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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters, CAS No 68515-40-2 (EC No 271-082-5)

Addressees: Registrant(s)[1] of 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters (Registrant(s))

This decision is addressed to the Registrant(s) of the above substance with active registration pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided as an Annex to this decision. This annex is confidential and not included in the public version of this decision.

Based on an evaluation by the Danish Environmental Protection Agency (Danish EPA) as the Competent Authority of Denmark (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 5 May 2015, i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Denmark has initiated substance evaluation for **1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters**, CAS No 68515-40-2 (EC No 271-082-5) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to Human health/suspected CMR (toxicity to reproduction); Exposure/Lack of exposure assessment, lack of RCR, high (aggregated tonnage), 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters, hereafter refered to as the registered substance, was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of Denmark was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified additional concern regarding possible endocrine disrupting properties. On this basis it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 25 March 2015.

On 5 May 2015 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrants' commenting phase

By 11 June 2015 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay. The evaluating MSCA considered the comments received from the Registrant(s) and on basis of this information, Section II and III of the draft decision were amended. The originally requested modified OECD TG 421 and the 90-day repeated dose toxicity study (OECD TG 408) was replaced with a modified version of the OECD TG 422 test.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 19 January 2017 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days. Subsequently, two Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 24 February 2017 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment and amended the draft decision accordingly. The originally requested pre-natal developmental toxicity study in a second species (OECD TG 414) was removed from the draft decision. The evaluating MSCA will reconsider whether this study needs to be requested in the follow-up evaluation, after the results from the requested modified OECD TG 422 study become available.

Referral to the Member State Committee

On 6 March 2017 ECHA referred the draft decision to the Member State Committee.

On 27 March 2017 the Registrant(s) provided comments on the proposed amendments.
A unanimous agreement of the Member State Committee on the draft decision was reached on 10 April 2017 in a written procedure launched on 30 March 2017.

ECHA took the decision pursuant to Article 51(6) and Article 52(2) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods and instructions (in accordance with Article 13(3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. Modified Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in rats, oral route. The study shall follow the test method described in the OECD TG 422, with the following modifications:

- The highest dose level should be chosen with the aim of inducing toxic effects but not death nor obvious suffering. Thereafter, a descending sequence of dose levels should be selected with a view to demonstrating any dosage related response and no adverse effects at the lowest dose level. Two- to four-fold intervals are frequently optimum and addition of a fourth test group is often preferable to using very large intervals (e.g. more than a factor of 10) between dosages. It is considered that doses similar to those used in the available non-guideline one-generation reproductive and developmental toxicity study (i.e. 0, 50, 250 and 500 mg/kg/day corresponding to 0, 750, 3750 and 7500 ppm) could be appropriate;
- Inclusion of 20 male and female animals per dose group;
- All parental males and females must be evaluated for haematology, clinical chemistry, and gross and microscopic pathology, including pathology investigations of additional tissues and organs that are required in the Sub-chronic (90-day) toxicity study (EU B.26, OECD TG 408);
- Dosing of parental males should be prolonged to not less than 70 days (70-77 days). Semen parameters should be investigated, including motility, morphology and sperm count;
- As default in the OECD TG 422 guideline, the pups are terminated on PND 13. However, the study may be extended to PND 21 if the Registrant(s) find the weighing of a number of organs in pups too challenging at PND 13. However, in such case dosing of pups shall also be continued to PND 21;
- Nipple retention shall be measured as quatitative count of retained nipples/areolae in males, and all suggested measured effects on thyroid hormone levels of males, dams and pups shall be included (T4 at PND 4 and 13 or 21 in pups, at PND 13 or 21 in dams and at termination in males);
- In pups, weight at sacrifice (PD 13 or 21): testis, epididymis, seminal vesicle (with dorsolateral prostate), ventral prostate, levator ani/bulbocavernosus muscle (LABC), bulbourethral glands.

The evaluating MSCA must have access to the full study report from the requested study including all relevant details of the study. Access to such detailed test report information is necessary to ensure that a clear conclusion regarding the result of the study can be drawn.

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **26 February 2019** an update of the registration(s) containing the information required by this decision[2], including robust study summaries, an update of the Chemical Safety Report, and the full study report.

III. Statement of reasons

The concern(s) identified

The initial concern triggering substance evaluation of the registered substance was based on the harmonised classification as Repr. 1B for developmental effects and Repr. 2 for effects on fertility of the structurally related substance 1,2-Benzenedicarboxylic acid, di-C7-11 branched and linear alkyl esters, EC no 271-084-6, CAS no 68515-42-4 (C7-11P).

The classification was agreed by the technical committee on classification and labelling (TC CL) under the dangerous substance directive (67/548/EC) in 2002. The TC CL concluded that C7-11P induced selective foetal effects (postimplantation loss and high malformation rate and variation rate), depending on the type and extent of branching of the substance, warranting a classification corresponding to Repr. cat 1B for developmental toxicity. The TC CL further concluded that branched C7-11P may cause testicular damage and thus may impair fertility and attributed a classification corresponding to Repr. cat 2 for toxicity to fertility. The registered substance under evaluation contains constituents with the same phthalate chain lengths (i.e. C7-9) as the classified substance C7-11P, and there is a concern that these constituents may cause the adverse effects on reproduction (development and fertility) seen with C7-11P, and thus a concern that the registered substance may have comparable effects.

As explained in more details in separate sections below, the initial concern regarding developmental effects related to male sexual development, as well as the concern for fertility is retained due to adverse effects on male reproductive development observed in a non-guideline one-generation reproductive and developmental toxicity study and adverse effects on sperm parameters seen in both F0 and F1 generation males in a two-generation reproductive toxicity study.

An additional concern for potential endocrine disrupting mode of action was identified, based on the adverse effects on male reproductive development in the non-guideline one-generation reproductive and developmental toxicity study. Furthermore, metabolism of phthalates in humans normally consist of phase I hydrolysis of the diester phthalate into the primary metabolite monoester phthalate (e.g. Frederiksen *et al.* 2007). Based on this well known general pattern of phthalate metabolism the registered substance is expected to have common metabolites (monoisononyl phthalate and monobenzyl pthtalate) with the anti-androgenic phthalates DINP and BBP. Finally, a concern for thyroid disrupting mode of action is identified based on information from structural similar phthalates with backbone lengths of C6-C8 (see section on *endocrine disrupting mode of action* for more details).

The registered substance under evaluation is a high production volume substance produced in tonnage between 10,000 and 100,000 tpa. It is used mainly for coatings in industrial settings, by professional workers and in consumer products.

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

Exposure to the substance can occur to workers e.g. via industrial and non-industrial sprayinig and roller application or brushing wereas consumers can be exposed via unintended release from products such as plastic articles, rubber articles and textiles.

The concern for toxicity to fertility

The available data on reproductive toxicity in the registration dossier include a full dietary two-generation reproductive toxicity study (OECD TG 416, 2013), a non guideline one-generation reproductive and developmental toxicity study (2005) and information from a 21-days repeated dose toxicity study (1999).

Information available from the repeated dose toxicity study indicates that 21 days of oral exposures through the feed at doses of 600 and 1200 mg/kg bw/day caused some adverse reproductive effects on males, e.g. testicular degeneration was reported in 67 % of the high dose males exposed to an EU marketed version of the registered substance. Significantly increased relative liver weights were seen at both doses. Absolute weights of brain, epididymides or testes were not significantly affected, but the relative weights of these organs were not mentioned in the robust study summary in the registration dossier(s).

In the two-generation reproductive toxicity study (2013), the animals were exposed to 0, 750, 2500 or 5000 ppm in diet for two generations. For the pregnant females these concentrations corresponded to 50, 167 and 333 mg/kg bw/day, thus, a lower dosing than in the previously performed non-guideline one-generation reproductive and developmental toxicity study was chosen (see below). The investigated endpoints included gonadal function, the oestrous cycle, mating behaviour, conception, gestation, parturition, lactation in the F0 and F1 generations and pre- and postnatal growth and development of the offspring in the F2 generation (to weaning). A detailed evaluation of reproductive toxicity data from the two-generation study did not indicate effects on fecundity, except for a dose-related increase in the percentage of abnormal sperm. At the F1 male necropsy around PND 105, reproductive organ weights were not significantly affected. However, a dose-related increase in the percentage of abnormal sperm was seen. This effect was seen in F1 adult males at 250, 750, 2500, and 5000 ppm and similarly so in F0 males, as these males also showed a dose-related increase in percentages of abnormal sperm from 750 ppm and above. The percentage of abnormal sperm values in this study were within the historical control values for this rat strain and supplier, but since the increase was statistically significant, dose-dependent and seen in both F0 and F1 males, it is considered that the effect was likely to be a fertility effect caused by exposure to the registered substance. Significantly increased relative and absolute liver weight was observed at the two highest dose groups.

The concern for developmental toxicity (male reproductive development)

In the two-generation study described above, no effects on pup sex ratio/litter, or on developmental landmarks were seen at any dose in either F1 or F2. Anogenital distances (AGD) on PND 1 for both F1 and F2 male and female pups were equivalent across all groups[2].

[2] By investigating study report data on AGD from individual pups, it became evident that a measuring unit of 0.18 mm was used in this study, making the precision of the AGD measurements quite low. In the modified pre-guideline extended one-generation study (2005) which was performed in the same laboratory eight years earlier, the measuring unit was 0.10 mm. This means that the AGD measurements performed in the modified pre-guideline extended one-generation study were clearly more precise than the ones used in this two-generation study. Using a less precise measuring unit inevitably reduces the sensitivity and reduces the power of finding statistically significant differences between groups, however, in the present case the lack of dose-related changes of AGD in the two-generation study could probably not be explained by the lower sensitivity of the measuring method.

F1 pup body weights were significantly reduced in the highest dose group in the preweaning period, but not after weaning. At the scheduled necropsy for F1 pups on PND 21, male absolute brain, spleen, and thymus weights were significantly reduced at the highest dose, but reproductive organs, testicular descent, AGD and malformations were not evaluated on PND 21. These endpoints are not mandatory in the OECD TG 416, but as they were evaluated and many of them were significantly affected in the previously conducted non-guideline one-generation reproductive toxicity and developmental study (2005), it would have been highly relevant if these endpoints had been included in the OECD TG 416 study because this would have made it possible to make a comparison between these two studies.

Age and body weight at vaginal patency was unaffected by exposure in F1 female offspring in the two-generation reproductive toxicity study. Preputial separation (PPS) in male F1 offspring appeared to show a non-monotonic dose-response relationship, however, the observed differences in age at preputial separation were not statistically significant. Thus, males dosed up to 2500 ppm appeared to show delayed sexual maturation, of 1½ days later than controls, whereas males from the high dose group (5000 ppm) acquired PPS 1½ day earlier than control males. These males also had a significantly lower body weight at acquisition of PPS than controls.

In a non-guideline one-generation reproductive and developmental toxicity study (2005) presented in the registration dossier, pregnant rat dams were exposed to 0, 750, 3750 or 7500 ppm of the registered substance via feed from GD 6-PND 21, corresponding to 50, 250 or 500 mg/kg bw/day during the gestation period.

Even at the lowest tested dose (750 ppm), some indications of adverse effect on the reproductive development were seen. On PND 1, absolute and adjusted anogenital distances in male and female offspring were statistically significant reduced, and on PND 21, the absolute weight of the Cowper's glands was statistically significant reduced by 20 % (even though body weight was only reduced by 4 % at this age). Furthermore, a statistically significant 1 day delay in preputial separation was seen, and on PND 75 a statistically significant 5 % increase in right relative testes weight was observed.

At the middle dose level (3750 ppm) pup body weights were reduced similarly to the low dose group (e.g. 3-4 %), however, more effects indicating reproductive toxicity were seen. Male AGDs in this group were reduced by around 11 % on PND 1 and by 6 % on PND 21. On PND 21, statistically significant reductions of between 7-28 % in the absolute weights of epididymis, prostate, LABC and Cowper's glands were seen, while body weight at this age were reduced by 4 %. A significant increase in the number of males with epispadias was also seen in this dose group. As in the lower dose group, female AGD on PND 1 was significantly reduced, and in males preputial separation was significantly delayed. Relative testes weights on PND 75 were significantly increased, as seen in the lowest dose group.

In the highest dose group (7500 ppm) pup body weights were reduced somewhat more than in the two lower dose groups (i.e. by 5-11 %). The same indications of adverse reproductive effects that were seen in the low and middle dose group were also present at 7500 ppm, but in some cases more pronounced and with some additional endpoints affected. Male AGD on PND 21 was reduced more than in the 3750 ppm group, and a statistically significant increase in areolas on PND 12 was also seen. PPS was delayed by 1.6 day, and statistically significant more animals showed epispadias and undescended testes on PND 21 compared to the control group. On PND 21 the absolute weights of testes, epididymis, prostate, LABC, Cowper's glands and pituitary were reduced by between 10-30 %, while body weight on PND 21 was reduced by 11%.

The relative weight of LABC on PND 21 was statistically significant reduced, whereas the relative weights of the other reproductive organs were not significantly affected, even though the relative weight of the Cowper's glands was reduced by 24%. On PND 75 absolute weights of prostates and LABC were still significantly reduced whereas testes weights were increased both as absolute and relative. Furthermore, relative weights of pituitary and adrenals were increased. Histopathology of males from the highest dose group additionally indicated dilatation of the lumen of the seminiferous tubules of the left testis in two males - a result considered treatment related by the Study Veterinary Pathologist and the Study Director.

Thus, the registered substance caused adverse developmental effects on male reproduction already from the lowest tested dose, and not all the adverse effects were reversible, as e.g. testes weights were significantly affected in male pups from all three doses on PND 75. It is possible that the delayed preputial separation, observed in all three dose groups, could be due to delayed development (i.e. a lower body size at a given age), but the observed effects on male AGD, increased nipple retention and reduced reproductive organ weights are all effects that have been seen for several other reproductive toxic phthalates (David 2006, Howdeshell *et al*., 2008).

The concern for adverse effects of the registered substance on the developing reproductive system is further strengthened by the fact that the registered substance, based on its structure, is expected to be metabolized to monoisononyl phthalate and monobenzyl phthalate, both of which are known to be reproductive toxicants. A prenatal developmental toxicity study by Ema *et al*. (2003), focused on the effects of monobenzyl phthalate (CAS 2528-16-7) on the developing reproductive system and showed a significant increase in the incidence of undescended testis from 250 mg/kg bw/day and decreased male AGD and AGD/cube root of bw from 250 mg/kg bw/day. Monoisononyl phthalate is known as a primary metabolite of diisononyl phthalate (CAS 68515-48-0 and 28553-12-0) (Clewell *et al*., 2013a). Diisononyl phthalate is known to cause adverse effects in the male reproductive system (i.e. reduced sperm count, reduced anogenital distance, and permanent changes in reproductive organs) via interference with fetal testosterone production (Clewell *et al*., 2013b, Boberg *et al*., 2011, Gray *et al*., 2000, ECHA 2013), although at highter doses.

The concern for endocrine disrupting mode of action

Anti-androgenic mode of action:
In the course of the evaluation, the evaluating MSCA identified an additional concern regarding endocrine disrupting properties. This concern was identified since exposure to anti-androgenic endocrine disruptors during development generally causes effects on the male reproductive system that are similar to the effects observed in the performed non-guideline one-generation reproductive and developmental toxicity study with the registered substance (Kay *et al*., 2014, Howdeshell *et al*., 2008, Wilson *et al*., 2008).

The concern for anti-androgenic mode of action of the registered substance leading to adverse effects on the developing reproductive system is further strengthened by the fact that the registered substance is expected to be metabolized to amongst others monoisononyl phthalate and monobenzyl phthalate. These metabolites are also the metabolites of benzyl butyl phthalate, BBP (CAS 85-68-7) and Diisononylphtalate, DINP (CAS 68515-48-0 and 28553-12-0), phthalates which are both recognized as possessing an anti-androgenic mode of action (ECHA 2013), primarily related to effects on stereoidogenesis. Also, it has been demonstrated by Ema *et al*. (2003), that monobenzyl phthalate (CAS 2528-16-7) in itself reduces AGD in fetal male rats which further supports that anti-androgenic effects of the registered substance are plausible.

Anti-androgenic effects on male reproductive development were not observed in the recently performed two-generation reproductive toxicity study (OECD TG 416). However, due to the lower doses used and the selection of only few investigations relevant to anti-androgenic mode of action, it is considered that the data from the two-generation reproductive toxicity study (2013) does not contradict the anti-androgenic effects observed in the non-guideline one-generation reproductive and developmental toxicity study (2005).

Thyroid hormone disrupting mode of action:
Thyroid toxicity, e.g. thyroid follicular hyperplasia, has been found for phthalates with backbone lengths of C6-C8 (Bhat *et al*., 2014, Howarth *et al*., 2001, Poon *et al*., 2007, Hinton *et al*., 1986). Also for di-isodecyl phthalate (DIDP CAS 68515-48-1, primarily C10) possible effects on thyroid glands have been described (ECHA 2013). However, it is unclear whether thyroid toxicity is related to phthalates with specific backbone lengths only. The registered substance contains constituents with backbone lengths of C7-9 and thus has constituents within the chain length range for which thyroid effects have been observed in other phthalates. Therefore, there is a concern that the registered substance may cause the same type of effects on the thyroid as observed for other structurally related phthalates.

Thyroid glands were weighed in adult F1 offspring in the two-generation reproductive toxicity study (OECD TG 416) on the registered substance, and here a non-sigificant 10 % increase in thyroid weight was seen. Effects on the thyroid glands were not evaluated in the 21-days repeated dose toxicity study, nor in the non-guideline one-generation reproductive and developmental toxicity study on the registered substance.

Why new information is needed

Further information is required to conclude on the potential risk to human health from effects on fertility, the developing male reproductive system as well as on the endocrine disrupting potential of the registered substance. This can be achieved by using a study design as requested, with sensitive parameters which may allow observation of adverse effects and changes in parameters sensitive to antiandrogenic and thyroid mode of action in the same study.

What is the possible regulatory outcome

If the concerns for fertility and developmental toxicity would be confirmed, this may lead to classification as Toxic to Reproduction. In adition the potential endocrine disrupting properties, (i.e. an endocrine mode of action linked to adverse effects) may lead to identification of the substance as SVHC according to REACH Art. 57 (f).

Considerations on the test method and testing strategy

The requested study aims to clarify the concern for fertility, developmental toxicity to male reproductive development and endocrine disrupting mode of action of the registered substance. The study shall follow the test method described in the OECD TG 422, with some modifications which are further justified below.

The number of animals have been increased to 20 males and 20 females per dose group, as this is considered to give a sufficient sensitivity to address the concern regarding possible developmental toxicity and/or endocrine disrupting mode of action of the registered substance.

To address the concern regarding male fertility, the dosing of the males has been prolonged for a period of not less than 70 days (70-77 days) to cover one complete spermatogenesis cycle in the rat and semen parameters including motility, morphology and sperm count shall be investigated in parental animals.

In addition, a prolonged exposure of dams to PND 13 as specified in the OECD TG 422 increases the possibility of detecting toxicity to the developing male reproductive system. A possible reduction in male AGD and/or an increase in nipple/areola retention in males would be regarded as an adverse effect that could support identification of the registered substance as a developmental toxicant. Therefore, a quantitative count of retained nipples/areolas in males is included in the test design, as this is considered to be more sensitive than evaluation of presence/absence only (OECD 2013). Effects on these endpoints could clarify the additionally identified concern for endocrine mode of action regarding developmental effects on male reproductive organs.

Effects on male reproductive organs of prepubertal rats (testis, epididymis, seminal vesicle, ventral prostate, LABC, bulbourethral glands) are also known to be sensitive to compounds with an endocrine mode of action, and are therefore requested as additional endpoints which are not included in the OECD TG 422. As default the pups are terminated on PD 13. However, the study may be extended to PD 21 if the Registrant(s) finds the weighing of a number of organs in pups too challenging at PD 13. However, in such case dosing of pups shall also be continued to PD 21. Additional information regarding the identified concern for thyroid toxicity of the registered substance justifies the inclusion of histological examination of thyroids from dams, males and day 13/21 pups and measurements of thyroid hormone T4.

A sub-chronic toxicity (90-day) study is not available for this substance. In their comments on the draft decision, the Registrant(s) proposed to include in the OECD TG 422 study design additional investigations and parameters which are normally included in the sub-chronic toxicity study (90 day). The evaluating MSCA notes that these additional investigations are relevant for the interpretation of the results in relation to the concerns for reproductive toxicity and endocrine mode of action, and therefore the proposal of the Registrant(s) is accepted. Therefore the OECD TG 422 is modified to include evaluation of all males and females as regards haematology, clinical chemistry, and gross and microscopic pathology, including pathology investigations of the additional tissues and organs required in the Sub-chronic toxicity (90-day) study OECD TG 408.

Consideration of alternative approaches

Another option could be to request an extended one-generation reproductive toxicity study (OECD TG 443). However, since two higher tier studies are already available (OECD TG 416 and a non-guideline one-generation reproductive and developmental study) it is considered more appropriate to request a less expensive study which is tailor-made to investigate the concerns identified during the substance evaluation. There are no non-animal test methods/approaches that could be used in order to clarify the identified concerns.

Consideration of Registrant(s)' comments on the draft decision and on proposals for amendments from other member states and ECHA

In their comments on the draft decision the Registrant(s) proposed, in the interest of animal welfare, study acceptability and the principle of proportionality, to replace the originally requested modified OECD TG 421 and the Sub-chronic toxicity study (90-day), oral route (OECD TG 408) with a modified OECD TG 422. This proposal and the suggested modifications were accepted with the following observations:

- The Registrant(s) proposal to use the option in OECD TG 422 to prolong the dosing of the males to 70-77 days to cover one complete spermatogesis cycle was accepted.
- The Registrant(s) proposal to include pathology investigations to tissues and organs that are not included in OECD TG 422 but are required in OECD TG 408 was accepted. This information is relevant to address the concerns.
- The Registrant(s) proposal that all males and all females will be evaluated for haematology, clinical chemistry, and gross and microscopic pathology was accepted. This information is relevant to support evaluation of relationship of general toxicity and reproductive toxicity.
- It is further specified that semen parameters including motility, morphology and sperm count shall be investigated in adults as was also requested in the original draft decision under the request for OECD TG 408. This information is relevant to address the concerns.

Evaluation of reproductive organs in pups
The Registrant(s) proposed to omit evaluations of reproductive organs in pups at sacrifice (PD 13). According to the Registrant(s) the size of these organs relative to those in adult animals might offer substantial technical challenges for laboratories. Furthermore, there is a lack of historical control data to compare findings. In a proposal for amendment two alternative options were proposed: 1) to extend the study up to PND 21 (this was possible in the available non-guideline one-generation reproductive and developmental toxicity study), or 2) to extend the study up to sexual maturation (around PND 42).

In the opinion of the evaluating MSCA, measurements of weight of reproductive organs is indeed possible on PND 13, and the current OECD 422 TG guideline requires weighing of thyroid glands from pups on PND 13. However, the evaluating MSCA acknowledges a potential lack of historical control values on PND 13. The weights of reproductive organs from around PND 13 would be preferred, but if the Registrant(s) find the technical challenges too difficult, a prolongation of the test and weighing the organs on PND 21 can be accepted. Prolonging the test to PND 21 is only acceptable if the dosing is also continued to PND 21. It is further noted that postponement of the weighing of reproductive organs until PND 21 may increase uncertainty about the dosing of the pups, as exposure after PND 13 may be through lactation but also directly via the feed. The option of extending the study up to the time of sexual maturation (PND 42) is not supported as the variation in organ weights at that time is expected to be large due to the difference in degree of sexual maturation between animals. The draft decision was amended to allow for extending the study to PND 21 if technically not feasible for the Registrant(s) to weigh the relevant reproductive organs at PND 13.

Dose selection
The Registrant(s) proposed to use a maximum dose of 1000 mg/kg bw/day. However, it was noted in a proposal for amendment that the suggested maximum dose of 1000 mg/kg bw/day may be too high based on the available data, and furthermore proposed to add additional explanation on the justification for dose selection. The draft decision was amended accordingly.

Exposure of females
Originally, the request for a modified OECD TG 421 included a delayed exposure period of the dams. In the comments on the draft decision, the Registrant(s) argued that the exposure period should not be delayed, since this might limit the applicability of the study within other legislative frameworks. This was accepted and the exposure period of females in the modified OECD TG 422 study shall therefore follow the requirements in the guideline.

Time frame
The Registrant(s) proposed a deadline of 24 months based on a sequential testing strategy with the modified OECD TG 422 study and potentially followed by the originally requested OECD TG 414 study. In a proposal for amendment a deadline of 27 months was proposed. However, this proposal also took into account that a sequential testing strategy is employed. Since the OECD TG 414 study in a second species was removed from the decision, a sequential testing strategy is no longer warranted. However, it is considered that the requested modified OECD TG 422 study will need a longer deadline than the standard OECD TG 422 study. In terms of complexity and length it should be more comparable to the OECD TG 408 study. Therefore, the standard deadline of 18 months for the OECD TG 408 study is used plus a standard additional 3 months for the Registrant(s) to decide on who will perform the test. Hence, the deadline for the requested study has been set to 21 months.

Other proposals and comments from the Registrant(s)
The Registrant(s) proposed to include an additional group of 10 unmated females in order to address difference between the pregnant and non-pregnant animals. This is not considered necessary to address the concern for reproductive toxicity and endocrine disruption. Therefore the inclusion of this group of 10 unmated females during the the requested study is at the Registrant(s)' discretion. However, the Registrant(s) should ensure that the performance of of any such additional investigation does not interfere with the performance of the requested study.

The Registrant(s) commented that the text in the original draft decision related to the sensitivity of the measurement method for AGD for the two-generation reproductive toxicity study was incorrect. The evaluating MSCA re-analysed the data from the study and on that basis agrees with the Registrant(s) that using a less precise measuring unit would probably mainly affect the probability of identifying statistically significant changes compared to controls. The text was amended although it is still considered that using a method with best possible precision would facilitate the interpretation of the data.

One Member State Competent Authority submitted a proposal for amendment suggesting that the request for a modified OECD TG 422 should either be deleted or the justification should be redrafted. The reasoning behind this request is that classification may already be possible based on existing information. The substance is a medium chain phthalate ester and some medium chain phthalates already have a harmonized classification based on a category approach (for example, DIPP and DHP have been classified as Repr 1B even in the absence of adequate fertility/developmental studies). Therefore, in the view of the Member State Competent Authority an adequate category approach should be envisaged before requesting any new studies. Furthermore, in the proposal for amendment it was proposed to clearly reflect in the decision if the modified OECD TG 422 study is requested for the purpose of risk characterization, i.e. to derive a DNEL.

It is considered that based on the existing evaluation it cannot be finally concluded that the substance would meet the criteria for classification with Repr 1B H360D based on a category approach and on the observed effects in male pups in the non-guideline one-generation reproductive and developmental toxicity study. Nor has it been concluded that the substance would meet the criteria for classification with Repr 1B H360F based on effects on sperm quality in the two-generation reproductive toxicity study and the testicular effects observed in a repeated dose toxicity study.

Several of the findings in the non-guideline one-generation reproductive and developmental toxicity study were not consistent across the two available reproductive toxicity studies, e.g. on AGD and PPS. Some findings were not investigated in both studies, e.g. reproductive organ weights on PND 21. Clear, dose-related findings of epispadias are reported in the non-guideline one-generation reproductive and developmental toxicity study on PND 21, but no findings were reported on PND 75. Furthermore, in the two-generation reproductive toxicity study, no records of epispadias (or hypospadias) in offspring at PND 21 or in adulthood were presented in the study report, and it is not clear whether this was investigated at all. Based on the available data, further information is needed to clarify whether the registered substance meets the classification criteria for Repr. 1B and to address the identified concern for endocrine disruptive properties of the registered substance.

Therefore, the request for an additional study to address the concerns is maintained. This study may also contribute to DNEL characterization, although this is not the primary purpose of the request. In conclusion, the request for the modified OECD TG 422 study has been maintained.

The Registrant(s) submitted comments on the proposals for amendment addressing a classification based on existing information. They propose that the substance should not be classified and agree that the proposed study should be conducted in order to clarify the identified concern.

Conclusion

Overall, with the presently available data, the spectrum of adverse effects described above from the non-guideline one-generation reproductive and developmental toxicity study and the knowledge on the mode of action of expected metabolites of the registered substance, indicate potential anti-androgenic and thyroid disrupting modes of action of the registered substance. The request for a study targeted at clarifying the concern on fertility, developmental toxicity and endocrine disrupting properties will provide the necessary information to address the identified concerns and to decide whether further testing is needed.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant is required to carry out the following study using the registered substance subject to this decision:

Modified Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test with the registered substance in rats, oral route, as specified in Sections II and III above.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental stud(y/ies), the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the test(s) must be shared by the Registrant(s).

V. Avoidance of unnecessary testing by data- and cost-sharing

In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at: https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the stud(y/ies) on behalf of all of them.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[3] by Leena Ylä-Mononen, Director of Evaluation

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

[3] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

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