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

For tert-butyl perbenzoate, CAS No: 614-45-9, EC No: 210-382-2

Addressees: Registrants of tert-butyl perbenzoate (Registrant(s))

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrants meeting the following criteria are *not* addressees of this decision: i) Registrants who exclusively use the above substance as an on-site isolated intermediate and under strictly controlled conditions and ii) Registrants who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by the National Institute of Health on behalf of the Ministry of Health as the Competent Authority of Italy (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 24 June 2014.

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 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 Italy has initiated substance evaluation for tert-butyl perbenzoate, CAS No 614-45-9 (EC No 210-382-2) based on registration submitted by the Registrants 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 the initial grounds for concern relating to sensitization andExposure/Wide dispersive use; Consumer use, tert-butyl perbenzoate was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013. The Competent Authority of Italy was

appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA noted additional concern regarding genotoxicity, pre-natal developmental toxicity and Human exposure assessment and risk characterisation with potential human risk via the environment.

The evaluating MSCA considered that further information was required to clarify the above-mentioned concerns. 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 20 March 2014.

On 29 April 2014 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. This deadline includes an extra seven-day period as addressed in the last update point 9(d) of the Terms of Conditions of REACH-IT.

Registrant commenting phase

By 5 June 2014 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). The information contained therein is reflected in the Statement of Reasons (Section III) and amendments to the Information Required (Section II) were made.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 5 March 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, two Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 10 April 2015 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and, where considered appropriate, the draft decision was amended accordingly.

Referral to Member State Committee

On 20 April 2015 ECHA referred the draft decision to the Member State Committee.

By 11 May 2015, in accordance to Article 51(5), the Registrant(s) provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposals for amendment into account.

A unanimous agreement of the Member State Committee on the draft decision was reached on 28 May 2015 in a written procedure launched on 18 May 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 instructions (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in rabbits, oral route;

2. *In vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay, OECD 489) in rats, oral route, with examination of liver and either glandular stomach or duodenum/jejunum;

3. Perfom a human exposure assessment and a quantitative risk characterisation for all relevant exposure scenarios taking into account the selected DNELs for long-term systemic effects;

4. Provide sufficient and consistent information on the specification of personal protective equipment and the duration of use for all scenarios where the use of personal protective equipment is advised (CSR).

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **21 November 2016** an update of the registration(s) containing the information required by this decision, including robust study summaries and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

1. **Pre-natal developmental toxicity study on a second, non-rodent species**

The request is based on a proposal of amendment by ECHA, with which the Registrant(s) disagreed. The request is based on the following considerations:
The technical dossier of tert-butyl perbenzoate contains a pre-natal developmental toxicity (PNDT) study performed in rats by the oral route (gavage) according to GLP and OECD Guideline 414 (Prenatal Developmental Toxicity Study).

The registered substance was tested at doses of 100, 300 and 1000 mg/kg bw/day and the Registrant(s) reported the following conclusion for this study: *"Treatment at 1000 mg/kg bw/day was associated with lower maternal body weight gain during gestation and an initial effect on food consumption. No similar effects were apparent at 300 mg/kg bw/day and this dosage is considered to represent the No Observed Effect Level (NOEL) for the pregnant female.*
In-utero survival of the developing conceptus was unaffected by maternal treatment at 1000 mg/kg bw/day although reduced fetal weight and external, visceral and skeletal findings indicated an adverse effect on fetal growth. The absence of any structural defects indicated that development per se was unaffected at this dosage. Only an equivocal increase in the incidence of fetuses/litter showing kinked/dilated ureter(s) prevented 300 mg/kg bw/day being classified as a fetal No Observed Effect Level and a dosage of 100 mg/kg bw/day is therefore considered to be a clear No Observed Effect Level (NOEL) for the developing conceptus."

Moreover, in the Chemical Safety Report, the Registrant(s) provided the following statement for justification for non-classification for developmental toxicity "*The only notable effect in an OECD 414 study was delayed developmental effects in the presence of reduced maternal weight gain and food consumption*".

However, ECHA considers that the slight maternal toxicity observed (5.3% reduction of adjusted maternal body weight) does not usually lead to such a significant reduction in fetal body weight like here, 21%. In addition, ECHA noted that there were findings in ureter at 300 mg/kg bw/day where there was no maternal toxicity and no reduction in fetal body weight and thus, increased incidence of kinked and/or dilated ureters cannot be considered secondary to the maternal toxicity or reduced fetal body weight and delayed development at 300 mg/kg bw/day.

The results from the first PNDT study suggest that tert-butyl benzoate may merit a classification for reproductive toxicity according to the CLP Regulation and could be a possible candidate for a proposal for harmonised classification and labelling according to Article 37 of Regulation (EC) No 1272/2008.

Therefore, based on this new information provided, ECHA considers that there is further concern on developmental toxicity and a PNDT study on a second species should be requested to obtain comprehensive information on developmental toxicity of tert-butyl perbenzoate and conclude on the classification.

As explained above, the information available on this endpoint for the registered substance in the technical dossier does not clarify the concern with developmental toxicity. Consequently it is necessary to provide further information for this endpoint. ECHA considers that there is no alternative to a study in vertebrate animals available to assess the possible developmental toxicity of the registered substance.

The Registrant(s) indicated in the comments to the proposal of amendment a disagreement with this request for a PNDT study on a second species since:
(i) the effect observed in the first species ('kinked/dilated ureters') should be considered a 'transient variations';
(ii) a possible classification would require 'significant toxic effects in the offspring' and
(iii) at Annex IX they considered the PNDT/2nd species not a requirement under REACH.

However, ECHA notes that:
(i) the available pre-natal developmental toxicity study in rats indicates that the developing organism is more susceptible than the adult to the toxicity of tert-butyl perbenzoate, in particular concerning the intrauterine growth and the development of urogenital system;
(ii) The effects observed in rats (markedly reduced fetal weight and markedly incread incidence of dilated ureters at dose levels inducing slight or no maternal toxicity) are considered developmental delays per se insufficient to trigger classification as Repro 1B; conversely, such effects provide sufficient evidence to trigger a study in a second species, in order to assess whether in non-rodents the substance might induce severe and irreversible developmental toxicity.
(iii) As there is a concern for pre-natal developmental toxicity, a PNDT study on second species is needed.

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: a pre-natal developmental toxicity study on a second, non-rodent species according to OECD TG 414 (rabbit, oral route).

2. An *In vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay, OECD 489)

This request was added to the decision as a result of a proposal for amendment by a Competent Authority of the Member State received during the consultation phase of the Draft Decision. The request takes into account the comments received by the Registrant(s). It is based on the following considerations:

Tert-butyl perbenzoate causes both chromosome aberrations and gene mutations *in vitro*. The substance yielded a positive result in the *in vitro* mammalian chromosome aberration test (NTP, Matthews, H.B. 1992) with and without metabolic activation (Klimisch score 2, reliable with restrictions) according to the Registrant(s).

The substance also yielded positive results in the AMES test (NTP, Matthews, H.B. 1992) in Salmonella typhimurium strains TA100, TA1537, and TA98, with and without metabolic activation, as well as in the Mouse Lymphoma Forward Mutation Assay (Pence, D.H.;1984) with and without metabolic activation. Both studies are Klimisch score 2 (reliable with restrictions) according to the Registrant(s). This indicates that the substance causes gene mutations *in vitro*.

According to REACH (Annex VIII column 2 point 8.4.) and the *REACH Guidance on Information Requirements and Chemicals Safety Assessment. Chapter R.7a: Endpoint Specific Guidance ver. 3.0, Aug 2014, Mutagenicity, c.f. e.g. Figure R 7.7.1,* in this particular case (higly reactive substance) the conducted in vivo micronucleus test alone is not appropriate because it only targeted the concern for chromosome mutations but did not target the gene mutagenicity concern. Therefore, appropriate in vivo mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies in Annex VII or VIII.

The negative *in vivo* micronucleus assay on peripheral lymphocytes (NTP, Matthews, H.B. 1992) submitted by the Registrant(s) cannot be considered an appropriate study, as no evidence of target cell exposure (local cytotoxicity, *i.e.* alteration of PCE/NCE ratio) was reported. Moreover, toxicokinetic studies (NTP, Matthews, H.B.; 1992) demonstrated that tert-butyl perbenzoate is rapidly degraded in the stomach and consequently no systemic exposure is observed after oral administration.
On the other hand, while systemic genotoxicity is unlikely, a genotoxic effect at the site of contact cannot be excluded in consideration of the positive results reported in the *in vitro* studies and of the chemical nature of the compound. In fact, there is empirical evidence that highly reactive substances such as acrylates, peroxides and epoxides are generally negative in bone marrow studies (chromosome aberration test and micronucleus test), while often showing genotoxicity in the liver or in the sites of initial contact (stomach after oral exposure; lung/nasal tissues after inhalation exposure).

The Registrant(s) reported in their comment to the proposals for amendment a study of a multistage model of carcinogenesis. This study used mouse skin to evaluate carcinogenic potential of tert-butyl perbenzoate (TBPB). In this study TBPB was evaluated for its ability to increase biomarkers of tumor promotion in mouse skin, i.e. sustained epidermal hyperplasia, dermal inflammation and 8-OH-dG in DNA. Evaluations were performed using SENCAR mice exposed topically for 4 weeks. In conclusion this study showed that t-BP did not exhibit tumor initiating or complete carcinogenic activity but induction of 8-OH-dG is reported (Hanausek, M. *et al*, 2004). This study cannot be used to rule out a local genotoxic potential, because it does not directly address genotoxicity but tumour initiation/promotion activity and because it is not a guideline study, currently used for risk

assessment. Moreover, in this study induction of 8-OH-dG is reported, indicating oxidative DNA damage at the site of contact.

In conclusion, the *in vivo* comet assay, for which OECD test guideline has been recently published, is considered the most appropriate test to address the identified concern for genotoxicity of the registered substance.

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: *In vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay, OECD 489) in rats, oral route, with examination of liver (distal site) and either glandular stomach or duodenum/jejunum (initial site of contact).

3. Quantitative risk assessment

Considering that DNEL values have been selected for long-term systemic effects, ECHA reckons as necessary that an occupational exposure assessment and a quantitative risk assessment for long-term systemic effects shall be provided by the Registrant(s) for all relevant exposure scenarios.
Whereas ECHA notes that some of the Registrant(s) may have provided the requested information already by updating their respective CSR, this is not the case for all Registrant(s). In particular, for possible uses not covered already by the updated CSR(s), the evaluating MSCA still needs the information requested to perform the risk assessment.

4. Personal protective equipment

To manage risks from hazardous substances appropriate risk management measures (RMM) have to be derived in the risk assessment, recommended and applied during use. The order of risk management measures is laid down in the Directive 98/24/EC. Personal protective equipment (PPE) is the last resort, in cases where the other measures are not applicable or could not sufficiently reduce the risks.

Directive 89/656/EEC (on the minimum health and safety requirements for the use by workers of personal protective equipment at the workplace) states that the personal protective equipment used must be appropriate for the risk involved, without itself leading to any increased risk. This Directive has to be considered for the derivation of exposure scenarios as REACH shall apply without prejudice to the community workplace legislation.

PPE specification is a requirement of REACH Annex II, 8.2.1. and the efficacy is needed to assess residual exposure occurring to workers when PPE are used. In Annex I 5.2.4. it is written that "*the estimation of the exposure level ... shall take into account (...) implemented and recommended RMM including the degree of containment.*" The specification of the recommended personal protective equipment is necessary to assure that the equipment does have a protective effect.

Therefore, the Registrant(s) are requested to provide sufficient and consistent information on the specification of personal protective equipment (PPE) and the duration of use for all scenarios where the use of personal protective equipment is advised. This means, where PPE is specified (e.g. gloves) information on the type of material to be used and the breakthrough time for the gloves and where respiratory protective equipment (RPE) is specified information specifying for air-purifying respirators, the proper purifying element (cartridge or canister) and the adequate masks, or self-contained breathing apparatus for the scenarios where the use of respiratory protection is advised.

IV. Information on right to appeal

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

[redacted]

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