EUROPEAN CHEMICALS AGENCY

Helsinki, 20 April 2016

Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXX-XX-XX/F)

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

For 4-tert-butylphenol, CAS No 98-54-4 (EC No 202-679-0)

Addressees: Registrant(s)[1] of 4-tert-butylphenol (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.

Based on an evaluation by 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 4-*tert*-butylphenol (ptBP), CAS No 98-54-4 (EC No 202-679-0) 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 potential endocrine disruptor and Exposure / High (aggregated)

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

tonnage, ptBP 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 Germany was appointed to carry out the evaluation.

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

The evaluating MSCA considered that further information was required to clarify the following concerns: repeated dose toxicity, developmental 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 07 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).

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).

On the basis of a proposal for amendment from a competent authority concerning the Prenatal developmental toxicity study, which was initially intended to be requested in the present decision, the Member State Committee decided that this information requirement can be more appropriately addressed in a possible compliance check by ECHA.

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 registered substance subject to the present decision:

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) with modifications as specified in Section III.

   Alternatively, an existing repeated dose toxicity study (90 day) on the principally accepted read-across 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 also 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 Chemical Safety Report (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.

4. A higher tier exposure assessment for dermal exposure for the application of liquid and solid end products containing ptBP as a hardener in paints, adhesives, thinners etc. (up to 30 %) 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 those scenarios with 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 27 January 2018 an update of the registrations containing the information required by this decision[2], including, where relevant, an up;date 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 27 October 2016 an update of the registrations containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

1. 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 registered substance 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 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

A two-generation reproductive toxicity study (OECD TG 416) and a reproduction/developmental screening study (OECD TG 422) performed with 4-tert-butylphenol (ptBP) are available. Further, the Registrant(s) have provided an oral 90-day toxicity study (OECD TG 408) performed with p-tert-nonylphenol (CAS 84852-15-3) without any justification on read-across (a brief discussion on this issue is provided in Annex II a). Therefore no oral 90 day repeat-dose toxicity for ptBP is available enabeling assessment of systemic toxicity of the substance.

[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

A 90-day toxicity study is not available for the registered substance which is considered a concern due to the following reasons:

(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. Furthermore, due to observations made in the above studies, systemic effects of the registered substance cannot be excluded. In particular, it cannot be decided, if kidney-related effects in males and effects related to reproductive organs in females are substance-specific or due to weight reduction and pregnancy, respectively.

(II) A number of occupational studies as well as animal studies using non-albino rodents and rabbits indicate that ptBP might have a skin depigmentating potential. However, most of the animal experiments are older (non-guideline) studies and/or often lack testing details or use different exposure routes, which makes a decision on a systemic depigmentation effect difficult.

(III) Several 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 ptBP may exert thyroid activity.

The Registrant(s) are concerned about the infrequent use and thus the poor historical record with regard to non-albino strains. Furthermore, the Registrant(s)s believe that available information related to depigmentation (mouse study by Hara and Nakajama, 1969 and German MAK value documentation) is sufficient for adequate risk control. New data would not further understanding of control measures and could be misleading. In addition, since the Registrant(s) favours an albino strain, the requested histopathological examination of the eye is dropped because this examiniation does not make sense with albino animals.

The Registrant(s) had further concerns to use gavage instead of feeding for oral administration when conducting the TG 408 study. It was admitted that a decrease weight gain could be related to reduced food consumption at the two highest concentrations of an available TG 416 study, it was noted that the NOAEL fo this study was similar to that one derived from a TG 422 gavage study. In addition, gavage was discouraged by arguing against the less realistic and kinetically less relevant bolus administration in case of gavage as well as the higher stress for the animals.

ECHA is of the opinion that leading test animal suppliers dispose of a variety of established non-albino strains with historical records. Accordingly, there should be no problem with this issue (if proper controls are used in the study, historical controls may not be an issue at all). Furthermore, the available (old) animal data and human references are considered to be not very reliable. Since depigmentation is an important component in overall risk characterisation, it is suggested to integrate this endpoint in a current animal testing protocol.

With regard to the eye examination, it is considered that retinal hypopigmentation promises to be a sensitive early indicator for chemically induced systemic depigmentation (clinically, vitiligo is often associated with hypopigmentation or atrophy of the retinal pigment epithelium, or both). Exploring depigmentation and thyroid acticity in one study also may inform on a possible link between vitiligo and adverse thyroid effects, both known to be

coinciding autoimmune disorders. Accordingly, the statement of reasons (section III) have been amended under d) Thyroid-related activity.

The Registrant(s) may consider to conduct the major study with an albino strain with additional adequate satellite groups using a non-albino strain to clarify the depigmentation concern.

ECHA proposes to test a dose range of < 50 mg/kg/d at the lower end and 200 mg/kg/d at the upper end for the TG 408 study (see amendments in section III for reasoning). Gavage is favoured for oral administration because it cannot be concluded whether the observed effects in the TG 416 study were actually substance-related or a consequence of lower food consumption. In particular in females, reduced weight gain in females was 16.7% in week 0-16 and initial food decrease in consumption was 15.1% and the weight gain was reduced by 16.7% in week 0-16 in the mid-dose range, which may have affected the observed sex-related effects. Furthermore, a TG 422 study applying gavage identified respiratory distress in females as the most sensitive adverse effect for risk characterisation by the Registrant(s) (labelled as key study), though this effect likely was an administration artefact. Hence, requesting oral gavage in the TG 408 study would shed further light on the relevance of this induced respiratory distress. Finally, since gavage is one method of choice in the OECD test guideline, the extra stress should be tolerable, ensuring that the doses are actually incorporated.

What is the request

Therefore, a subchronic study, oral route, following OECD test guideline 408 (EU B.26) is required. Besides a thorough and complete analysis of the standard parameters layed out in the guideline, a number of additional parameters are requested to address several open questions which rose during the substance evaluation, i.e.:

a) Nephropathy

A detailed kidney histopathology and urinalysis in male rats is necessary because the OECD TG 416 study performed with ptBP raised a concern that ptBP may exert 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 & 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 ptBP having a skin depigmentation potential, which is 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 from animal studies. 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 and therefore, ECHA requests to carry out the above 90 day toxicity study with an appropriate non-albino rat strain. This will allow to clarify the concern for a (systemic) depigmentation potential of ptBP and confirm older, poorly documented animal studies, which reported systemic depigmentation in black mice by ptBP where only rudimentary information was available. 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 techniques as it may be a sensitive site for depigmentation.

d) Thyroid-related activity

The initial concern of an endocrine effect for the environment prompted the evaluating MSCA to assess a putative thyroid-related activity of 4-tert-butlyphenol. The existing animal data either do not provide information on the thyroid (OECD TG 422 study performed with 4-tert-butlyphenol) or report findings in the F1 and F2-generation which are not indicative of a thyroid activity (OECD TG 416 study performed with 4-tert-butlyphenol). On the other hand, in a number of occupational studies, which investigated the depigmentation potential of 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 p-tert-butylphenol 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 the registered substance subject to this decision:

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 vaginal epithelial atrophy, ovary weight as well as histopathology and staging of estrous cycle in females;
- 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;
- Histopathological examination of the eye and the ear.

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 medium dose of the 2-generation feeding study with PTBP which showed still acceptable values reduced weight gains and food consumption in males. As gavage excludes feeding-related effects, this dose should be acceptable for females as well.

Concurrently to the substance evaluation of p-tert-butylphenol, the evaluating MSCA performed a substance evaluation of the substance p-(1,1-dimethylpropyl)phenol, CAS No 80-46-6 (EC No 201-280-9). As a result of this evaluation, the Registrant(s) of p-(1,1-dimethylpropyl)phenol are also requested to perform a repeated dose 90-day oral toxicity study on p-tert-butylphenol. Therefore, the addressees of this decision are requested to coordinate with the Registrant(s) of p-(1,1-dimethylpropyl)phenol in order to avoid unnecessary testing on vertebrate animals. A justification of read across between p-(1,1-dimethylpropyl)phenol, CAS No 80-46-6 and p-tert-butylphenol is given in Annex II b to this document.

Registrant(s) comments and proposals for amendment

ECHA noted that the Registrant(s) informed about the existence of a 90-day repeated dose study on the principally accepted read-across substance ptAP (CAS 80-46-6) in response to a proposal for amendment.

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 the proposal for amendment of a competent authority 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 at doses below those when skin depigmentation becoming 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 database 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 handling 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 the Registrant(s) described 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 ptBP, inter alia the use of ptBP 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 substance is handled either as flakes or as molten ptBP 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 occurs 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 ptBP 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 combined 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).

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. In this context, the Registrant(s) state that a higher tier exposure modelling is unlikely to be possible for the dermal route since there are no calibrated models available. The Registrant(s) are willing to present measurement data if available and otherwise a detailed description of all worker contributing scenarios.

According to the ECHA "Guidance on information requirements and chemical safety assessment, Chapter R.14: Occupational exposure estimation", '*Risk of Derm*' is a higher tier model and exposure assessment with measurement data is a higher tier assessment as well. Therefore, the evaluating MSCA does agree that a detailed description of all worker-contributing scenarios is sufficient.

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 the usage of the molten substance.

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 was received from a MSCA 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 ptBP 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 exposure scenarios. These exposure scenarios are related to the usage of the molten ptBP e.g. transfer of molten substance, unloading from bulk containers, bulk quantity additions.

The following PROCs are of concern:
- Manufacture of ptBP: PROC 2, 9, 15.
- Use as an intermediate: PROC 2, 3, 4, 5, 8a, 8b, 9.
- Use as a monomer in the production of polymers – large scale: PROC 4, 5, 8a, 8b, 9, 14, 15.

- Use as a monomer in the production of polymers – small scale: PROC 4, 5, 8a, 8b, 9, 14, 15.

Most of the PROCs represent several contributing scenarios. 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 ptBP. 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 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 ptBP 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 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.

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 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 ptBP, inter alia the use of ptBP 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. There are some measurement data available 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 recalculated the estimates for inhalation and dermal exposure to dust. For the dermal exposure route the evaluating MSCA observed significant deviations from the values provided by the Registrant(s) 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.

An overview of the RCRs per each exposure route indicates that RCRs for inhalation exposure in all contributing scenarios are well below 1. However, it has to be noted that ECETOC TRA v3 seems to underestimate the inhalation exposure to solids 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/m³ (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/³, 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.

The Registrant(s) are of the opinion that the cited measurement data is too old and not reliable. However, it is maintained that the ECETOC TRA model may underestimate inhalation exposure. All measured data available so far for ptBP generally exceeds the modelled exposure levels of ECETOC TRA v3. To date, no other measurement data is available for these situations (including cleaning, maintenance and sampling activities) and it is up to Registrant(s) to demonstrate that risks are adequately controlled and that exposure is in the range predicted by ECETOC TRA v3. The reference to these publications is therefore 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[3]). The results of the ETEAM study are available on BAuA's website.[4]

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. The Registrant(s) considered the exact duration of use for the dermal exposure estimates for some contributing scenarios. For example if a duration of activity of 1 h is stated, a modifying factor of 0.125 was applied. This approach is neither in the scope of ECETOC TRA v2 nor v3. The model only provides dermal exposure duration modifiers for non-dusty solids which are banded. For example, if the duration of activity is between 15 min – 1h a modifying factor of 0.2 is applied.

In addition, for some contributing scenarios the Registrant(s) modified the exposure estimates for mixtures on the basis of the actual percentage of ptBP. This approach is not in the scope of ECETOC TRA v3, which applies (more conservative) banded modifiers for dermal and inhalation exposures. In some contributing scenarios a combination of these inapplicable modifying factors was applied yielding a deviation by a factor of approx. 10 from the values calculated by the evaluating MSCA.

As a result, the recalculated combined RCRs which consider both the inhalation and dermal exposure pathways can significantly exceed 1. Therefore, usage of ptBP for these ES implies unacceptable risks.

The evaluating MSCA is not able to calculate exposure levels using a tier 2 model due to a lack of information on the details of the exposure relevant parameter and concludes 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.

The Registrant(s) state that the ECETOC Technical Report 107, 2009, pg. 78 offers a clear option for deviating from the banding model for dermal exposure to mixtures. However, the Registrants did not use ECETOC TRA v2 but ECETOC TRA v3. The quoted passage of the ECETOC Technical Report refers to v2. ECETOC TRA v2 does not "*account for exposure duration, substance concentration ..., or the quantity efficiency of dermal RMMs*" (ECETOC Technical Report 107, 2009, p. 13). Therefore, only for "*specific situations 'simple' exposure modifiers may be applied ..., but as this may lead to a possible increase in uncertainty of the final exposure estimate ... these factors have not been formally implemented into version 2 of the TRA*".

In Appendix D-3 these modifiers are described in more detail. Concentration of the substance in a mixture is as well considered as personal protective equipment. The described exposure modifiers are the same as for inhalation exposure. However, the duration of use is not considered at all for the estimation of dermal exposures in this version.

Nevertheless, the <u>used</u> version of ECETOC TRA (v3) implemented exposure modifiers for dermal exposure within the model. It aligns the basis for dermal exposure prediction with that adopted for inhalation exposure. These factors are no longer 'simple' exposure

[3] J Lamb, S Hesse, B 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 , Dortmund/ Berlin/ Dresden 2015
[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

modifiers, which may be applied. These factors are now defined and part of the model. They are described in Chapter 2.3.3, 2.3.4 and 2.3.5 of the Technical Report No. 114.
The Registrant(s)are requested to use the model within its scope and is not permitted to add further modification factors or to modify the existing factors, at least not without detailed justification.

According to REACH Article 2(4) the REACH Regulation 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 basically agrees with the information requests. The commenting MS CA 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 ptBP 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?

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 monomer in the production of polymers.
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.

The following PROCs are of concern:

- Use as an intermediate: PROC 8b, 9
- Use as a monomer in the production of polymers – large scale: PROC 4, 5, 8a, 8b
- Use as a monomer in the production of polymers – small scale: PROC 4, 5, 8a, 8b

The Registrant(s) are required to provide an exposure assessment that demonstrates the safe use of ptBP. 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 ptBP 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 4

Conduct a higher tier exposure assessment for dermal exposure for the application of liquid and solid end products containing ptBP (up to 30 %) as a hardener in paints, adhesives, thinners etc. 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 those scenarios with RCR > 1 (End use as hardener e.g. in coatings and paints, fillers, putties, thinners, polymer preparations and compounds with increased (up to 30 %) ptBP content).

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 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?

The Registrant(s) describe the application of end products containing ptBP (up to 30 %) as a hardener in e.g. coatings, paints, thinners, putties etc. Dermal exposure is assessed using the tier 1 model ECETOC TRA.

Justification why new information is needed

The evaluating MSCA recalculated the estimates for dermal exposure and observed significant deviations from the estimates provided by the Registrant(s) in the CSR. Calculations performed by the evaluating MSCA are based on the actual version of ECETOC TRA (v3) using the default values defined in the model.

The Registrant(s) modified the exposure estimates for mixtures on the basis of the actual percentage of ptBP. This approach is not in the scope of ECETOC TRA v3, which applies (more conservative) banded modifiers for dermal exposures. As a result, the values estimated by the evaluating MSCA already deviate by a factor of up to 7.
In addition, the Registrant(s) considered the exact duration of use for the exposure estimates. This approach is not in the scope of ECETOC TRA, neither in version 2 nor in version 3. If ECETOC TRA v3 applies duration modifiers for dermal exposure, these modifiers are banded. However, these banded modifiers do not apply to low/very low volatility liquids. As a consequence of this, the values estimated by the evaluating MSCA deviate by an additional factor of 16 (exact duration: 30 min) or 2 (exact duration: 4 h). Altogether, the application of modifying factors which are not in the scope of the model yields a deviation by a factor of approx. 53 for PROC 8a (Filling of mixing vessel) and PROC 5 (Mixing), by a factor of approx. 107 for PROC 8a (Filling of paint gun) and by a factor of approx. 13 for PROC 7 (Spray application) from the evaluating MSCA values. As a consequence the application of these modifying factors yield RCRs > 1.

The evaluating MSCA is not able to calculate exposure levels using a tier 2 model due to a lack of information on the details of the exposure relevant parameter and concludes 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 using the end products containing ptBP as a hardener in adhesives, paints, putties etc.

The Registrant(s) state that the ECETOC Technical Report 107, 2009, pg. 78 offers a clear option for deviating from the banding model for dermal exposure to mixtures.
Again, the Registrant(s) did not use ECETOC TRA v2 but ECETOC TRA v3. The quoted passage of the ECETOC Technical Report refers to v2. ECETOC TRA v2 does not "*account for exposure duration, substance concentration ..., or the quantity efficiency of dermal RMMs*" (ECETOC Technical Report 107, 2009, p. 13). Therefore, only for "*specific situations 'simple' exposure modifiers may be applied ..., but as this may lead to a possible increase in uncertainty of the final exposure estimate ... these factors have not been formally implemented into version 2 of the TRA*".

In Appendix D-3 these modifiers are described in more detail. Concentration of the

substance in a mixture is as well considered as personal protective equipment. The described exposure modifiers are the same as for inhalation exposure. However, the duration of use is not considered at all for the estimation of dermal exposures in this version. Nevertheless, the used version of ECETOC TRA (v3) implemented exposure modifiers for dermal exposure within the model. It aligns the basis for dermal exposure prediction with that adopted for inhalation exposure. These factors are no longer 'simple' exposure modifiers, which may be applied. These factors are now defined and part of the model. They are described in Chapter 2.3.3, 2.3.4 and 2.3.5 of the Technical Report No. 114. If further modification factors are introduced into the model or existing factors are modified, this should be done with a detailed justification.

According to REACH Article 2(4) the REACH Regulation 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).

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 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 ptBP 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?

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to conduct a higher tier exposure assessment for dermal 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 exposure scenario concerning the usage of the products containing up to 30 % ptBP.

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. The corresponding PROCs are:

PROC 5, 7, 8a.

The Registrant(s) are required to provide an exposure assessment that demonstrates the safe use of ptBP. Thus, in this particular case, 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.

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 substanceHowever, it is considered that a safe use of ptBP 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 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.

Annex II a

Read-across between 4-tert-butylphenol (ptBP) and nonylphenol (NP)

REACH regulation, Annex XI specifies possibilities under which read-across can be applied, i.e. making use of use of analogous substances to predict properties for the registered substance.

The Chemical Safety Report (CSR) for the registered substance ptBP applies a read-across approach to the related substance nonylphenol (CAS 84852-15-3) to address a number of human health endpoints or even to waive certain studies, such as:

5.6.1.1. Repeated dose toxicity: oral (Test material: Phenol, 4-nonyl-, branched)
5.9.1. Effects on fertility (Test material Nonylphenol)
5.9.2. Developmental toxicity (Test material: nonylphenol)

Justification for read-across in the CSR is limited to the following general statements:

"In addition, cross-reading to a high quality 90d study conducted with a structurally related material (p-nonylphenol) is possible and therefore, taking into account animal welfare aspects, no further testing for this endpoint required."

"In a 90d study on a closely related alkylphenol (p-nonylphenol) a NOAEL of 50 mg/Kg bw. was observed."

A detailed analysis which would justify read-across is not provided by the Registrant(s), and there is no further substantiation for this structural similarity, as specified in REACH regulation, Annex XI, 1.5, 1-3, respectively.

This is in clear contrast to the CSR for the related substance p-(1,1-dimethylpropyl)phenol (ptAP), where the Registrant(s) for ptAP substantiates a read across approach between ptAP and ptBP referring to the document ENVIRON, [redacted]. This justification has been deemed acceptable by the evaluating MSCA and was actually used for the hazard assessment of the registered substance ptBP in the substance evaluation. This approach was not considered in the CSR for ptBP.

However, a broad read-across approach to other p-substituted alkylphenols applied in the CSR for ptBP without proper justification is not accepted by the evaluating MSCA.

This is in line with the fulfillment of information requirements under REACH, which says that the Registrant(s) may adapt requested testing according to general rules (Annex XI, here specifically 1.5) but any adaptation needs a scientific justification as well as adequate and reliable documentation.

The evaluating MSCA is aware of the structural similarity among the various p-substituted

alkylphenols. Accordingly, physico-chemical and toxicokinetic parameters may show similarities between ptBP, ptAP, NP, which would need further elaboration (see below). Therefore, if studies which tested different p-substituted alkylphenols provide hints on toxic effects that have been suspected or proved for ptBP (or ptAP), this data has been considered for the substance evaluation of ptBP as supporting information on a case-to-case basis.

There is one exception, where the evaluating MSCA considers a more general read-across between various p-substituted alkylphenols acceptable, that is estrogen receptor (ER)-binding studies, which are related to the initial ED concern (with regard to human health, the ED concern is discussed in detail in the substance evaluation, while the CSR did not refer to it at all). A number of experimental studies is available, which compared the relative binding affinities of different p-substituted alkylphenols, grossly demonstrating that p-substituted alkylphenols with larger and more branched side chains exert a stronger ER-binding potential in vitro. Furthermore, it is understood that those binding studies are usually performed with pure analytical-grade substances. This may differ from toxicity studies, which usually test the commercial product. In case of nonylphenol, this is actually a mixture of many nonylphenol isoforms. Therefore, for this particular case, there appears to be sufficient evidence to apply the grouping and analogy concept according to REACH, Annex XI, 1.5, No. 3 ("a constant pattern in the changing of the potency of the properties ..."). These studies may be indicative for an endocrine activity of a p-substituted alkylphenol in vitro, but extrapolation to higher-tier studies should be treated carefully, because of increasingly complex and compensating mechanisms may add to higher uncertainty .

Recently, a read-across assessment framework (RAAF)[6] has become available, providing guidance and a systematic approach for evaluating read-across cases, based on a grading system. This may then also help Registrant(s) to improve the quality of their registration dossiers.

Annex II b

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

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[7].

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

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

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, 2014)

3) Supporting evidence in physico-chemical data:
"ptAP, [...] and ptBP display similar physico-chemical properties [the Registrant(s) provide 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, 2014).

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.

Conclusion

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 PptP and ptBP. In some points (e.g. with respect to metabolism) the evaluating MSCA disagrees with the arguments provided by the Registrant(s). Thus, read-across is feasible only on a case-by-case (and endpoint-by-endpoint) basis. With respect to developmental toxicity read-across between ptBP and ptAP is considered appropriate.
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