Helsinki, 27 May 2019

Addressee: [redacted]

Decision number: CCH-D-2114470769-31-01/F
Substance name: 3,4,5,6-tetrachloro-N-[2-(4,5,6,7-tetrachloro-2,3-dihydro-1,3-dioxo-1H-inden-2-yl)-8-quinolyl]phthalimide
EC number: 250-063-5
CAS number: 30125-47-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28/03/2013
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487) with the registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that both studies requested under 1. and 2. have negative results;**

4. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats with the registered substance. The study must include measurements of lung burden and bronchoalveolar lavage fluid (BALF) analysis as described in the current version (25 June 2018) of the test guideline;**

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance ;**

You have to submit the requested information in an updated registration dossier by **3 December 2021**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in

Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Wim De Coen, Head of Unit, Hazard Assessment.

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

Appendix 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1983 equivalent or similar to OECD TG 471, not GLP with an assigned reliability score of 2. The test used five different strains of S. typhimurium TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, the 5th strain used (TA 1538) is not recognised by the test guideline. Since the test was conducted, significant changes have been made to OECD TG 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

In your comments to the initial draft decision, you acknowledged that information on strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is not included in the study performed with the registered substance. Furthermore, you refer to a test performed with the analogue substance '6-Quinolinesulfonic acid, 8-(4,5,6,7-tetrachloro-1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-2-(4,5,6,7-tetrachloro-3-hydroxy-1-oxo-1H-inden-2-yl)-' (EC 439-610-0; PGMS);this read-across from this substance was not included in the dossier evaluated for this decision.

You provided a revised read-across justification and robust study summaries as Annexes 6 and 3 to your comments on the draft decision. You base your read-across on structural similarity and increased bioavailability of the source substance compared to the registered substance, as well as similar genotoxicity.

The read-across adaptation may be accepted only once it is included in the registration dossier. The request for an *in vitro* gene mutation study in bacteria with the registered substance will remain in the decision as the read-across approach does not currently comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

Accordingly, your adaptation of the information requirement is currently rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.)

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex VIII, Section 8.4.2., column 2 (adequate data from an in vivo cytogenicity test). In the technical dossier you have provided a study record for an *in vivo* mammalian erythrocyte micronucleus test (study similar or equivalent to OECD TG 474) performed in mice with oral administration of the registered substance in doses up to 4000 mg/kg bw/d. The results of

the test indicate that the substance does not cause genotoxicity. The acceptability criteria for the test guideline (OECD TG 474) state that target tissue (bone marrow) exposure must be demonstrated. However, in the endpoint study record there is no data showing exposure of the target tissue (bone marrow) to the test substance. Hence, in the absence of such evidence, the provided test is not adequate and your adaptation must be rejected because this study does not meet one of the acceptability criteria for this test.

In your comments to the initial draft decision, you explained that the substance is not systemically available after oral or inhalation exposure and cannot be detected in blood plasma samples. As the exposure of the target tissue is not demonstrated, ECHA considers that the provided test is not adequate. In addition you provided information on an in vitro mammalian cell micronucleus test performed with the analogue substance '6-Quinoline-sulfonic acid, 8-(4,5,6,7-tetrachloro-1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-2-(4,5,6,7-tetrachloro-3-hydroxy-1-oxo-1H-inden-2-yl)-' (EC 439-610-0; PGMS); read-across from this substance was not included in the dossier evaluated for this decision.

As discussed in section 1. of this Appendix, read-across to that analogue substance will be re-assessed after the deadline set out in this decision has passed. The request for an *in vitro* cytogenicity study in mammalian cells with the registered substance will remain in the decision, as the read-across approach does not currently comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

Accordingly, your adaptation of the information requirement is currently rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473 or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487)..

3. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an "Unscheduled DNA synthesis (UDS) test in rats with mammalian liver cells" *in vivo* (OECD TG 486) with the analogue substance Benzoic acid, 2,3,4,5-tetrachloro-6-cyano-, methyl ester, reaction products with p-phenylenediamine and sodium methoxide (EC no 600-736-8) in doses up to 2000 mg/kg bw/d.

You provided the following read-across justification: *"The substances share high similarity in structure and have comparable physico-chemical properties. Both substances are solids of poor water solubility and insoluble/poorly soluble in most of the common organic solvents".*

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

However, you have not addressed the obvious structural dissimilarity between the registered and the analogue substance (differences in bond-reactivity, e.g. imido-bond versus direct link from the phthalimide to the aromatic core structure; (heterocyclic) differences in aromatic core structure) and you did not explain why those differences would not lead to differences in the toxicity profile of target and source substances. The provided explanation is not considered as valid to establish a scientific credible link between the structural similarity and the prediction.

Furthermore, although the substance has low solubility in water and octanol, a demonstration of lack of absorption or dissolution of the substance in the lung environment following inhalation exposure or the gastrointestinal tract following oral exposure on that basis is speculative and unsubstantiated and, therefore, cannot be accepted.

Therefore, ECHA considers that this read-across approach does not provide a reliable basis whereby the mutagenic effects of the registered substance in mammalian cells may be predicted from data for the source substance. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation and your adaptation of the information requirement is rejected.

You have also sought to adapt this information requirement according to Annex VIII, Section 8.4.3., column 2. You provided the following justification for the adaptation: *"According REACH Regulation Annex VIII, 8.4.3 : "The study does not need to be conducted if adequate data from a in vivo mammalian gene mutation test are available." Data from a micronucleus assay in mouse as well as data from an UDS in rats are available".* However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VIII, Section 8.4.3., column 2, because the UDS test is an indicator test detecting putative DNA lesions which should be used only when it can be reasonably assumed that the liver is a target organ. For further information, see ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a, Section R.7.7.6.3. However, you did not provide any information to demonstrate that the liver is a target organ. Hence, in the absence of such evidence, the provided test cannot be considered as adequate data from a reliable *in vivo* mammalian gene mutation test or as valid to identify a mutagenic property of the registered substance. Therefore, your adaptation of the information requirement is rejected.

In your comments to the initial draft decision, you agreed to perform the requested study (test method OECD TG 476) with the registered substance.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under 1. and 2. have negative results.

4. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

You have sought to adapt this information requirement according to Annex IX, Section 8.6.2., column 2, fourth indent. You provided the following justification for the adaptation *"In the course of an OECD 422 study it was clearly shown that the material does not cause any effect; the NOAEL is considered to be 1000 mg/kg bw. Furthermore, yellowish disoloration of the feces indicates that the substance will be excreted unchanged. Furthermore, the solubility of the test item is below 0.05 mg/l water. In conclusion, there is no need for a 90 day study".*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.6.2., column 2, fourth indent, for the following reasons:

- You did not provide evidence to show that the substance is unreactive.
- The registration dossier indicates that the registered substance is inhalable. Indeed, according to the particle size distribution data the registered substance itself is a powder consisting of particles with significant proportion (>1% on weight basis) in the inhalable size range (MMAD < 50 µm).
- You did not provide sufficient information demonstrating that there is no evidence of absorption. Although the substance has low solubility in water, a demonstration of lack of absorption or dissolution of the substance in the lung environment following inhalation exposure or the gastrointestinal tract following oral exposure on that basis is speculative and unsubstantiated. A discoloration of the feces does not provide sufficient evidence (e.g. toxicokinetic data) to show that the substance is excreted unchanged or to show no evidence of absorption.

In your comments to the initial draft decision, you explained that you consider that the specific rules for adaptation according to Annex IX, Section 8.6.2., column 2, fourth indent are fulfilled. You described that biosolubility and biopersistence tests have been performed, indicating that the test item is not dissolved or degraded after cellular uptake. However, you

did not provide the results of those tests. In the attachments you included in your comments, it is said that such studies are planned/ongoing.

In the CSR/IUCLID file attached to your comments you present physicochemical properties and exposure scenarios (ES). For the granulometry you describe that the MMD is 11 μm and D90 is 23 μm for the registered substance. Many of the provided ESs have conditions of use that create dust or aerosol e.g. spraying (PROC 11, [redacted]), rolling application and brushing (PROC 10 , [redacted]) and low or high energy manipulation of substances bound in/on materials or articles (PROC 21 and 24). You also predict notable exposures via inhalation in many mixing and transferring tasks ([redacted] for PROCs 5, 8a and 8b). You compare your estimated exposure levels to a general dust limit value for inhalable dust ([redacted]). According to ECHA Guidance R.5 (version 1.2 December 2011), the negligible exposure assessment should be based on robust information and the formation of dust or aerosol should not be significant due to the specific operational conditions. Due to the granulometry, the registered substance is inhalable and the predicted exposure levels do not describe "limited human exposure". Hence, ECHA considers that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.6.2., column 2, fourth indent.

In your comments to the initial draft decision, you also refer to a screening study performed according to OECD TG 422. Results of OECD TG 422 may support low toxicity of the substance (if no effects are observed at the limit dose); however as discussed above, it is not sufficient to demonstrate that there is no evidence of absorption.

Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. The information provided in the technical dossier and the chemical safety report on properties of the registered substance and its uses (including for example transfer of substance or mixture at non-dedicated facilities, non-industrial spraying, and abrasion by professionals and consumers) indicate that human exposure to the registered substance by the inhalation route is likely. More specifically, the substance is reported to occur as a dust with a significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm). Furthermore, the substance is respirable, of low water solubility and consequently there is a potential for accumulation of the substance in the lungs. Hence, the test shall be performed by the inhalation route using the test method OECD TG 413.

There is evidence that the lower respiratory tract is a site of deposition and retention of the registered substance because the substance is poorly soluble in water and respirable. Therefore, you are requested to perform measurements of lung burden and bronchoalveolar lavage fluid (BALF) which are specifically designed to address such situation. The latest guidance on how to perform such measurements are described in the revised version of the OECD 413 test guideline adopted on 25 June 2018. The measurements shall therefore be conducted as described in the guideline version adopted on 25 June 2018.

According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to carry out the study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats inhalation route (test method: OECD TG 413). The study must include measurements of lung burden and bronchoalveolar lavage fluid (BALF) analysis as described in the current version (25 June 2018) of the test guideline.

5. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

In the technical dossier you have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422). However, this study does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected.

In your comments to the initial draft decision, you agreed to perform the requested study with an analogue substance (EC 600-736-8, PY110).

You provided a revised read-across justification as Annex 6.2 to your comments on the draft decision. Therein you indicated future performance of a combined repeated dose toxicity with the screening for reproductive/developmental toxicity study (OECD TG 422) and a pre-natal developmental toxicity study (test method OECD TG 414) with this analogous substance. You proposed read-across based on structural similarity and similar absence of bioavailability, as well as similar toxicity.

ECHA acknowledges these clarifications and notes that any potential confirmation of the read-across hypothesis depends on the outcome of the proposed experimental studies with the analogous substance. The study outcomes and their impact on the read-across adaptation should be included in a dossier update. ECHA will assess this information after the deadline set out in this decision has passed.

Your adaptation of the information requirement is rejected.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction

as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 24 July 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.