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

For p-(1,1-dimethylpropyl)phenol, CAS No 80-46-6 (EC No 201-280-9)

Addressees: Registrant(s)[1] of p-(1,1-dimethylpropyl)phenol (Registrant(s))

This decision is addressed to the Registrant(s) of the above substance with an 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.

Based on an evaluation by the Federal Institute for Occupational Safety and Health (BAUA) as the Competent Authority of Germany (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 15 July 2015, i.e. the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

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 Germany has initiated substance evaluation for p-(1,1-dimethylpropyl)phenol (ptAP), CAS No 80-46-6 (EC No 201-280-9) 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.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to being apotential endocrine disruptor for the environment, exposure/wide dispersive use and consumer use ptAP was included in the Community rolling

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

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 Germany was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding repeated dose toxicity and occupational exposure.

The evaluating MSCA considered that further information was required to clarify the following concerns: repeated dose toxicity and occupational exposure. Therefore, 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 6 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.

Registrant(s) commenting phase

By 12 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 the dossier update(s).

On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 3 September 2015 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 of the receipt of the notification.

Subsequently, three MSCAs submitted proposals for amendment of the draft decision.

On 9 October 2015 ECHA notified the Registrant(s) of the proposal 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 proposal for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment and Registrant(s) comments and amended section III of the draft decision.

Referral to Member State Committee

On 19 October 2015 ECHA referred the draft decision to the Member State Committee.

By 9 November 2015, in accordance to Article 51(5), the Registrant(s) provided comments on the proposals for amendment. In addition, the Registrant(s) provided comments on the draft decision. The Member State Committee took the comments on the proposal(s) for amendment of the Registrant(s) into account. The Member State Committee did not take into account the Registrant(s)' comments on the draft decision as they were not related to the proposal(s) for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 7 to 11 December 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 10 December 2015. ECHA took the decision pursuant to Article 52(2) and Article 51(6) 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 the structurally related substance 4-tert-butylphenol (ptBP) (CAS No 98-54-4; EC No 202 679-0).

1. Repeated dose 90-day oral toxicity study in a non-albino rat strain rat, by oral gavage; test method: OECD TG 408 (EU B.26) with modifications as specified in Section III using the structurally related substance ptBP (CAS No 98-54-4; EC No 202 679-0) (see Annex II of this document for read-across justification).

   Alternatively, an existing repeated dose toxicity study (90 day) on the registered substance, p-(1,1-dimethylpropyl)phenol (ptAP) (CAS 80-46-6) performed with an albino strain may be submitted to fulfil part of this information requirement as specified in Section III. If this approach is chosen the evaluating MSCA will assess in the follow-up evaluation (Article 46(3) of the REACH Regulation) which of the information requests as specified in Section III were already addressed. Independent of the outcome of the evaluation of the exisiting 90 day study with an albino strain, it is already foreseeable that there is at least a remaining concern on depigmentation which needs to be addressed by a request for further information.

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information regarding the registered substance subject to the present decision:

2. A higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for missing exposure scenarios related to the usage of the molten substance with anticipated risk characterisation ratio (RCR) > 1.

   In addition, for dermal exposure, the Registrant(s) are required to provide evidence that performing the tasks described in the CSR does not yield an additional risk for the worker caused by the prolonged wearing of gloves.

3. A higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for exposure scenarios related to the usage of the substance as flakes with anticipated risk characterisation ratio (RCR) > 1.

   In addition, for dermal exposure, the Registrant(s) are required to provide evidence that performing the tasks described in the CSR does not yield an additional risk for the worker caused by the prolonged wearing of gloves.

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by 28 January 2018 an update of the registration(s) containing the information required by

this decision[2], including, where relevant, an update of the Chemical Safety Report.

If the existing information from the 90 day study on ptAP is used to fulfill parts of the requirements of request 1, the Registrant(s) shall submit to ECHA by 28 October 2016 an update of the registration(s) containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

Information request 1

Repeated dose 90-day oral toxicity study in a non-albino rat strain, by oral gavage; test method: OECD TG 408 (EU B.26) using the structurally related substance 4-tert-butylphenol (ptBP) (CAS No 98-54-4; EC No 202-679-0) (see Annex II of this document for read-across justification) with the following modifications:

- Detailed kidney histopathology and urinalysis in males including assessment of hyaline content on the presence of α-$_{2u}$-globulin by immunohistochemistry
- Assessment of thyroid weight and histopathology, thyroid hormone levels and thyroid autoantibodies.
- Assessment of vaginal epithelial atrophy, ovary weight as well as histopathology and staging of estrous cycle in females
- Histopathologic examination of the eye and the ear

Alternatively, an existing repeated dose toxicity study (90 day) on the registered substance, p-(1,1-dimethylpropyl)phenol (ptAP) (CAS 80-46-6) performed with an albino strain may be submitted to fulfil part of this information requirement as specified below.

What relevant data is available

ptAP has been investigated in a repeated dose 90-day toxicity study by the dermal route. In this study, local effects occurred due to the corrosive nature of the substance. Therefore, only low doses could be used for the study which most probably precluded the occurrence of systemic effects. Thus, systemic effects of ptAP could not be addressed by the dermal 90-day study.

In order to address repeated dose toxicity of ptAP by the oral route, the Registrant(s) referred to a two-generation reproductive toxicity study (OECD TG 416) and a reproduction/developmental screening study (OECD TG 422) performed with the structurally similar substance ptBP (CAS 98-54-4; EC No 202 679-0). In principle, the evaluating MSCA considers read across between ptAP and ptBP acceptable to address 90-day repeat-dose toxicity (see Annex II of this document for read-across justification).

The dermal repeated dose 90-day toxicity study performed with ptAP as well as the OECD TG 416 and OECD 422 studies performed with ptBP do not however fully address potentially systemic effects covered by an oral 90 d repeat dose toxicity study. Therefore the lack of an oral 90-day study is considered as a concern.

[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).

Justification why new information is needed

Although the read across between ptAP and ptBP is considered acceptable to address 90-day repeat-dose toxicity (see Annex II of this document for read-across justification), the following issues are considered of concern:

(I) The available OECD TG 422 study and OECD TG 416 study performed with ptBP are insufficient as the information provided does not cover the whole spectrum of investigations required in the OECD test guidelines for subchronic toxicity, in particular with regard to non-reproductive organs and they do not fully cover the required treatment duration of 90 days.

(II) The available OECD TG 422 study and OECD TG 416 study performed with ptBP indicated that kidneys might be a potential target tissue of ptBP (and therefore also for ptAP). Furthermore, it cannot be decided, if effects related to reproductive organs in females are substance-specific or due to weight reduction and pregnancy.

(III) A number of occupational studies , which investigated the depigmentation potential of ptBP, identified the thyroid gland as a target organ in single vitiligo cases. Though the underlying mechanisms of toxicity may be completely different (involving autoimmunity in one case of thyroid dysfunction in the context of depigmentation, but other thyroid effects in other cases), it cannot be excluded that ptAP may exert thyroid activity.

(IV) There are indications on skin depigmentation potential of both ptAP and ptBP. However, this effect has not yet been addressed adequately in experimental studies.

Therefore, an oral repeated dose 90-day study is requested for the structurally related compound ptBP (CAS-No. 98-54-4) from which read-across to ptAP is considered acceptable (see Annex II of this document for read-across justification).

What is the request

An oral repeated dose 90-day study is requested for the structurally related compound ptBP from which read-across to ptAP is considered acceptable (see Annex II of this document for read-across justification).

In theory, both substances (ptAP or ptBP) would be suitable to address the identified concerns. ECHA is of the opinion that for animal welfare reasons as a first step only one of the two structurally similar substances should be tested. ECHA is in favour of performing the study with the structurally related substance ptBP as this substance has a higher tonnage and exhibits a more extended toxicological database. Thus, data generated by an oral repeated dose 90-day toxicity study performed with ptBP can be used to compare with already existing data for ptBP and also to complement the database for ptBP.

Testing of ptAP itself could be reconsidered based on the outcome of the requested oral 90-day repeat-dose study with ptBP.

A number of issues have been identified which should be addressed in the repeated dose 90-day toxicity study:

a) Nephropathy

A detailed kidney histopathology and urinalysis in males is necessary because the OECD TG 416 study performed with ptBP raised the concern of sex-specific nephrotoxic effects, as there were histological abnormalties, in particular with regard to hyaline droplets in the

renal ducts of males. An irregular incidence of hyaline droplets is often associated with certain levels of α-2u-globulin which is a rat-specific protein. However, to exclude a human concern, the hyaline content has to be assessed on the presence of α-2u-globulin by immunohistochemistry.

b) Effects on the female reproductive tract

For some effects observed in the OECD TG 416 study performed with ptBP such as vaginal epithelial atrophy, changes in ovary weight and effects on estrous cycle it is difficult to conclude whether they were due to the body weight loss observed in the animals. Therefore, effects such as vaginal epithelial atrophy and ovary weight and histopathology as well as staging of the estrous cycle should be re-examined in non-pregnant females.

c) Depigmentation

During substance evaluation, a human health concern was identified of ptAP having a skin depigmentation potential, which might be induced both by topical as well as by systemic exposure. Acquired vitiligo is a depigmentation disorder that is known to affect the skin and eyes and may also affect melanocytes at other sites (e.g. inner ear). Depletion of the ocular melanocytes is of clinical importance as it can lead to increased photosensitivity and night blindness. Likewise, depletion of melanocytes in the inner ear results in hearing loss (Tolleson (2005); Lotti and DÉrme, 2014). There is evidence available from occupational studies as well as animal studies performed with ptBP. These are exhaustively summarized in the EU RAR (2008), the OECD SIDS (2000) and in the opinion of the German Commission for the Investigation of Health Hazards of Chemical Compoundsin the Work Area, MAK (MAK, 1995). However, this data is not very robust or complete with regards to possible targets of a systemic depigmentation. For ptAP itself there is less data compared to ptBP, however there are some indications of a depigmentation potential. Therefore, ECHA requests to carry out the above 90-day toxicity study with an appropriate non-albino rat strain to address the endpoint (systemic) depigmentation. Thorough retina histopathology may be indicative of an early depigmentation event, which may become manifest even when skin depigmentation in the 90-day exposure duration is not yet detected. In addition to the routine organ 'skin' in the 90-day study design, the eye as a non-standard organ should be examined by an appropriate histopathologic technique as it may be a sensitive site for depigmentation.

d) Thyroid-related activity

The initial concern of an endocrine effect prompted the evaluating MSCA to assess a putative thyroid-related activity. The existing animal data obtained from ptBP either do not provide information on the thyroid (OECD TG 422 study performed with ptBP) or report findings in the F1 and F2-generation which are not indicative of a thyroid activity (OECD TG 416 study performed with ptBP). On the other hand, in a number of occupational studies, which investigated the depigmentation potential of structurally similar substance ptBP, the thyroid gland was identified as a target organ in single vitiligo cases (Kroon et al. (2013). Though the underlying mechanisms of toxicity may be completely different (involving autoimmunity in one case of thyroid dysfunction in the context of depigmentation, but other thyroid effects in other cases), it cannot be excluded that ptBP may exert thyroid activity. Apart from thyroid histopathology, further investigation of the thyroid activity should be included: estimates of thyroid hormone levels (thyroxine (T4), triiodthyronine (T3), and thyroid stimulating hormone (TSH) as well as the presence of thyroid autoantibodies (e.g. thyroglobulin antibody, anti-Tg and thyroid peroxidase antibody, anti-TPO).

Testing should be performed via the oral route in order to be able to compare with results

from already existing studies. The dermal or inhalative route may have more relevance in occupational safety and specifically in the context of chemically induced vitiligo. However, experimental depigmentation by ptBP has been induced in rodents following oral exposure as well. Moreover, the postulated autoimmune mechanism of chemically induced vitiligo indicates systemic manifestation of the skin disease.

Oral exposure should be done by gavage rather than via the diet to minimize possibly confounding effects of body weight losses due to food avoidance that has been observed in repeated dose diet studies on reproductive toxicity.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using ptBPl (CAS 98-54-4):

Repeated dose 90-day toxicity study in an appropriate non-albino rat strain, by oral gavage; test method: OECD TG 408 (EU B.26), modified to include:

- Detailed kidney histopathology and urinalysis in males including assessment of hyaline content on the presence of α-$_{2u}$-globulin by immunohistochemistry;
- Assessment of thyroid weight, thyroid histopathology, thyroid hormone levels and thyroid autantibodies;
- Assessment of vaginal epithelial atrophy, ovary weight as well as histopathology and staging of estrous cycle in females;
- Histopathological examination of the eye and the ear.

Concurrently to the substance evaluation of ptAP, the evaluating MSCA performed a substance evaluation of the substance ptBP (CAS No 98-54-4; EC No 202 679-0). As a result of this evaluation, the Registrant(s) of ptBP are also requested to perform a repeated dose 90-day oral toxicity study on ptBP. Therefore, the addressees of this decision are requested to coordinate with the Registrant(s) of ptBP in order to avoid unnecessary testing on vertebrate animals. A justification of read-across between ptAP, CAS No 80-46-6 and ptBP, CAS No 98-54-4 is given in Annex II to this document.

The dose range for the TG 408 study should be ≥ 50 mg/kg/d at the lower end and 200 mg/kg/d at the upper end. The minimum dose refers to the NOAEC of 50 mg/kg/d derived from the oral prenatal developmental study with the analogous substance ptAP. The maximum dose reflects the effect level at which reduced relative weights of ovaries and adrenal glands as well as an increase in vaginal epithelium atrophy in the 2-generation study with ptBP was observed.

Registrant(s) comments and proposals for amendment

ECHA has noted that the Registrant(s) in their comments and their intervention at the Member State Committee plenary informed about the existence of a 90-day repeated dose study on the ptAP (CAS 80-46-6).
The Registrant(s) may provide the detailed study results with regard to information request 1.

Once the information is available in the registration dossiers, the evaluating MSCA will be in a position to assess which of the information requests as specified above were addressed by this study.From the Registrant(s)' short summary (delivered with the response to a proposal for amendment) it appears that this study may cover a number of the requests above. Weight determinations and microscopic observations are mentioned for target organs (kidney, ovaries, thyroid) as well as T3, T4 levels and estrous cycling. However, details and information on the doses tested are not yet available. Furthermore, it is not clear if the

study also addresses others identified concerns such as vaginal atrophy, detailed kidney histopathology including α-2u-globulin immunohistochemistry.

Since the study was performed with albino rats, it does not tackle the requested information on the concern of (systemic) depigmentation which may also affect the eye and the ear. Therefore, in case that the 90-day albino study adequately informs on the other endpoints of concern, there is a remaining concern on systemic depigmentation which needs to be addressed in a separate study. The dose levels and study duration should be adequately chosen to sensitively allow detection of clinical signs of systemic depigmentation e.g. eye depigmentation in addition to skin leukoderma.

With regards to the impact on the risk management information on eye depigmentation supports to clarify whether the systemic depigmentation (vitiligo) induced by ptBP affects other sites than skin at which melanocytes contribute to the physiological organ functions. Melanocytes in mammalians are found in the skin, eye, inner ears (intact melanocytes in the cochlea contribute to normal hearing) and meninges. Pigmented cells in the uveal tract (choroid, ciliary body and iris) and the retina provide photoprotection and regulate the entry of light. Acquired vitiligo is a depigmentation disorder that is known to affect the skin and eyes and may also affect melanocytes at other sites (e.g. inner ear). Depletion of the ocular melanocytes is of clinical importance as it can lead to increased photosensitivity and night blindness. Likewise, depletion of melanocytes in the inner ear results in hearing loss. The administration of ptBP to pigmented rats should clarify the concern whether ptBP (and ptAP) have the potential to destroy ocular and otic melanocytes at doses below those where skin depigmentation becomes manifest (thus also demonstrating that ocular melanocyte destruction would be the most sensitive adverse effect).

Viteligo-like skin depigmentation after exposure to ptBP is recognized as an occupational disease. As described above, the current data basis is not sufficient to allow a proper DNEL derivation with respect to depigmentation. A qualitatively different clinical concern is the systemic depigmentation, which is usually underdiagnosed or neglected and may become manifest even earlier or at lower exposure levels than skin depigmentation. Therefore, the information obtained from the study will be of relevance for risk management measures at the workplace.

Information request 2

Conduct a higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for missing exposure scenarios related to the usage of the molten substance with anticipated risk characterisation ratio (RCR) > 1. This requirement is valid for exposure scenarios describing the production of the substance, its use as an intermediate and its use as a monomer in the production of polymers.

In addition, for dermal exposure, the Registrant(s) are required to provide evidence that performing the tasks described in the Chemical Safety Report (CSR) does not yield an additional risk for the worker caused by the prolonged wearing of gloves.

In some contributing scenarios durations of tasks > 4 h (input parameter of the used model for exposure assessment) are described by the Registrant(s). This indicates an up to 8 h use of personal protective equipment (PPE) such as gloves whenever such PPE is recommended (wearing of PPE, including gloves is also used as an input parameter for the model).

What relevant data is available?

Some of the Registrant(s) including the lead registrant submitted an updated CSR between September and October 2014. This CSR takes into account the occupational life cycle of ptAP, including the use of ptAP as a monomer in the production of resins and polymers and as an intermediate in the production of derivatives. The substance is obtained and used either as flakes or in a molten form at elevated temperatures covered by a nitrogen blanket. Inhalation and dermal exposure of worker is assessed by the tier 1 model ECETOC TRA v3 and extended TRA. The Registrant(s) did not provide any measurement data.

Justification why new information is needed

Based on information given in the CSR and information provided by the lead Registrant in an informal meeting during the evaluation period it is non-controversial that the pure substance is handled either as flakes or as a molten substance covered with a nitrogen blanket at elevated temperatures. However, the exposure assessment presented in the CSR considers only the production and use of the substance as flakes as a starting material for further processing but does not take into account using the molten substance, e.g. unloading from bulk containers and bulk quantity additions. Here the substance may occur in a molten form and as solidified melt on equipment surfaces (gaskets, flanges etc.) after cooling down. In this context, it is clear that direct dermal contact to molten substance is not relevant due to the elevated temperature (130 °C).

Based on calculations using a tier 1 model it is assumed that this situation leads to considerable higher inhalation exposure levels than using flakes. However, the possible exposure reducing effect of the nitrogen blanket cannot be considered in tier 1 models. For dermal exposure, contacts with the cool, solidified substance are considered.

Calculations performed by the evaluating MSCA are based on the actual version of ECETOC TRA (v3) using the default values defined in the model. For example, inhalation exposure for transfer of the molten substance is considerably higher than transfer of flakes and the resulting exposure level leads to a risk characterisation ratio > 1. It has to be mentioned that for some scenarios the tier 1 estimation in application of ECETOC TRA v3 leads to very high exposure levels for the input parameter "liquid substance". In addition, the possible exposure reducing effect of the nitrogen blanket cannot be considered in tier 1 models. This indicates that a tier 2 model with more detailed information on the processes has to be used. The Registrant(s) are required to perform a tier 2 assessment according to R.14 for scenarios related to the molten substance. For dermal exposure, contacts with the cool, solidified substance have been considered. The recalculated dermal exposure estimates deviate significantly from the values provided by the Registrant(s). As a consequence the dermal risk characterisation ratios for some contributing scenarios exceed 1. These observations indicate that a tier 2 assessment with more detailed information on the processes has to be used. The Registrant(s) are required to perform a tier 2 assessment for inhalation and dermal exposure according to R.14 for scenarios related to the molten substance (inhalation) and the cool, solidified substance (dermal).

It is currently not possible to calculate inhalation and dermal exposure levels using a tier 2 model due to a lack of information on the details of the exposure relevant parameter and therefore it is concluded that it is not possible to clarify the burden of the worker based on the submitted information. The Registrant(s) are required to perform additional exposure estimations or present measurements for usage of the molten substance.

In their comments to the draft decision, the Registrant(s) agree to update the CSR to include a higher tier exposure assessment for dermal and inhalation exposure related to the usage of the molten substance. ECHA acknowledges the comments of the Registrant(s) and

welcomes the willingness to update the CSR. It is noted that the exposure assessment should focus on dermal contact to the solidified melt that may occur on equipment surfaces (sampler, gaskets, flanges etc.) after cooling down because it is clear that direct dermal contact to molten substance is not relevant due to the elevated temperature (130 °C). The Registrant(s) also agrees to clarify accordingly in the updated CSR that dermal exposure potential (i.e. wearing of gloves) will be less than 4 hours per day.

In this context it has to be noted that the DNELs applied by Registrant(s) for workers cannot be accepted. In their assessment, the Registrant(s) used data on general systemic toxicity obtained from a 2-generation reproduction toxicity study in rats exposed orally to the read across substance ptBP as a starting point to calculate the long-term systemic DNEL (inhalation) of 2.47 mg/m^3 ptAP in the air. The long-term systemic DNEL (dermal) of 0.25 mg/kg bw/day was derived from a subchronic dermal toxicity study with the registered substance where no systemic effects were reported up to the highest dose level tested. Neither of these DNELs consider vitiligo-like depigmentation of the skin observed in workers occupationally exposed to ptAP (Stevenson, 1981, 1984). Boissy and Manga (2004) state in a review report that phenolic compounds such as ptBP and ptAP are involved in the formation of occupational vitiligo (Boissy & Manga, 2004). While the association between occupational vitiligo and exposure to ptAP does not appear to have been studied systematically, there is clear link between the occurrence of vitiligo and exposure to the read across substance ptBP (EC, 2008; Malten, Seutter, Hara, & Nakajima, 1971). In the absence of specific scientific data demonstrating the lack of depigmentation potential of ptAP, ECHA considers this substance equipotent with ptBP with respect to the induction of vitiligo. For ptBP, long-term systemic DNELs of 0.5 mg/m^3 (inhalation) and 0.07 mg/kg bw/d (dermal) were established based on studies investigating the occurrence of vitiligo in workers handling this substance. ECHA considers these DNELs more appropriate for risk evaluation than the values initially suggested by the Registrant(s) because vitiligo is regarded as the most early and sensitive toxicity endpoint associated with occupational exposures to ptBP. The RCRs recalculated by the evaluating MSCA are therefore based on long-term systemic DNELs of 0.5 mg/m^3 (inhalation) and 0.07 mg/kg bw/d (dermal).

In their comments to the draft decision, the Registrant(s) did not agree that the initially proposed inhalation and dermal DNELs are not sufficiently protective of human health effects including vitiligo. In Registrant(s)' opinion, there is no evidence of vitiligo development under conditions of low occupational exposure as reported by O'Sullivan et al. (1981) who didn't find any cases of vitiligo among 129 men that had been occupationally exposed to ptAP and/or hydroquinone monomethylether. ECHA, however, considers the study by O'Sullivan et al. (1981) not sufficient to dismiss the concern for occupational vitiligo supported by the reports discussed earlier (Boissy and Manga 2004; Stevenson, 1981, 1984). Specifically, the study by O'Sullivan et al. (1981) provides no details on the scope of exposure and only limited information on the level of personal protection used during handling of ptAP. Due to the very irritant properties of the handled chemicals, masks have always been used in addition to protective clothing. These "stringent protective measures" have been further intensified (no specific details) after reports on two vitiligo cases. Thus, it is likely that exposure to ptAP at this facility was only of very limited scope. The authors speculate that "the irritant nature of this chemical in particular may be a safeguard against careless use and contamination" concluding on low potential for depigmentation in this industrial setting (O'Sullivan et al., 1981). Therefore, this report indicates that the safe use of ptAP is possible under strictly controlled conditions, however it does not disregard the general concern of its intrinsic hazard properties (vitiligo). ECHA still considers biomonitoring data on the read across substance ptBP derived in relevant occupational settings as the more appropriate base for calculating the long-term systemic DNELs of 0.5 mg/m^3 (inhalation) and 0.07 mg/kg bw/day (dermal).

According to Article 2(4) of the REACH Regulation it shall apply without prejudice to community workplace legislation, including Directive 98/24/EC. Article 6(2) of Directive 98/24/EC states that application of PPE is only permitted where exposure cannot be prevented by other means (substitution, technical and organizational measures). In addition, PPE must be appropriate for the risks involved, without itself leading to any increased risk (Directive 98/656/EEC, Article 4(1)).

Therefore, it is the responsibility of the Registrant(s) to prove, within the scope of his chemical safety assessment, that an inappropriate burden of the worker caused by PPE is excluded.
It should be noted that extended use of gloves under occlusive conditions is considered as "wet work" since the hands become moist due to sweat (accumulation of heat and moisture). It has been demonstrated, e.g. by Behroozy and Keegel, that "wet work" conditions caused by a prolonged wearing time of gloves present a burden to the worker and increases the risk (Behroozy & Keegel, 2014).

Registrant(s)' comments and proposals for amendment

A proposal for amendment from a MSCA was received. that basically agrees with the information request. The commenting MSCA states that the use of gloves during 8 h shifts cannot represent an ideal situation. However, the commenting MSCA is of the opinion that the information requested might go beyond the legal obligations set out in Directive 89/656/EEC and Annex II of the REACH Regulation. Therefore, the commenting MSCA finds a recommendation rather than a requirement in the Draft Decision more appropriate.

According to REACH, it is the obligation of the Registrant(s) to provide an exposure scenario which describes how the risks can be adequately controlled. The exposure scenarios provided by the Registrant(s) indicate, that the risks arising from the use of ptAP are only adequately controlled if gloves are worn. As the use of gloves for longer than 4 h might yield a "wet work" situation, the use of gloves for longer than 4 h is associated with an additional risk for the worker. Therefore, the Registrant(s) needs to provide evidence that performing the described tasks for the times intended in the CSR, does not yield an additional risk for the worker caused by use of gloves. To take the comments and suggestions made in the proposal for amendment into account the decision was amended to reflect on this topic.

What is the request?

Based on the new calculations of exposure levels or on the basis of measurements, the evaluating MSCA would be able to identify the relevant exposure scenarios with risk characterisation ratio (RCR) > 1. Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to conduct a higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for the missing scenarios. These exposure scenarios are related to the usage of the molten ptAP e.g. transfer of molten substance, unloading from bulk containers, bulk quantity additions, bulk material, sampling.

The following PROCs are of concern:

- Manufacture of ptAP: PROC 2, 9, 8a, 8b,15.
- Use of ptAP as a monomer in production of polymers (phenolic resins): PROC 2, 3, 4,

5, 8a, 8b, 9, 15.
- Use of ptAP as an intermediate in the production of perfumes & fragrances: PROC 4, 5, 8a, 8b, 9, 14, 15.

In order to enable evaluation of the assessment all used models and parameters and measurement data shall be clearly stated and documented. When using non-standard parameters a justification must be given, otherwise the use of the parameter cannot be assumed to be justified.

The Registrant(s) are required to provide an exposure assessment that demonstrates the safe use of ptAP. Thus, in this particular case, the Registrant(s) need to provide evidence that performing the described tasks for the times intended in the CSR, does not yield an additional risk for the worker caused by use of gloves.

Note for consideration of the Registrant(s)

There are several ways to reduce the risk arising from wet work situations. One possibility is the reduction of the wearing time of gloves to less than 4 h per day to prevent "wet work". If, for example, gloves are only required for special activities during the task, this should be clearly stated in the corresponding ES. In this case, it might be useful to divide the exposure assessment in two parts: estimation of the inhalation exposure (up to 8 h) and estimation of the dermal exposure (< 4 h).

Other possibilities for organizational measures are, for example, described in the German Technical Rule for Hazardous Substances 401 "Risks resulting from skin contact - identification, assessment, measures" . As the liquid-tight effect of protective gloves prevents the dissipation of perspiration to the outside, the skin swells, which lessens its barrier effect. Therefore, the German Technical Rule for Hazardous Substances 401 limits the duration of use of liquid-tight gloves to a maximum of 4 h (AGS, 2011).

In addition, the application of technical and/or organizational measures might also reduce the dermal exposure itself, with the result that wearing of gloves is unnecessary for the task considered.

The chemical safety assessment includes the generation of exposure scenarios, which should demonstrate the safe use of the considered chemical substance. However, it is considered that a safe use of ptAP cannot be demonstrated if wearing of gloves for longer than 4 h is necessary as this is regarded as a burden and may not be permitted as a permanent measure.

Information request 3

Conduct a higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for exposure scenarios related to the usage of the substance as flakes with anticipated risk characterisation ratio (RCR) > 1.

In addition, for dermal exposure, the Registrant(s) are required to provide evidence that performing the tasks described in the CSR does not yield an additional risk for the worker caused by the prolonged wearing of gloves.

In some contributing scenarios durations of tasks > 4 h (input parameter of the used model

for exposure assessment) are described by the Registrant(s). This indicates an up to 8 h use of personal protective equipment (PPE) such as gloves whenever such PPE is recommended (wearing of PPE, including gloves is also used as an input parameter for the model).

What relevant data is available?

Some of the Registrant(s) including the lead registrant submitted an updated CSR between September and October 2014. This CSR takes into account the whole life cycle of ptAP, including the use of ptAP as a monomer in the production of resins and polymers and as an intermediate in the production of derivatives. The substance is obtained and used either as flakes or in a molten form at elevated temperatures covered by a nitrogen blanket. For scenarios related to the usage of the substance as flakes the lead registrant has estimated workplace exposure to ptAP using the tier 1 model ECETOC TRA v3 and extended TRA. No measured data were submitted with the registration. There are some measurement data available for usage ptBP in the Risk Assessment Report (EC, 2008). Within a literature search performed by the evaluating MSCA some measurement data were identified that are related to the usage of ptBP flakes (Ebner et al., 1979; Kosaka, Ueda, Yoshida, & Hara, 1989).

Justification why new information is needed

Occupational exposure levels given in the CSR were obtained by application of the tier 1 model ECETOC TRA v3. The evaluating MSCA has recalculated a sample of exposure estimates for inhalation and dermal exposure to dust but did not found evidence for significant deviations between the values obtained by the evaluating MSCA and the estimates provided in the CSR. The Calculations performed by the evaluating MSCA are based on the actual version of ECETOC TRA (v3) using the default values defined in the model.

However, it has to be noted in this context that the Registrant(s) used DNELs for workers that are not acceptable (for the justification see Information request 1). The recalculated risk characterisation ratios (RCR) for inhalation and dermal exposure are therefore based on lower DNELs of 0.5 mg/m^3 (inhalation) and 0.07 mg/kg bw/d (dermal).

In several exposure scenarios the recalculated RCRs exceed the value of 1 (Manufacture of ptAP: PROC 8a, 8b, 9; Use of ptAP as a monomer in production of polymers (phenolic resins): PROC 4, 5, 8a, 8b; Use of ptAP as an intermediate in the production of perfumes and fragrances: PROC5 8a, 8b, 9). An overview of the RCRs per each exposure route indicates that RCRs for inhalation exposure in all listed ESs are well below 1, while dermal exposure is not sufficiently controlled. However, it has to be noted that ECETOC TRA seems to underestimate inhalation exposure significantly. This statement is supported by measurements described in the in the Risk Assessment Report for ptBP (EC, 2008). Measurements taken during flaking by a cooling roller and filling show exposure levels of up to 3.1 mg/m³ (150 days a year). According to publications describing the handling of ptBP flakes, inhalation exposure to ptBP dust during loading of reactors can be up to 0.96 mg/m^3 (Ebner et al., 1979; Kosaka et al., 1989).The processes and activities correspond clearly with the generic process category PROC 8a and PROC 8b (transfer of substance or preparation) used by the ECETOC TRA v3 model. In addition, there is no indication that the used technical conditions differ from the ones currently used. A comparison of the measured exposure levels (up to 3.1 mg/m³, 150 days/year) with the modeled ones for PROC 8b (low dustiness, LEV, > 4h) 0.001 mg/m³ and for PROC 8a (low dustiness, LEV, > 4h) 0.05 mg/m³ reveal strong deviations.

Since ptBP and ptAP are handled in very similar physical forms (flakes) the measurement data of ptBP can be used as analogous data for ptAP and can therefore be compared with the ECETOC TRA estimates. In addition, ECHA has no information that the used technical conditions differ from the ones currently used. As a result, the combined RCRs that account for both the inhalation and dermal exposure pathways can significantly exceed 1 (up to 6). Therefore, the usage of ptAP for these ES can lead to unacceptable risks.

In their comments to the draft decision, the Registrant(s) agree to review the CSR to include a higher tier exposure assessment for dermal and inhalation exposure related to the usage of the substance as flakes. If available, representative inhalation and/or dermal measurement data (for ptAP itself or for other substances within the reaction, as appropriate) will be presented as part of the assessment. With regard to the need for glove protection, as above the Registrant(s) will clarify accordingly in the updated CSR that dermal exposure potential (i.e. wearing of gloves) will be less than 4 hours per day. The updated exposure assessments and risk characterisations will be added to the registration dossier within the agreed upon time.
ECHA acknowledges the comments of the Registrant(s) and welcomes the willingness to perform a higher tier exposure assessment for dermal and inhalation exposure related to the usage of the substance as flakes.

However, it is maintained that the ECETOC TRA model may underestimate inhalation exposure. All measured data available so far for the analogue substance ptBP (which is handled as flakes in analogy to ptAP) generally exceed the modelled exposure levels of ECETOC TRA v3 (PROC 8b (low dustiness, LEV 90%, > 4h) 0.01 mg/m³ and for PROC 8a (low dustiness, LEV 90%, > 4h) 0.05 mg/m³).
Since up to now there are no other measurenment data available for these situations (including cleaning, maintenance and sampling activities) it is up to Registrant(s) to demonstrate (preferably by measured data) that risks are adequately controlled and that exposure is in the range predicted by ECETOC TRA v3. Therefore the reference to these publications is maintained.

Finally it has be noted that for ECETOC TRA v3 a tendency to underestimate dust exposure especially for PROC 8a has been found by a study that aims at the evaluation of tier 1 exposure assessment models (ETEAM). The results of the ETEAM study are available on BAuA's website.[3,4]

According to Article 2(4) of the REACH Regulation it shall apply without prejudice to community workplace legislation, including Directive 98/24/EC. Article 6(2) of Directive 98/24/EC states that application of PPE is only permitted where exposure cannot be prevented by other means (substitution, technical and organizational measures). In addition, PPE must be appropriate for the risks involved, without itself leading to any increased risk (Directive 98/656/EEC, Article 4(1)). Therefore, it is the responsibility of the Registrant(s) to prove, within the scope of his chemical safety assessment, that an inappropriate burden of the worker caused by PPE is excluded.

It should be noted that extended use of gloves under occlusive conditions is considered as "wet work" since the hands become moist due to sweat (accumulation of heat and

[3] J. Lamb, S. Hesse, B. G. Miller, L. MacCalman, K. Schroeder, J. Cherrie, M. van Tongeren:
Evaluation of Tier 1 Exposure Assessment Models under REACH (eteam) Project - Final Overall Project Summary Report, 1. Auflage. Dortmund: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin 2015. http://www.baua.de/de/Publikationen/Fachbeitraege/F2303-D26-D28.html
[4] J. Lamb, B. G. Miller, L. MacCalman, S. Rashid, M. van Tongeren:
Evaluation of Tier 1 Exposure Assessment Models under REACH (eteam) Project - Substudy Report on External Validation Exercise, 1. Auflage. Dortmund: Bundesanstalt für Arbeitsschutz und Arbeitsmedizin 2015.
http://www.baua.de/de/Publikationen/Fachbeitraege/F2303-D16.html

moisture). It has been demonstrated, e.g. by Behroozy and Keegel, that "wet work" conditions caused by a prolonged wearing time of gloves present a burden to the worker and increases the risk (Behroozy & Keegel, 2014).

Registrant(s)' comments and proposals for amendment

ECHA A proposal for amendment from a MSCA was received that basically agrees with the information request. The commenting MSCA states that the use of gloves during 8 h shifts cannot represent an ideal situation. However, the commenting MSCA is of the opinion that the information requested might go beyond the legal obligations set out in Directive 89/656/EEC and Annex II of the REACH Regulation. Therefore, the commenting MSCA finds a recommendation rather than a requirement in the Draft Decision more appropriate.

According to REACH, it is the obligation of the Registrant(s) to provide an exposure scenario which describes how the risks can be adequately controlled. The exposure scenarios provided by the Registrant(s) indicate, that the risks arising from the use of ptAP are only adequately controlled if gloves are worn. As the use of gloves for longer than 4 h might yield a "wet work" situation, the use of gloves for longer than 4 h is associated with an additional risk for the worker. Therefore, the Registrant(s) need to provide evidence that performing the described tasks for the times intended in the CSR, does not yield an additional risk for the worker caused by use of gloves. To take the comments and suggestions made in the proposal for amendment into account the decision was amended to reflect on this topic.

What is the request?

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to conduct a higher tier exposure assessment for dermal and inhalation exposure in accordance with the procedure laid down in the 'REACH Guidance on Information Requirements and Chemical Safety Assessment', Chapter R.14 and a risk assessment in accordance with the procedure laid down in Part E for particular exposure scenarios related to the usage of the substance as flakes with risk characterisation ratio (RCR) > 1. This requirement is valid for exposure scenarios describing the production of the substance, its use as an intermediate and its use as a monomer in the production of polymers.

The following PROCs are of concern:

- Manufacture of ptAP: PROC 8a, 8b, 9
- Use of ptAP as a monomer in production of polymers (phenolic resins): PROC 4, 5, 8a, 8b; Use of ptAP as an intermediate in the production of perfumes & fragrances: PROC5 8a, 8b, 9).

The Registrant(s) are required to provide an exposure assessment that demonstrates the safe use of ptAP. Thus, in this particular case, the Registrant(s) need to provide evidence that performing the described tasks for the times intended in the CSR, does not yield an additional risk for the worker caused by use of gloves.

In order to enable evaluation of the assessment all used models and parameters and measurement data shall be clearly stated and documented. When using non-standard parameters a justification must be given, otherwise the use of the parameter cannot be assumed to be justified.

Note for consideration of the Registrant(s)

There are several ways to reduce the risk arising from wet work situations. One possibility is the reduction of the wearing time of gloves to less than 4 h per day to prevent "wet work". If, for example, gloves are only required for special activities during the task, this should be clearly stated in the corresponding ES. In this case, it might be useful to divide the exposure assessment in two parts: estimation of the inhalation exposure (up to 8 h) and estimation of the dermal exposure (< 4 h).

Other possibilities for organizational measures are, for example, described in the German Technical Rule for Hazardous Substances 401 "Risks resulting from skin contact - identification, assessment, measures". As the liquid-tight effect of protective gloves prevents the dissipation of perspiration to the outside, the skin swells, which lessens its barrier effect. Therefore, the German Technical Rule for Hazardous Substances 401 limits the duration of use of liquid-tight gloves to a maximum of 4 h (AGS, 2011).
In addition, the application of technical and/or organizational measures might also reduce the dermal exposure to the substance of concern itself, with the result that wearing of gloves becomes no longer necessary for the task considered.

The chemical safety assessment includes the generation of exposure scenarios, which should demonstrate the safe use of the considered chemical substance. However, it is considered that a safe use of ptAP cannot be demonstrated if wearing of gloves for longer than 4 h is necessary as this is regarded as a burden and may not be permitted as a permanent measure.

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).

IV. 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/regulations/reach/registration/data-sharing.

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

V. 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://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[5] by Leena Ylä-Mononen Director of Evaluation

Annex I: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.
Annex II: General considerations on read-across

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

Annex II General considerations on read-across

This Annex contains additional explanations on read-across in the context of information requests of this decision pertaining to human health endpoints.

A read-across between p-(1,1-dimethylpropyl)phenol (ptAP), CAS 80-46-6 EC No 201-280-9 and 4-tert-butylphenol (ptBP), CAS 98-54-4, EC No 202-679-0 is discussed based on a justification document provided by the Registrant(s) of ptAP, CAS 80-46-6 EC No 201-280-9[6].

Considering the adaptation possibilities under REACH as laid down in Annex XI, 1.5., this report substantiates the read-across hypothesis on:

1) Structural similarity:
[Both] "substances consist of a branched tertiary alkyl chain attached to a phenolic ring in the 4-position (para) to the hydroxyl substituent. The source chemical ptAP has five carbon atoms in the alkyl chain substituent connected to the phenol moiety. The alkyl chain in ptAP can be called either an 'amyl' or 'pentyl' substituent in the chemical name, synonymously. In this respect, ptAP and ptBP analogues are very close structurally as they all have a tertiary alkyl substituent. More specifically, the substituent is specifically present in a branched structure form, and not in a linear n-alkyl chain form. This enables similarity to be inferred in the steric (shape-related) properties of this substituent. The source chemical ptBP has four carbon atoms in a tertiary alkyl chain connected to the phenol moiety, just one methyl group different from the target chemical ptAP. Importantly, the alkyl group is also in the same tertiary form as in ptAP and in the same 4-position relative to the hydroxyl." (ENVIRON, 2013)

2) Degradation and/or metabolism:
"ptAP and ptBP are expected to be absorbed and metabolised similarly in the body. The rationale for this is as follows:
Log Kow: 3.6 for ptAP and 3.3 for ptBP. Given these are very similar values, it is expected that simple absorption by diffusion across biological membranes will be similar and extensive via all routes for both substances.
Metabolism: it is assumed from similar structure and function, that the Phase I and Phase 2 metabolism of ptAP and ptBP will be similar. Phase 1 metabolism – it is expected that ptAP and ptBP will be dealkylated to generate phenol and tert-amyl alcohol (2-methyl-2-butanol; CAS 75-85-4) and tert-butyl alcohol (2-methyl -2-propanol; CAS 75-65-0) for PTAP and PTBP, respectively. In the REACH registration dossiers for these two alcohols, there is no evidence of significant toxicity, and no special considerations are needed in the form of considering these alcohols as potential metabolites here. Given the alkyl substituent is similarly on the para position of both ptAP and ptBP, it is expected that the nature of hydroxylation and catechol formation via the action of cytochromes P450 on the phenolic ring should be similar for the two chemicals. Phase 2 metabolism - ptBP has been shown to be extensively cleared from the body in urine via the formation of glucuronide and sulphate conjugates [Kosta et al 1981]. Radiolabelled ptBP was given intravenously to Wistar rats (single dose 1.2-10.4 mg/kg bw) and bile and urine were collected for four hours. Total recovery was 91-93% of which 65-71% was excreted as glucuronide conjugate, 17-21 % as sulphate conjugate. Given the same functionality (ie the hydroxyl group) is present in both ptAP and ptBP, and similar physicochemical properties, metabolic clearance is also expected to be rapid and effected by similar phase 2 metabolism for ptAP." (ENVIRON, 2013)

[6] "Read-across between p-tert-amylphenol (CAS 80-46-6) and Sodium p-tertiary amylphenol (CAS 31366-95-78) and p-tert-butylphenol (CAS 98-54-4)", ENVIRON 2013".

3) Supporting evidence in physico-chemical data:
"ptAP, […] and ptBP display similar physico-chemical properties [the Registrant(s) provides a table showing the similarities]. The physico-chemical properties determine environmental distribution and fate (e.g. molecular weight, partition coefficients such as log Kow, water solubility) and contribute to toxicokinetic properties in mammals." (ENVIRON, 2013).

4) Supporting evidence in toxicological data
Evidence was provided for acute toxicity and reproductive toxicity (the latter established by comparison of systemic toxic effects in a developmental toxicity study performed with ptAP and OECD TG 422 and OECD TG 416 studies performed with ptAP).

Remarks:

With respect to 1) and 3) the evaluating MSCA agrees on structural similarity and similarity of physico-chemical properties.

With respect to 2) the evaluating MSCA agrees with the conclusions drawn on absorption, however the evaluating MSCA disagrees with the conclusions drawn with respect to metabolism:

Toxicokinetics is mainly determined by physico-chemical properties such as chemical structure, molecular weight, water solubility, n-octanol-water partition coefficient and vapour pressure. As both substances have similar physico-chemical properties and as the structural difference consists in one methyl group of the substituent in ortho-position, comparable toxikokinetic behaviour of the two substances is expected. However, the evaluating MSCA disagrees with the statements given in ENVIRON 2013 with respect to metabolism: dealkylation, i.e. removal of the alkyl substituent, is considered unlikely. Rather, glucuronidation and sulphation (as also described for other o-substituted phenols) are considered to be the main metabolic pathways. However, for estimates of percent absorption for the oral, dermal and inhalative uptake route, this issue is of minor importance.

With regard to metabolism, from OECD toolbox predictions as well as from information obtained from toxicokinetic studies performed with other branched o-alkylphenols, it appears likely that the metabolism of ptAP and ptBP consists in hydroxylation reactions in the phenolic ring and in the alkyl chain, followed by conjugation (glucuronidation and sulfation). In this respect there is a difference between ptAP and ptBP as ptAP can form more hydroxylated metabolites. Hydroxylation is a prerequisite for subsequent conjugation which is considered as a detoxifying step. Although not experimentally proven for ptAP and ptBP itself, toxicokinetic and toxicity studies performed with other branched p-substituted alkylphenols support this assumption. For instance, in case of 4-(1,1,3,3-tetramethylbutyl)phenol (CAS 140-66-9) a large number of repeat-dose and reproductive toxicity studies have been performed by different routes of administration. The substance was more potent (with respect to endocrine related activities as well as with respect to other systemic effects, such as decrease in liver or kidney weights) when administered subcutaneously or intraperitoneally (i.e. when first-pass metabolism was circumvented) in comparison to the oral application route. That means that the subcutaneous or i.p. administration routes in these studies were chosen in order to maximise toxicity. Likewise, in vitro studies performed with nonyl- or octylphenol glucuronides demonstrated that the glucuronides (in contrast to unmetabolized parent compounds) did not show any evidence of estrogen-, antiestrogen-, androgen-, or anti-androgen-like activity (Moffat et al., 2001).

In comparison to ptBP, ptAP is capable of forming more hydroxylated metabolites which are a prerequisite for subsequent conjugation which is considered as detoxification. Therefore, ptBP might be assumed as being of slightly higher toxicological potency.

With respect to 4), NOAELs obtained from a two generation reproductive toxicity study performed with ptBP, a combined repeated dose and reproductive/developmental toxicity performed with ptBP and a developmental toxicity study performed with ptAP indicate comparable systemic toxicity based on NOAELs obtained, but an estrogen binding assay points to a slightly higher estrogen binding potential of p-(1,1-dimethylpropyl)phenol. However, the significance of the latter finding is unclear since it is based on one study only.

Because of structural similarity, similar physico-chemical properties and likely a comparable bioavailability, the evaluating MSCA considers read-across between ptBP and ptAP acceptable with regard to the endpoint prenatal developmental toxicity. Metabolism (glucuronidation and sulfphatation, eventually preceded by hydroxylation) likely contribute to detoxification of the parent compounds, although comparing experimental data is scarce.

The evaluating MSCA concludes that the Registrant(s) have provided reliable but incomplete data to support the read across between ptAP and ptBP. In some points (e.g. with respect to metabolism) the evaluating MSCA disagrees with the arguments provided by the Registrant(s).Recently, a read-across assessment framework (RAAF)[7] hasbecome available, providing guidance and a systematic approach for evaluating read-across cases, based on a grading system. This may then also help Registrant(s)s to improve the quality of their registration dossiers.

The evaluating MSCA admits that there is a lack of knowledge with respect to the modes of action of ptBP and ptAP leading to adverse (vitiligo) or potentially adverse effects (probable thyroid toxicity, kidney toxicity). With respect to non-vitiligo endpoints the available information of branched p-phenols in general point to the fact that metabolism (glucuronidation and sulfphatation, eventually preceeded by hydroxylation) would contribute to detoxification of the parent compounds.

There are several reports on the occurrence of vitiligo, a depigmentation of the skin, in workers occupationally exposed to ptAP. Furthermore it has been reported that phenolic compounds such as ptBP and ptAP are involved in the formation of occupational vitiligo. The association between vitiligo and ptAP does not appear to have been studied systematically, whereas there is clear association between the occurrence of vitiligo and exposure to the structurally similar substance ptBP. There are numerous human studies providing evidence for leukoderma- and vitiligo-like effects in humans exposed to ptBP and ptBP-containing products.

As ptAP
a) is structurally similar to ptBP,
b) belongs to phenolic compounds generally known to be inducers of vitiligo
c) bioavailability between ptBP and ptAP is likely to be comparable
d) there are indications from the literature on depigmentation in workers caused by ptAP and
e) in the absence of scientific data demonstrating the absence of a depigmentation potential of ptAP
the evaluating MSCA considers ptAP equipotent with ptBP with respect to the induction of

[7] http://echa.europa.eu/en/support/grouping-of-substances-and-read-across

vitiligo.

Thus, the evaluating MSCA is of the opinion that read-across should be extended to the endpoint depigmentation (vitiligo).

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