the mammary gland (m).

In a 90-day repeated dose toxicity study (OECD TG 408; GLP; Anonymous 17, 2014), bisphenol S was administered orally via gavage to groups of 10 Wistar rats/sex/dose at doses of 0, 100, 300 and 1000 mg/kg bw/day (changed from 1000 to 600 mg/kg bw/day for males after 70 days). No treatment-related mortalities occurred. Toxic effects included changes in faeces appearance and salivation (immediately after dosing, recovery within 30 minutes) in all animals in the mid- and high doses tested (m/f), decreased terminal body weights in the high dose (males -21%; females unaffected), histopathological changes (dilation of the cecum (m), enlarged liver (f), kidney mineralisation (m/f), extramedullary haematopoiesis of the spleen (m/f), uterus dilation), and changes in absolute and/or relative organ weights of several organs (e.g. kidneys, liver, adrenals, spleen, epididymis, testes). Furthermore, males in the mid- and high dose groups showed an increased incidence of multifocal mammary gland atrophy. Females showed an increased incidence of squamous metaplasia in all treated groups compared to controls.

In a reproduction/developmental toxicity screening test (OECD TG 421; GLP; Anonymous 12, 2000), bisphenol S was administered orally via gavage to groups of 12 Sprague/Dawley rats/sex/dose at doses of 0, 10, 60 or 300 mg/kg bw/day for 45 days (m) or 40-46 days (f). No treatment-related mortalities occurred. Parental toxicity at the high dose consisted of salivation right after dosing (m/f), and slight reductions in body weight as compared to controls at several time-points during pre-/post-mating and gestation (m/f) (treatment day 14: f -5%; m -7%). No statistical significance in body weight reduction was reached at any of the other days, apart from gestation day (GD) 20 when body weight of the females was 10% lower than the controls. This was not attributed to maternal toxicity, since no difference compared to controls in body weight was found on lactation day 0. In the high dose males, weight changes of the liver (increased

relative to bw), the pituitary (increased relative to bw), the seminal vesicles (increased absolute weight), as well as slight histopathological changes in the liver and the cecum were observed. Females of the high dose group showed a prolonged mean oestrus cycle (5.57 days at 300 mg/kg bw/day compared to 4.08 days in controls), and an irregular oestrus cycle (5/12 at 300 mg/kg bw/day compared to 0/12 in controls). Most of the females that had a continued dioestrus phase, were not fertilised and consequently the fertilisation index was reduced to 58% (7/12). Furthermore, a decrease in mean number of implantation sites (10.7 compared to 15.9 in controls) and a statistically significantly decreased implantation index of 65% were noted at 300 mg/kg bw/day. Information on the number of pups at birth and the mean number of liveborn pups is summarised in the developmental toxicity section.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422; GLP; Anonymous 14, 2017) performed as a range-finding study for the EOGRTS, bisphenol S was administered orally via gavage to groups of 10 Sprague/Dawley rats/sex/dose at doses of 0, 30, 100 or 300 mg/kg bw/day for 6 weeks of premating period (m/f), 2 weeks of mating period (m/f) and 4 weeks post mating period (m) or continued through gestation and lactation (f). No treatment-related mortalities occurred. Parental toxicity included slightly decreased terminal body weights (-7% (m) and -6% (f)), compared to controls at the high dose, and slight toxicity of the liver (m), the kidney (m), the cecum (m), and the mammary gland (m) at 300 mg/kg bw/day, compared to the control group. An increased number of females showed a prolonged mean oestrus cycle (5.16 days at 300 mg/kg bw/day compared to 4.02 days in controls), an increased absolute uterus terminal weight, and a fertility index of 80%[1] at the highest dose. Furthermore, a statistically significant decrease in mean number of implantation sites was noted in pregnant females at 300 mg/kg bw/day (10.4 compared to 15.8 in controls). Two out of eight females had complete intrauterine litter losses at the highest dose tested. Information on the number of pups at birth, the mean number of liveborn pups, and post-implantation loss is summarised in the developmental toxicity section below.

In an extended-one generation reproductive toxicity study (EOGRTS; OECD TG 443; GLP; Anonymous 13, 2019) with inclusion of cohorts 1A and 1B (with extension of cohort 1B to produce the F2 generation) and cohorts 2A/2B and 3, bisphenol S was administered orally via gavage to groups of 10-24 Sprague/Dawley rats (m/f) at doses of 0, 20, 60 or 180 mg/kg bw/day.

F0 animals

In females, body weights were significantly increased compared to controls at some timepoints (treatment day 7 and 14) at the mid dose (60 mg/kg bw/day), whereas body weights did not differ from controls in males in any of the treated groups. Water- (m/f) and food consumption (f) were significantly increased at 180 mg/kg bw/day. In the high dose males (180 mg/kg bw/day), very slight toxicity was observed in the form of enlarged cecum and changes in kidney weights. A statistically significant reduction in percentage of sperm motility was apparent in males from all treated groups; however, this reduction did not increase with increasing dose (84, 85 and 86% for the 20, 60 and 180 mg/kg bw/day dosed groups compared to 88% in controls). An increased number of females showed a prolonged mean oestrus cycle (4.1 days at 180 mg/kg bw/day compared to 3.9 days in controls), and some females showed an irregular oestrus cycle pattern at 20 and 180 mg/kg bw/day. The mean number of days in the prooestrus, oestrus, metoestrus

[1] Note that this specific effect was initially mentioned to be 60% at the highest dose tested in the CLH dossier and in IUCLID, but during the consultation it was noted that this effect size was incorrect and should be changed into 80% fertility at the highest dose tested. The information in IUCLID was updated to this regard as well (ECHA dissemination website consulted on 18-08-2020). The corrected value has been used in the RAC assessment; see 'Assessment and comparison with the classification criteria'.

and dioestrous stage (data generated during the last 3 weeks prior to mating), changed dose-dependently from 4.7, 5.1, 5.8, and 6.3, respectively, in controls to 2.2, 5.2, 5.9, and 9.0, respectively, in the 180 mg/kg bw/day dosed group. Fertility index was unaffected. A decrease in mean number of implantation sites was also noted in pregnant females at 180 mg/kg bw/day (14.3 compared to 15.3 in controls). Other parameters were unaffected. For information on developmental toxicity, see the developmental toxicity section.

F1 animals

Cohort 1A

Males had slightly decreased mean terminal body weight at 180 mg/kg bw/day compared to controls (-6%, not statistically significant), whereas females from the mid- and high dose groups had increased mean body weights at several timepoints (+7% for both doses at both PND14 and PND28) as well as an increased mean food consumption (+21%) at 180 mg/kg bw/day. In males, but not in females, absolute and/or relative weights of the adrenal glands, kidneys, liver, spleen, thymus, and prostate were statistically significantly altered compared to controls. Furthermore, in the high dose males an increased incidence in atrophy of the mammary gland was observed. Other parameters in treated animals (e.g. sperm parameters, mean oestrus cycle, ovarian follicle count) were unaffected. However, females in the high dosed group showed a prolonged dioestrus stage, as the mean number of days in the proestrus, oestrus, metoestrus, and dioestrus stage, measured during the last 3 weeks prior to mating, changed dose-dependently from 2.2, 3.5, 3.8, and 4.5, respectively, in controls to 1.3, 3.2, 4.1, and 5.4, respectively, at 180 mg/kg bw/day.

Cohort 1B

Terminal body weights for males were slightly lower (-5%) and for females slightly higher (+6%) at the highest dose tested; not statistically significant. In males, absolute and/or relative weights of the adrenals, kidneys, and the liver were statistically significantly altered compared to controls. In females, the absolute (but not relative) weight of the kidneys was statistically significantly altered compared to controls. An increased number of females showed a prolonged mean oestrus cycle (4.1[1] ± 1.51 days at 180 mg/kg bw/day compared to 3.9 ± 0.29 days in controls). Females in the high dose group showed a prolonged dioestrus stage, as the mean number of days in the proestrus, oestrus, metoestrus, and dioestrus stage (data generated during the last 3 weeks prior to mating), changed dose-dependently from 4.7, 5.4, 6.0, and 6.8, respectively, in controls to 1.3, 4.6, 5.9, and 11.2, respectively, at 180 mg/kg bw/day. Furthermore, a decrease in mean number of implantation sites was noted in pregnant females at 180 mg/kg bw/day (13.7 compared to 15.2 in controls). Other parameters were unaffected. For information on developmental toxicity, see the developmental toxicity section below.

Cohort 2A/2B

For information on developmental toxicity, see the developmental toxicity section.

Cohort 3

For information on developmental toxicity, see the developmental toxicity section.

F2 animals

For information on developmental toxicity, see the developmental toxicity section.

[1] This value was originally given as 4.5 in the CLH report, but later changed into 4.1 based on comments received during PC. The corrected value was used in the RAC assessment.

The dossier submitter (DS) noted that the highest dose of the EOGRTS (i.e. 180 mg/kg bw/day) was relatively low compared to the highest doses of the two reproductive/developmental screening test (i.e. 300 mg/kg bw/day), and that hardly any general toxicity was seen in the animals of the EOGRTS, including the high dose group. However, at the high dose some slight effects on reproductive parameters were observed, which, if the high dose selected would have been higher would have been more pronounced, according to the DS.

Conclusion by the DS

Based on treatment-related adverse effects on fertility, reproduction and pregnancy outcome (i.e. decreased number of implantation sites and prolonged oestrus cycle) in three different studies in animals, seen together with only limited general toxicity, the DS concluded that bisphenol S meets the criteria for classification for adverse effects on sexual function and fertility as Repr. 1B; H360F.

Adverse effects on development

The potential of bisphenol S to adversely affect development was investigated in a prenatal developmental toxicity study, a reproduction/developmental screening test, an EOGRTS, and a range-finding study (in the form of a combined repeated-dose toxicity study with the reproduction/developmental screening test) preceding the EOGRTS. All studies were conducted in rats exposed via oral gavage.

In a prenatal developmental toxicity study (OECD TG 414; GLP; Anonymous 19, 2014), bisphenol S was administered orally via gavage to groups of 25 pregnant female Wistar rats/dose at doses of 0, 30, 100 or 300 mg/kg bw/day for 14 days during GD 6 to 19. No treatment-related mortalities occurred. No absolute changes in body weights were noted between groups at any timepoint. There was no effect on mean percentage post-implantation loss (4.7, 3.9, 3.9, and 6.3% at 0, 30, 100 and 300 mg/kg bw/day, respectively) or other parameters. In the offspring there were no effects on body weights, sex ratio, or mean number of live foetuses. No relevant abnormalities were observed regarding external, soft tissue or skeletal malformations or variations.

In a reproduction/developmental toxicity screening test (OECD TG 421; GLP; Anonymous 12, 2000), bisphenol S was administered orally via gavage to groups of 12 Sprague/Dawley rats/sex/dose at doses of 0, 10, 60 or 300 mg/kg bw/day for 45 days (males) or 40-46 days (females). No treatment-related mortalities occurred. Parental toxicity at the high dose consisted of salivation right after dosing (m/f), slight reductions in body weight as compared to controls at several timepoints during pre-/post-mating and gestation (m/f) (treatment day 14: females -5%; males -7%; no statistical significance was reached at any of the other days, apart from GD 20 when body weight of the females was 10% lower than the controls; this was not attributed to maternal toxicity, since no difference was found on body weight on Lactation day 0). In the high dose males, weight changes of the liver (increased relative to bw), the pituitary (increased relative to bw), the seminal vesicles (increased absolute weight), as well as slight histopathological changes in the liver and the cecum were observed. The mean number of pups at birth (9.1 compared to 14.3 in controls), the mean number of liveborn pups at birth (9.1 compared to 14.2 in controls) and the mean number of live offspring at PND4 (9.1 compared to 14.1 in controls) was lower at 300 mg/kg bw/day. The offspring in the treated groups did not show any deviations from controls based on external appearance and clinical signs, body weight changes, viability index or anogenital distance.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422; GLP; Anonymous 14, 2017) performed as a range-finding study for the EOGRTS, bisphenol S was administered orally via gavage to groups of 10 Sprague/Dawley rats/sex/dose at concentrations of 0, 30, 100 or 300 mg/kg bw/day for 6 weeks of premating

period (m/f), 2 weeks of mating period (m/f) and 4 weeks post mating period (m) or continued through gestation and lactation (f). No treatment-related mortalities occurred. Parental toxicity included slightly decreased terminal body weights (-7% and -6% for males and females respectively, compared to controls) at the high dose, and slight toxicity of the liver (m), the kidney (m), the cecum (m), and the mammary gland (m) at 300 mg/kg bw/day compared to the control group. The total number of pups delivered was reduced and the mean number of pups delivered was statistically lower. The post-implantation loss in the high dose group was statistically significantly increased (34.6% and 3.6% for the animals in the high dose and control group, respectively). In the offspring, the mean number of pups delivered was significantly decreased (10.8 and 15.2 for the animals in the high dose and control group, respectively). Other parameters were unaffected. Information regarding fertility is summarised in the fertility section above.

In an extended-one generation reproductive toxicity study (OECD TG 443; GLP; Anonymous 13, 2019) with inclusion of cohorts 1A and 1B (with extension of cohort 1B to produce the F2 generation) and cohorts 2A/2B and 3, bisphenol S was administered orally via gavage to groups of 10-24 Sprague/Dawley rats (m/f) at concentrations of 0, 20, 60 or 180 mg/kg bw/day.

F0 animals

In females, body weights were significantly increased compared to controls at some timepoints (treatment day 7 and 14) at the mid dose (60 mg/kg bw/day), whereas body weights did not differ from controls in males from all treated groups. Water- (m/f) and food consumption (f) were significantly increased at 180 mg/kg bw/day. In the high-dose males (180 mg/kg bw/day), very slight toxicity was observed in the form of enlarged cecum and changes in kidney weights. The mean number of post-implantation loss in high dose group and the mid dose group was significantly increased (1.5 and 1.3 pups/dam, respectively, compared to 0.5 pups/dam in controls) and the mean percentage post-implantation loss was 3.1, 5.9, 9.4*, and 10.5**% at 0, 20, 60 and 180 mg/kg bw/day, respectively. Litter size showed a non-statistically decreased trend (14.9, 14.0, 13.5, and 12.7 at 0, 20, 60 and 180 mg/kg bw/day, respectively). Other parameters were unaffected. Information regarding fertility is summarised in the fertility section above.

F1 animals

The total number of pups delivered was 342, 294, 325, and 293 at 0, 20, 60, and 180 mg/kg bw/day, respectively. There were statistically significant changes in the total number of live pups (285 live pups at 180 mg/kg bw/day compared to 340, 289, 322 at 0, 20, and 60 mg/kg bw/day, respectively) and the number of stillborn pups (8 stillborn pups at 180 mg/kg bw/day compared to 2, 5 and 3 at 0, 20, and 60 mg/kg bw/day, respectively). Furthermore, the mean body weight in F1 pups at PND1 (+9%) and PND4 (+10%) was statistically significantly increased compared to controls at the mid- and high dose tested, and stayed pronounced until PND21 in the mid-dose group. T4 levels were unchanged in both sexes, but TSH was decreased in females in all treated groups at PND4 (range of -15 to -5%; reaching statistical significance at 20 and 180 mg/kg bw/day only), but not at PND22. Changes in TSH were not apparent in males.

Cohort 1A

Males had a slightly decreased mean terminal body weight at 180 mg/kg bw/day compared to controls (-6%, not statistically significant), whereas females from the mid- and high dose tested had an increased mean body weight at several timepoints (+7% for both doses at both PND14 and PND28) as well as an increased mean food consumption (+21%) at 180 mg/kg bw/day. In males, but not in females, absolute and/or relative weights of the adrenal glands, kidneys, liver, spleen, thymus, and prostate were statistically significantly altered from controls. Furthermore, in the high dose males an increased incidence in atrophy of the mammary gland was observed.

Other parameters (e.g. thyroid hormones) were unaffected. Information regarding fertility is summarised in the fertility section above.

Cohort 1B

Terminal body weights for males were slightly lower (-5%) and for females slightly higher (+6%) at the highest dose tested (not statistically significant). In males, absolute and/or relative weights of the adrenals, kidneys, and the liver were statistically significantly altered from controls. In females, the absolute (but not relative) weight of the kidneys was statistically significantly altered from controls. At 180 mg/kg bw/day, the mean number of post-implantation loss in this group was significantly increased (3.3 compared to 0.9, 0.8 and 1.1 at 0, 20 and 60 mg/kg bw/day, respectively). The mean percentage implantation loss was 6.4, 5.3, 11.1* and 24.6**% at 0, 20, 60 and 180 mg/kg bw/day, respectively. Consequently, litter size for the F2 generation was statistically significantly affected at the highest dose group (11.4 at 180 mg/kg bw/day compared to 14.3, 13.8 and 14.9 at 0, 20 and 60 mg/kg bw/day, respectively). Other parameters were unaffected. Information regarding fertility is summarised in the fertility section above.

Cohort 2A/2B

There was trend in increased body weights in males (from PND 21 onwards) and females (from PND 0 onwards). There were some effects observed regarding brain morphometry in the 180 mg/kg bw/day dosed group in cohort 2A. Statistically significant results were noted on the left nucleus caudatus width in males (10% reduced) and females (9% increased). Moreover, the corpus callosum width was statistically significantly reduced (-17%) in males at this dose. All other parameters were unaffected.

Cohort 3

Clinical signs, and food intake were unaffected. In females, body weights were statistically significantly increased at PND14 and PND28 in the high dose group. Also in males a non-statistically significantly trend in increased bw was observed at 60 and 180 mg/kg bw/day at PND14, and at all treated dose-groups at PND28. Relative thymus weight, but not absolute thymus weight, was significantly decreased in males at the highest dose compared to controls (-19%). Furthermore, in the females of the low- and mid dose, there was a slight decrease in T-cell dependent antibody response to sheep red blood cells (SRBC) compared to controls (13647 ± 12787, 8239 ± 5678, 9598 ± 8936, and 14555 ± 11711 U/mL at 0, 20, 60, and 180 mg/kg bw/day respectively).

F2 animals

The total number of pups delivered was 342, 332, 313, and 240 at 0, 20, 60 and 180 mg/kg bw/day, respectively. Furthermore, the number of liveborn pups was decreased (although not reaching statistical significance) to 234 at 180 mg/kg bw/day compared to 336, 330 and 311 at 0, 20 and 60 mg/kg bw/day, respectively. No effect was seen on the number of stillborn pups. The mean number of pups delivered was statistically significantly reduced at the highest dose tested (14.3, 13.8, 14.9, and 11.4 at 0, 20, 60, and 180 mg/kg bw/day, respectively). There was a trend in increased bw of the pups, reaching statistical significance in female pups (+7%) at PND1. Other parameters (e.g. sex ratio, anogenital distance) were unaffected.

The DS noted that the highest dose of the EOGRTS (i.e. 180 mg/kg bw/day) was relatively low compared to the highest doses of the two reproductive/developmental screening studies (i.e. 300 mg/kg bw/day), and that hardly any general toxicity was seen in the animals of the EOGRTS including the top dose group. However, at the high dose some slight effects on developmental parameters were observed, which, if the top dose selected would have been higher would have been more pronounced, according to the DS.

Conclusion by DS

Based on treatment-related adverse effects on development (i.e. post-implantation loss) in three different studies in animals, seen together with only minimal general toxicity, the DS concluded that bisphenol S meets the criteria for classification for adverse effects on development in the category Repr. 1B; H360D.

Consequently, the DS concluded that a combined entry as Repr. 1B; H360FD is warranted.

Adverse effects on or via lactation

No information available. Consequently, no proposal for classification due to lack of data.

Comments received during consultation

Ten comments from seven commenting parties were received during the consultation: three Member State Competent Authorities (MSCAs), one Company-Manufacturer, two NGOs and one Academic Institution. The comments received from the MSCAs were all in agreement with the proposal for harmonised classification as Repr. 1B; H360FD. One MSCA noted that there were adverse effects on the weight of reproductive organs in males in several studies and atrophy of the mammary gland, which have no implications for reproductive performance in itself, but may provide an indication of hormonal disturbance, together with the increased pituitary weight observed in one of the reproductive/developmental screening studies. Furthermore, this MSCA provided several additional studies obtained from the public literature.

One NGO agreed with the proposal for harmonised classification as Repr. 1B; H360FD and noted that besides harmonised classification for reproduction, also harmonised classification for acute toxicity (adverse effects on the heart) should be scrutinised and also identification as an endocrine disruptor may be warranted. Another NGO also agreed with the proposal for Repr. 1B; H360FD and provided two additional studies obtained from the public literature.

Also a representative of an Academic Institution agreed with the proposal for harmonised classification as Repr. 1B; H360FD. This respondent also provided an additional study obtained from the public literature.

One Company-Manufacturer did not agree with the proposal for harmonised classification as Repr. 1B; H360FD. They provided comments in which specific elements were brought forward, noting incorrect information in the CLH dossier and placing certain adverse effects in the context of historical control data. They concluded that the EOGRTS should be seen as the most relevant and conclusive study to assess reproductive and developmental effects of bisphenol S, and that some of the information in this study, in their view, could be useful for classification and labelling of the substance. According to the Company-Manufacturer, safe use of the substance is however safeguarded as the EOGRTS provides a NOAEL for DNEL derivation, which will be included after an update of the REACH registration dossier.

All comments as well as the responses by the DS and RAC are compiled in the RCOM in Annex 2 to the RAC Opinion.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

In line with the DS, RAC places most weight on the guideline studies in the assessment of the reproductive effects of bisphenol S.

Mean number of implantation sites

The mean number of implantation sites was affected in three different guideline studies (OECD TG 421, OECD TG 443, OECD TG 422) from 180 mg/kg bw/day onwards, with increasing severity at 300 mg/kg bw/day (see table below). Considering the size of the effect and the consistency of the effect among studies, RAC considers this effect as relevant for classification for sexual function and fertility.

Table: *Mean number of implantation sites per dam*

Dose level (mg/kg bw/day)	0	10	20	30	60	100	180	300
OECD TG 421	15.9	13.3	-	-	14.8	-	-	10.7
OECD TG 443 F0 F1B	 15.3 15.2	 - -	 14.8 14.6	 - -	 14.9 15.4	 - -	 14.3 13.7	 - -
OECD TG 422	15.8	-	-	15.0	-	15.5	-	10.4**
HCD (mean; range): 15.2 (12.3-17.8)[a] HCD (mean; range): 15.0 (13.8-16.0)[b] HCD (mean; range): 14.1 (12.1-15.3)[c]								

[a] Historical control data (Charles River Ashland, Crl:CD(SD), OECD 412/422/443, 89/91 studies in a time period from 12/2000 to 08/2018)

[b] Historical control data (Janvier or Charles River France, RjHan:SD (Rats CD®), two-generation studies F0, time period 02/2016 to 04/2020)

[c] Historical control data (Janvier or Charles River France, RjHan:SD (Rats CD®), two-generation studies F1, time period 02/2016 to 04/2020)

Fertility index

Both the OECD TG 421 and 422 studies show a dose-dependent decrease in fertility index at 300 mg/kg bw/day (see table below). In the OECD TG 421 study, most of the females at 300 mg/kg bw/day, which had a continued dioestrus phase, were not fertilised. In the OECD TG 422 study, there were two females without implantation sites at 300 mg/kg bw/day. Considering the severity, RAC considers these effects relevant for classification.

Table: *Fertility index*

Dose level (mg/kg bw/day)	0	10	20	30	60	100	180	300
OECD TG 421	91.7%	91.7%	-	-	100%	-	-	58%
OECD TG 443 F0 F1B	 100% 100%	 - -	 100% 100%	 - -	 100% 100%	 - -	 100% 100%	 - -
OECD TG 422	100%	-	-	90%	-	100%	-	80%[1]

Disturbed and prolonged oestrus cycle

The oestrus cycle was prolonged in female rats in several studies (OECD TG 421; OECD TG 443; OECD TG 422) (see table below). Furthermore, results from the OECD TG 443 illustrated that females in the F0, F1A and F1B cohorts tended to be in the diestrus stage for a longer period and

[1] Note that this specific effect was initially mentioned to be 60% at the highest dose tested in the CLH dossier and on IUCLID, but during the consultation it was noted that this effect size was incorrect and should be changed into 80% fertility at the highest dose tested. The information in IUCLID was updated to this regard as well (ECHA dissemination website consulted on 18-08-2020). The RAC rapporteur was unable to verify the exact number as it had no access to the underlying study report. However, RAC wants to highlight that, either way, a dose-dependent decrease in fertility index is observed in this study.

in the proestrus stage for a shorter period in all treated dose-groups (>20 mg/kg bw/day) compared to controls (see table below).

In the OECD TG 421 study, the incidence of females with an irregular oestrus cycle was 0/12, 0/12, 1/12, and 5/12 at 0, 10, 60 and 300 mg/kg bw/day, respectively. Four out of five females in the highest dose group, which had a continued dioestrus phase, did not conceive at all and consequently this led to a steep decrease of the fertilisation index of 58%.

The biological relevance and adversity of the effects on the oestrus cycle, in the presence of indications of decreased fertility parameters (i.e. decreased mean number of implantation sites, decreased fertility index) is apparent. Taking this and the consistency of the effect among studies into account, RAC considers the effects on the oestrus cycle as relevant for classification.

Table: *Mean duration of the oestrus cycle in days*

Dose level (mg/kg bw/day)	0	10	20	30	60	100	180	300
OECD TG 421	4.08	4.01	-	-	4.14	-	-	5.57**
OECD TG 443 F0 F1A F1B	 3.9 4.1 3.9	 - - -	 3.9 4.1 4.0	 - - -	 3.9 4.1 4.0	 - - -	 4.1* 4.1 4.1[1]	 - - -
OECD TG 422	4.02	-	-	3.97	-	4.01	-	5.16**
HCD (mean; range): 4.2 (3.9-5.2)[a] HCD (mean; range): 4.9 (4.0-5.8)[b] HCD (mean; range): 4.5 (4.4-4.9)[c]								

[a] Historical control data (Charles River Ashland, Crl:CD(SD), OECD 412/422/443, 89/91 studies in a time period from 12/2000 to 08/2018)

[b] Historical control data (Janvier or Charles River France, RjHan:SD (Rats CD®), two-generation studies F0, time period 02/2016 to 04/2020)

[c] Historical control data (Janvier or Charles River France, RjHan:SD (Rats CD®), two-generation studies F1, time period 02/2016 to 04/2020)

Table*: Mean number of days in the proestrus, oestrus, metoestrus and dioestrus stage of the oestrus cycle for females in the OECD TG 443, measured during the last 3 weeks prior to mating.*

Dose level (mg/kg bw/day)		0	20	60	180
F0	prooestrus	4.7	3.5	3.8	2.2
	oestrus	5.1	5.1	5.0	5.2
	metoestrus	5.8	6.0	5.8	5.9
	dioestrus	6.3	7.4	7.7	9.0
F1A	prooestrus	2.2	2.0	2.2	1.3
	oestrus	3.5	3.6	3.5	3.2
	metoestrus	3.8	3.9	3.6	4.1
	dioestrus	4.5	4.6	4.8	5.4
F1B	prooestrus	4.7	2.8	2.2	1.3
	oestrus	5.4	5.2	5.4	4.6
	metoestrus	6.0	6.0	6.3	5.9
	dioestrus	6.8	8.4	9.2	11.2

<u>General toxicity</u>

The results from the repeated dose studies indicate that dosing with 600 to 1000 mg/kg bw/day for 28-90 days results in body weight changes in males (but not in females), as well as liver

[1] Note that this specific effect was initially mentioned to be 4.5 days at the highest dose tested in the CLH dossier and on IUCLID, but during the PC was noted that this effect size was incorrect and should be changed into 4.1 days. The information in IUCLID was updated to this regard as well (ECHA dissemination website consulted on 09-09-2020).

toxicity, kidney toxicity, and other systemic effects in both sexes. In the OECD TG 421/422 studies, adverse effects on sexual function and fertility were observed at the top dose of 300 mg/kg bw/day, and at this dose level only very slight to no general toxicity was observed. The results from the 90-day repeated dose toxicity study indicate that females tolerate doses up to 1000 mg/kg bw/day without marked general toxicity. In view of that, RAC is of the opinion that the effects observed on sexual function and fertility at 180 and 300 mg/kg bw/day are not due to general toxicity.

Comparison with the criteria

Bisphenol S was shown to consistently and severely disturb reproductive parameters. Overall, RAC observes the following:

a) Exposure to bisphenol S consistently resulted in a decrease in mean number of implantation sites at 300 mg/kg bw/day;
b) Exposure to bisphenol S consistently resulted in a prolongation of the oestrus cycle at 300 mg/kg bw/day, as well as in an irregular oestrus cycle with a decreased pro-oestrus stage and an increased dioestrus phase from 20 mg/kg bw/day onwards;
c) Exposure to bisphenol S resulted in a decrease in the fertility index of 58% and 80% at 300 mg/kg bw/day.

RAC concludes that the adverse effects of bisphenol S on the mean number of implantation sites, the decrease in fertility index, and the effect on the oestrus cycle warrant **classification as Repr. 1B; H360F.**

RAC would like to emphasis that the dosing regimen in the guideline studies is also taken into account in the overall weight of evidence assessment for classification.

The top dose of 180 mg/kg bw/day, used in the EOGRTS, is not supported by adequate argumentation, and its correctness is questionable, especially in light of the effects seen in repeated dose studies where doses up to 1000 mg/kg bw did not exert severe toxicity in females, while 600 mg/kg bw/day did result in clear but not in severe toxicity in males.

Adverse effects on development

In the OECD TG 414, hardly any statistically significant effects were observed, either in foetuses or maternal animals. RAC notes that the dose levels were comparable to the reproductive screening studies, where slight effects were seen in the top dose. In the OECD TG 414, the following is stated:

"Unless limited by the physical/chemical nature or biological properties of the test substance, the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering. At least one intermediate dose level should produce minimal observable toxic effects."

The absence of effects in the TG 414 study is likely due to the shorter exposure duration and/or due to the different strain of rats used. RAC notes that considering the limited toxicity in the developmental study, this study is not fully in line with the prevailing guideline and is as such of limited relevance for the assessment of adverse effects on development.

<u>Increased post-implantation loss</u>

Three studies evaluated the post-implantation loss of offspring upon exposure to bisphenol S (see table below). In the OECD TG 422 study and the OECD TG 443 study (both cohorts), the mean number of post-implantation loss was statistically significantly increased from controls. This effect was apparent from 180 mg/kg bw/day onwards.

The DS noted that the post-implantation loss was increased by treatment and cannot be explained by maternal toxicity as the general condition of the animals was unaffected by treatment. Based on this, the DS concluded that the post-implantation loss was a clear adverse effect on development, that cannot be related to general toxicity, and observed in two studies.

Nitzsche *et al*. (2017) shows that post-implantation loss is, in general, not considered to be a secondary developmental effect resulting from non-specific maternal toxicity. Furthermore, there was no marked systemic toxicity observed at the doses at which these developmental effects were observed. Therefore, RAC agrees with the DS in this respect, and concludes that the consistently observed, severe effect on post-implantation loss justifies classification.

Table: *Mean percentage of post-implantation loss*

Dose level (mg/kg bw/day)	0	10	20	30	60	100	180	300
OECD TG 421	NA	NA	-	-	NA	-	-	NA
OECD TG 443 F0 F1B	 3.1 6.4	 - -	 5.9 5.3	 - -	 9.4* 11.1	 - -	 10.5** 24.6**	 - -
OECD TG 422	3.6	-	-	5.2	-	6.5	-	34.6*
OECD TG 414	4.7	-	-	3.9	-	3.9	-	6.3
HCD (mean; range): 7.1 (4.7-12.0)[b]								

[a] Charles River Ashland, Crl:CD(SD), OECD 412/422/443, 89/91 studies in a time period from 12/2000 to 08/2018
[b] BASF, Wistar, OECD TG 414

Number of pups delivered

The mean number of pups delivered/mean number of live foetuses was evaluated in four studies. In three of those (the OECD TG 421, OECD TG 443, and the OECD TG 422), there was a dose-dependent decrease in the mean number of pups delivered (see table below). RAC considers this effect to be a direct consequence of the exposure to the substance but notes that it is difficult to discriminate whether this is due to fertility or developmental effects.

Table*: Mean number of pups delivered*

Dose level (mg/kg bw/day)	0	10	20	30	60	100	180	300
OECD TG 421	14.3	12.5		-	13.5	-	-	9.1
OECD TG 443 F1 F2	 14.9 14.3	 - -	 14.0 13.8	 - -	 13.5 14.9	 - -	 12.7 11.4**	 - -
OECD TG 422	15.2	-	-	14.1	-	14.5	-	10.8**
OECD TG 414[a]	10.6	-	-	10.6	-	10.6	-	10.1
HCD (mean; range): 14.3 (12.1-15.9)[b]								

[a] Mean number of live foetuses
[b] Charles River Ashland, Crl:CD(SD), OECD 412/422/443, 89/91 studies in a time period from 12/2000 to 08/2018

Increased body weight in pups

Male and female pups consistently showed an increase in body weights from PND0 onwards (see table below) in the OECD TG 421 and OECD TG 443 studies; up to +14% and +18% at 300 mg/kg bw/day on PND4 in females and males respectively.

The DS did not consider these effects for classification. RAC considers this consistent increase in body weights of the pups insufficient for classification on its own, but it contributes to the overall concern for effects on the developing organism and might be indicative of an endocrine mode of action.

***Table**: Change in body weight of pups (in grams (%))*

Dose level (mg/kg bw/day)	0	10	20	60	180	300
Females						
	PND0					
OECD 421	6.9	7.0 (+1%)	-	6.9 (+0%)	-	7.3 (+6%)
	PND1					
OECD 443 F1 F2	 6.7 7.2	 - -	 7.0 (+4%) 7.0 (-3%	 7.2* (+7%) 7.0 (-3%)	 7.3* (+9%) 7.7* (+7%)	 - -
	PND4					
OECD 421	11.7	11.7 (+0%)	-	11.5 (-2%)	-	13.3 (+14%)
OECD 443 F1 F2	 9.9 10.9	 - -	 10.3 (+4%) 10.5 (-4%)	 10.9* (+10%) 10.5 (-4%)	 10.9* (+10%) 11.8 (+8%)	 - -
	PND21					
OECD 443 F1 F2	 52.0 56.9	 - -	 54.3 (+4%) 56.2 (-1%)	 54.8* (+5%) 56.5 (-1%)	 53.7 (+3%) 58.3 (+2%)	 - -
Males						
	PND0					
OECD 421	7.4	7.5 (+1%)	-	7.3 (-1%)	-	7.8 (+5%)
	PND1					
OECD 443 F1 F2	 7.1 7.5	 - -	 7.4 (+4%) 7.5 (+0%)	 7.7* (+8%) 7.4 (-1%)	 7.7 (+8%) 8.0 (+7%)	 - -
	PND4					
OECD 421	12.0	12.4 (+3%)	-	12.1 (+1%)	-	14.1 (+18%)
OECD 443 F1 F2	 10.5 ND	 - -	 10.9 (+4%) ND	 11.5* (+10%) ND	 11.4* (+9%) ND	 - -
	PND21					
OECD 443 F1 F2	 54.0 59.1	 - -	 56.8 (+5%) 58.9 (+0%)	 57.8* (+7%) 58.6 (-1%)	 55.7 (+3%) 61.1 (+3%)	 - -

Specific neuro- and immuno-developmental effects

In cohort 2A and 3 of the OECD TG 443, there were some effects observed regarding brain morphometry and immune effects:

- statistically significant alteration in left nucleus caudatus width in males (10% reduced) and females (9% increased) at 180 mg/kg bw/day;
- reduction in the corpus callosum width in males (17% reduced) at 180 mg/kg bw/day;
- decrease in relative thymus weight in males (-19%) at 180 mg/kg bw/day;
- decrease T-cell dependent antibody response to sheep red blood cells (SRBC) in females at 20 and 60 mg/kg bw/day

Although marginal, some effects on specific neuro- and immune developmental effects were noted in the OECD TG 443 study. The DS did not consider these effects for classification. As with

the increase in body weights of the pups, RAC considers these effects insufficient for classification on their own, but they contribute to the overall concern for effects on the developing organism.

Increased incomplete ossification

In the OECD TG 414 study, there were some effects on skeletal development observed at the highest dose tested (see table below). Although several of these effects were not outside the historical control range, it is noted that for some showed a dose-related trend. Especially the unossified sternebra was statistically significantly increased compared to controls in the high dose group.

According to the DevTox database[1], dumbbell ossification of the thoracic centrum and unossified sternebra are considered grey zone skeletal anomalies, and incomplete ossification of the pubis, incomplete ossification of supraoccipital, and incomplete ossification of the ischium are considered skeletal variations.

The DS did not consider these effects for classification. RAC notes that usually skeletal ossification is an effect indicative of decreased growth, not sufficiently severe for classification in itself. Although, considering the observation that this study is not in line with the prevailing guideline (no toxicity observed in any of the groups) and as such of minor relevance for the assessment of the developmental toxicity, the statistically significant effects are noteworthy. Especially since none of the effects observed in the pups could be attributed to reduced growth.

***Table**: Incidence of significant increased foetal skeletal variations (mean percentage of affected foetus/litter)*

Dose level (mg/kg bw/day)	0	30	100	300	HCD mean % (range)
Incomplete ossification of supraoccipital (unchanged cartilage)	34.1	35.2	37.6	45.2*	43.5 (10.3 – 64.3)
Dumbbell ossification of thoracic centrum (unchanged cartilage)	0.7	3.0	0.0	5.6**	6.9 (0.0 – 14.5)
Unossified sternebra (unchanged cartilage)	1.5	5.0	4.6	11.0**	8.2 (2.6 – 20.7)
Incomplete ossification of pubis (cartilage present)	0.0	0.8	2.0*	1.7	0.3 (0.0 – 2.4)
Incomplete ossification of ischium (cartilage present)	0.0	0.0	2.0*	1.7	0.2 (0.0 – 0.8)

Comparison with the criteria

The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects.

Overall, RAC observes the following:

a. Post-implantation loss was increased in two studies, from 60 mg/kg bw/day onwards. Furthermore, a decrease in the mean number of pups delivered per dam was consistently observed in three studies from 180 mg/kg bw/day onwards. This effect is a result of both increased implantation loss and post-implantation loss.
b. A consistent pattern of increased pup weight was observed in both sexes (up to 14/18% in f/m at 300 mg/kg bw/day), that is attributed to gestational bisphenol S exposure.

[1] https://www.devtox.org/nomenclature/ml_organ.php?lan=en

c. And although marginal, some specific neuro- and immuno-developmental effects were noted in the OECD TG 443 study. RAC considers these effects insufficient for classification as Repr. 1B; H360D on their own, but they contribute to the overall concern for effects on the developing organism and therefore also contribute to the weight-of-evidence in support of this classification. For considerations regarding the dose selection, see Adverse effects on sexual function and fertility

RAC concludes that the adverse effect of bisphenol S on the post-implantation loss and the mean number of pups delivered per dam warrant **classification as Repr. 1B; H360D.** The effects observed are severe and are not resulting from maternal toxicity.

RAC notes the difficulty in determining whether the effect on the mean number of pups delivered per dam is related to fertility or development. However, the significant increase in post-implantation loss in two studies is a consistent and severe finding, which increased with treatment. The CLP Regulation states that classification in Category 2 is appropriate when "*there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1*". RAC considers that the evidence for bisphenol S on post-implantation loss is a clear effect on development, and therefore does not consider classification in Category 2 appropriate.

Adverse effects on or via lactation

No information was available. As a consequence, RAC proposes **no classification for lactation due to lack of data**.

Overall, RAC concludes that **bisphenol S warrants classification as Repr. 1B; H360FD**

Additional references

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ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).