ECHA
EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

27 August 2024

(Article 42(1) – Follow-up to a compliance check – Section 8.7.3. of Annex X – Histopathological investigations missing from an EOGRTS – Errors of assessment – Effects of a follow-up decision)

Case number	A-004-2023
Language of the case	English
Appellant	Evonik Operations GmbH, Germany
Contested Decision	Decision of 9 December 2022 on the follow-up to a compliance check of the registration for the substance 2,4,6-tris(dimethyl-aminomethyl)phenol, adopted by the European Chemicals Agency pursuant to Article 42(1) of the REACH Regulation The Contested Decision was notified to the Appellant under annotation number CCH-D-2114621395-51-01/F

THE BOARD OF APPEAL

composed of Antoine Buchet (Chairman), Nikolaos Georgiadis (Technically Qualified Member and Rapporteur), and Katrin Schütte (Technically Qualified Member)

Registrar: Alen Močilnikar

gives the following

Decision

1. Background to the dispute

1. This appeal concerns the follow-up to a compliance check of the registration for the substance 2,4,6-tris(dimethylaminomethyl)phenol (the **Substance**).[1]

2. The Appellant is the legal successor of another company, Air Product Chemicals PLC, which registered the Substance at the tonnage band of 1 000 tonnes or more per year, corresponding to Annex X to the REACH Regulation[2].

1.1. The compliance check decision of 22 November 2016

3. On 22 November 2016, the Agency adopted and notified to Air Product Chemicals PLC a compliance check decision in accordance with Articles 41 and 50. By that decision, the Agency required Air Product Chemicals PLC to submit information on:

   - a 90-day sub-chronic toxicity study (the **90-day study**) in accordance with test guideline No 408 of the Organisation for Economic Cooperation and Development (**OECD TG 408**), as required under Section 8.6.2. of Annex IX, by 29 November 2017, and
   - an extended one-generation reproductive toxicity study (the **EOGRTS**) in accordance with test guideline No 443 of the Organisation for Economic Cooperation and Development (**OECD TG 443**), as required under Section 8.7.3. of Annex X, by 29 May 2020.

4. The decision stated that the EOGRTS should be commenced after 1 March 2018 unless the Agency gave an '*indication to the contrary*' by that date.

5. On 29 November 2017, the Appellant, which had by then succeeded in the rights and obligations of Air Products Chemicals PLC, updated its registration by including the results of the 90-day study in its registration dossier.

6. On 31 January 2018, the Agency informed the Appellant that it should not yet commence the EOGRTS, and that the Agency would issue a new decision in that regard.

1.2. The compliance check decision of 29 October 2018

7. On 29 October 2018, the Agency adopted and notified to the Appellant a new compliance check decision in accordance with Articles 41 and 50. In that decision, the Agency found that the Substance may have endocrine disrupting properties. It consequently required the Appellant to provide, by 5 November 2020, information on an EOGRTS including cohorts 1A and 1B with extension to mate the Cohort 1B animals to produce the F2 generation.[3]

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1 EC No 202-013-9, CAS No 90-72-2.

2 Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (OJ L 396, 30.12.2006, p. 1). All references to Articles and Annexes hereinafter concern the REACH Regulation unless stated otherwise.

3 Under Column 1 of Section 8.7.3. of Annex X in conjunction with point (a) and the third indent of Point (b) of the first paragraph of Column 2 of Section 8.7.3. of Annex X.

8. By 5 November 2020, the Appellant updated its registration by including in its registration dossier the results of the EOGRTS, following the study design set out in the decision of 29 October 2018.

1.3. The Contested Decision

9. The Agency examined the information submitted in consequence of the compliance check decision of 29 October 2018 and, on 24 February 2022, notified to the Appellant a draft follow-up decision in accordance with Articles 42(1) and 50(1).

10. On 29 March 2022, the Appellant submitted comments on the draft decision in accordance with Article 50(1).

11. On 1 September 2022, the Agency notified a revised draft of the decision to the competent authorities of the Member States in accordance with Articles 50(1) and 51(1).

12. On 9 December 2022, as no competent authority submitted a proposal for amendment, the Agency adopted the Contested Decision in accordance with Article 51(3).

13. The Contested Decision states:

'*The study provided is described as a EOGRT study according to OECD TG 443.*

However, the following specifications are not according to the requirements of the OECD TG 443:

[–] the systemic toxicity was not fully investigated, in particular, the following investigations are missing:

a. Organs of Cohort 1B, all dose levels,

b. Target organs in Cohort 1B (only liver and spleen were preserved) and

*c. Organs of [the parental generation (the **P0 generation**)] and Cohort 1A animals at low and mid dose.*

*In this case, the extension of Cohort 1B was triggered to address a concern for endocrine disrupting modes of action. Therefore, reproductive and endocrine tissues from all cohort 1B animals, processed to the block stage (OECD TG 443, paragraph 67), should have been examined for histopathology as in cases of suspected reproductive or endocrine toxicants. Furthermore, organs and tissues demonstrating treatment-related changes in high dose animals and all gross lesions should also have been examined in all animals in the lower dose groups to aid in determining a [no observed adverse effect level (**NOAEL**)].*

In the study you have provided histopathology was not investigated in Cohort 1B animals (all dose levels) for organs listed in OECD TG 443 paragraph 67 as you have reported histopathological investigations only for high dose and control animals of [the P0 generation] and Cohort 1A. Therefore, based on the provided information, a reliable NOAEL value for organ toxicity cannot be derived because the histopathology of organs showing vacuolation or vacuolar changes in smooth muscle cells/fibers of several organs at the highest dose level were not investigated at mid and low dose levels in [the P0 generation] and Cohort 1A (OECD TG 443, paragraphs 70 and 71).

[…]

On this basis, the request in the original decision was not met and the information requirement is not fulfilled.'

14. It is therefore apparent from the Contested Decision that the Agency concluded that histopathological investigations of the following organs are missing from the EOGRTS submitted by the Appellant:

- selected reproductive organs listed in paragraph 67 of OECD TG 443 in the animals in cohort 1B at all dose-levels,
- identified target organs (liver and spleen) in the animals in cohort 1B at all dose-levels, and
- organs demonstrating treatment-related changes in male and female animals in the P0 generation and Cohort 1A at the low and mid-doses.

15. As a consequence, in the operative part of the Contested Decision, the Agency:

- declared that the Appellant's registration still does not comply with the requirements of Section 8.7.3. of Annex X,
- declared that the Appellant continues to be required to provide the information required in the compliance check decision of 29 October 2018, and
- stated that the enforcement authorities of the Member States would be informed of this decision.

2. Procedure before the Board of Appeal

16. On 7 March 2023, the Appellant filed its appeal.

17. On 8 May 2023, the Agency submitted its Defence.

18. On 22 June 2023, the Appellant submitted its observations on the Defence.

19. On 9 August 2023, the Agency submitted its observations on the Appellant's observations on the Defence.

20. On 9 February 2024, Katrin Schütte, alternate member of the Board of Appeal, was designated to replace Marijke Schurmans in this case, in accordance with the first subparagraph of Article 3(2) of the Rules of Procedure[4].

21. On 21 February 2024, the written procedure was closed. As neither party requested an oral hearing to be held, and the Board of Appeal did not consider an oral hearing to be necessary, no such hearing took place in this case.

3. Form of order sought

22. The Appellant requests the Board of Appeal to:

(a) annul the Contested Decision insofar as it requires histopathological investigations of:

- selected reproductive organs listed in paragraph 67 of OECD TG 443 in the animals in cohort 1B at all dose-levels,
- identified target organs (liver and spleen) in the animals in cohort 1B at all dose-levels, and
- organs demonstrating treatment-related changes in male animals in the P0 generation at the low and mid-doses.

(b) order the refund of the appeal fee;

[4] Commission Regulation (EC) No 771/2008 laying down the rules of organisation and procedure of the Board of Appeal of the European Chemicals Agency (OJ L 206, 2.8.2008, p. 5).

(c) take other or further measures as justice may require; and

(d) in the event that the appeal should be dismissed, rule that the deadlines set in the Contested Decision should run from the date of the decision of the Board of Appeal.

23. The Agency requests the Board of Appeal to dismiss the appeal as unfounded.

4. Assessment of the case

4.1. Interpretation of the form of order sought by the Appellant

24. By the first point of its form of order,[5] the Appellant requests the Board of Appeal, in essence, to annul the Contested Decision insofar as it requires the Appellant to carry out the investigations which the Agency considers to be missing from the Appellant's EOGRTS.

25. The Contested Decision is a follow-up decision under Article 42(1), based on the reasoning that the results of the EOGRTS carried out by the Appellant show that certain investigations are missing.

26. The Agency stated, without being contradicted by the Appellant, that the relevant organs or tissues were preserved following the EOGRTS carried out by the Appellant, so that the study does not need to be repeated to carry out the investigations which the Agency considers to be missing. In practice, therefore, the Agency wishes the Appellant to carry out the relevant investigations on the preserved organs or tissues and submit their results.

27. A follow-up decision under Article 42(1) is strictly limited to assessing whether the data-gaps identified in the initial compliance check decision have been filled. A follow-up decision does not contain any new or further requests for information.[6]

28. The operative part of the Contested Decision confines itself to stating that the Appellant has failed to satisfy the requirements of the compliance check decision of 29 October 2018, that the Appellant remains bound by the requirements of that decision, and that the competent authorities of the Member States will be informed. The Contested Decision does not set out further information requirements and does not set any deadlines.

29. Against this background, the first point of the form of order sought by the Appellant must be interpreted as requesting the Board of Appeal to annul the Contested Decision insofar as it declares that the Appellant has failed to fill the data-gap identified in the compliance check decision of 29 October 2018 because it omitted the following histopathological investigations in the EOGRTS:

- selected reproductive organs listed in paragraph 67 of OECD TG 443 in the animals in cohort 1B at all dose-levels,
- identified target organs (liver and spleen) in the animals in cohort 1B at all dose-levels, and
- organs demonstrating treatment-related changes in male animals in the P0 generation at the low and mid-doses.

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[5] See point (a) in paragraph 22 above.

[6] Decision of the Board of Appeal of 23 August 2022, *Celanese Production Germany*, A-004-2021, paragraphs 149 and 150.

30. The Appellant's two pleas in law will be assessed with reference to the form of order thus interpreted.

4.2. First plea, concerning histopathological investigations of organs of animals in cohort 1B at all dose-levels

Arguments of the Parties

31. The Appellant argues that the Contested Decision breaches Articles 10 and 12 and Section 8.7.3. of Annex X, read in conjunction with OECD TG 443, and is vitiated by an error of assessment, insofar as it finds that the Appellant was required to carry out histopathological investigations of the following organs:

- selected reproductive organs listed in paragraph 67 of OECD TG 443 in the animals in cohort 1B at all dose-levels; and
- identified target organs (liver and spleen) in the animals in cohort 1B at all dose-levels.

32. Those investigations are required only if a substance is a suspected reproductive or endocrine toxicant or if the results from cohort 1A are equivocal. According to the Appellant, firstly, the results from cohort 1A were not equivocal in this case. Secondly, the Appellant argues that, although effects were observed on reproductive organs (epididymis, prostate gland, seminal vesicles, ovaries, uterus) and endocrine organs (pituitary and adrenal glands) in the 90-day study, those effects are due to phospholipidosis and/or vacuolation of arteries and smooth muscle cells. The Appellant argues that they are therefore secondary effects, and not indicative of reproductive or endocrine toxicity.

33. Consequently, according to the Appellant, no histopathological investigations of the organs of animals in cohort 1B are needed as neither of the conditions which could lead to such investigations being required is fulfilled.

34. The Agency disputes the Appellant's arguments.

Findings of the Board of Appeal

35. The compliance check decision of 29 October 2018 required the Appellant to submit information on an EOGRTS including cohorts 1A and 1B with extension to mate cohort 1B animals to produce the F2 generation. The applicable test method was EU test method B.56/OECD TG 443.[7]

36. By 5 November 2020 the Appellant updated its registration by including the results of an EOGRTS in its registration dossier. In the Contested Decision, the Agency examined those results in accordance with Article 42(1) and concluded that certain required elements were missing from the Appellant's EOGRTS.

[7] OECD TG 443 was identical to EU test method B.56 until 26 March 2023. Since then, OECD TG 443 is recognised as an appropriate test method in Table 2 of Part 0 of the Annex to the Test Methods Regulation. See Commission Regulation (EU) 2023/464 amending, for the purpose of its adaptation to technical progress, the Annex to the Test Methods Regulation (OJ L 68, 6.3.2023, p. 37).

37. In the context of a follow-up decision under Article 42(1), the Agency has the power to verify that studies submitted by registrants in consequence of a compliance check decision under Article 41 were carried out correctly in accordance with the relevant test guideline.[8]

38. To decide on the first plea, it is consequently necessary to examine whether OECD TG 443 required the Appellant to carry out histopathological investigations of the selected reproductive organs referred to in paragraph 67 of OECD TG 443, as well as the liver and spleen, in the animals in cohort 1B at all dose-levels.

39. Paragraph 67 of OECD TG 443 provides (emphasis added):

'*Cohort 1B animals should have the following organs weighed and corresponding tissues processed to the block stage:*

- *Vagina (not weighed)*
- *Uterus with cervix*
- *Ovaries*
- *Testes (at least one)*
- *Epididymides*
- *Seminal vesicles and coagulating glands*
- *Prostate*
- *Pituitary*
- *Identified target organs.*

Histopathology in cohort 1B would be conducted if results from cohort 1A are equivocal or in cases of suspected reproductive or endocrine toxicants.'

40. Similarly, paragraph 72 of OECD TG 443 provides (emphasis added):

'*Reproductive and endocrine tissues from all cohort 1B animals, processed to the block stage as described in paragraph 67, should be examined for histopathology in cases of suspected reproductive or endocrine toxicants. Cohort 1B should also undergo histological examination if results from cohort 1A are equivocal*.'

41. It follows that a registrant who carries out an EOGRTS is required to carry out histopathological investigations of the reproductive organs referred to in paragraph 67 of OECD TG 443, as well as of identified target organs, in the animals in cohort 1B at all dose-levels if the tested substance is a suspected reproductive or endocrine toxicant or the results from cohort 1A are equivocal.

42. The results from cohort 1A in the Appellant's EOGRTS are not equivocal. However, the Substance may be a suspected endocrine toxicant. A substance is a suspected endocrine toxicant if available information shows that the substance in question may cause endocrine disrupting effects.

43. It is not contested that the 90-day study, which was available before the commencement of the EOGRTS, showed statistically significant decreases in weight of prostate and seminal vesicles (-22%), ovaries (-27%) and uterus (-28%) as well as in the pituitary gland and adrenal glands.

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[8] See, to that effect and by analogy, decision of the Board of Appeal of 11 December 2018, *Climax Molybdenum*, A-006-2017, paragraph 43; see also judgment of 8 May 2018, *ESSO Raffinage* v *ECHA*, T-283/15, EU:T:2018:263, paragraph 62.

44. As the Agency stated in the compliance check decision of 29 October 2018, which is referred to in the Contested Decision, those findings in reproductive and endocrine organs give sufficient grounds to believe that the Substance may cause endocrine disrupting effects. The Substance is therefore a suspected endocrine toxicant within the meaning of paragraphs 67 and 72 of OECD TG 443.

45. The Agency's conclusion that the Substance is a suspected endocrine toxicant is not called into question by the Appellant's argument that the effects observed in the 90-day study may be secondary effects due to phospholipidosis and/or vacuolation of arteries and smooth muscle cells rather than to endocrine disrupting effects.

46. The Agency acknowledges that this is a possible explanation. However, it is not proven that the effects at issue are caused exclusively, or even mainly, by phospholipidosis and/or vacuolation of arteries and smooth muscle cells. The Appellant's argument does not therefore resolve the concern identified by the Agency based on the results of the 90-day study, namely that the Substance is a suspected endocrine toxicant because it may cause endocrine disrupting effects.

47. In addition, the Appellant's actions are contradictory. The Appellant did not challenge the compliance check decision of 29 October 2018, which required the inclusion of the F2 generation in the EOGRTS due to the suspected endocrine disrupting properties of the Substance. At the same time, however, the Appellant did not carry out the histopathological investigations in cohort 1B, which are based on the same reason and would contribute to clarify the suspected endocrine disrupting properties.

48. It follows that the Contested Decision is not vitiated by an error insofar as it is based on the conclusion, first set out in the compliance check decision of 29 October 2018, that the Substance is a suspected endocrine toxicant. The Appellant was consequently required to carry out histopathological investigations of:

- the selected reproductive organs referred to in paragraph 67 of OECD TG 443 in the cohort 1B animals at all dose-levels, and
- the liver and spleen, which were identified target organs within the meaning of the last indent of the first subparagraph of paragraph 67 of OECD TG 443, in the cohort 1B animals at all dose-levels.

49. Those investigations were not carried out in the EOGRTS conducted by the Appellant. Therefore, the Agency did not commit an error in concluding that the Appellant failed to fill the data gap identified in the compliance check decision of 29 October 2018 with regard to the two elements referred to in the previous paragraph.

50. The first plea must consequently be rejected.

4.3. Second plea, concerning histopathological investigations of organs of male animals in the P0 generation at the low and mid-doses

Arguments of the Parties

51. The Appellant argues that the Contested Decision is vitiated by errors of assessment insofar as it finds that histopathological investigations of organs of male animals in the P0 generation at the low and mid-doses are missing from the results of the EOGRTS carried out by the Appellant.

52. First, the Appellant argues that the information requirements set out in the REACH Regulation must be interpreted and applied so as to be consistent with the requirements of the principle of proportionality. According to the Appellant, the Agency failed to take into account the fact that generating the information in question would not contribute to ensuring a high level of protection of human health and the environment.

53. Second, the Appellant argues that the Agency failed to take into account relevant information in its assessment. According to the Appellant, the examinations at issue were already conducted as part of the 90-day study under the same conditions, so that repeating those examinations in the EOGRTS would not provide any additional information.

54. The Agency disputes the Appellant's arguments.

Findings of the Board of Appeal

55. The Contested Decision finds that, in addition to the elements addressed above under the first plea, the EOGRTS submitted by the Appellant lacks histopathological investigations of organs demonstrating treatment-related changes in male and female animals in the P0 generation and Cohort 1A at the low and mid-doses.

56. The Appellant challenges the findings of the Contested Decision only as regards histopathological investigations of organs demonstrating treatment-related changes in male animals in the P0 generation at the low and mid-doses.

57. In the context of a follow-up decision under Article 42(1), the Agency has the power to verify that studies submitted by registrants in consequence of a compliance check decision under Article 41 were carried out correctly in accordance with the relevant test guideline.[9]

58. To decide on the second plea, it is consequently necessary to examine whether the Appellant was required to carry out the histopathological investigations of organs of male animals in the P0 generation at the low and mid-doses.

59. Paragraph 70 of OECD TG 443/EU test method B.56 provides (emphasis added):

'*Full histopathology of the organs listed in paragraphs 63 and 64 is performed for all high-dose and control P animals. Organs demonstrating treatment-related changes should also be examined in all animals at the lower dose groups to aid in determining a NOAEL.*'

60. It is not contested that, in the results of the EOGRTS carried out by the Appellant, organs listed in paragraphs 63 and 64 of OECD TG 443 showed treatment-related changes (vacuolisation) at the high dose. The Appellant was consequently required to carry out histopathological investigations of those organs in the P0 generation not only in the high-dose and control groups, but also at the low and mid-doses.[10]

61. The Appellant argues that it was entitled to omit the histopathological investigations of organs of male animals in the P0 generation at the low and mid-doses based on the information derived from the 90-day study. According to the Appellant, repeating those same investigations in the EOGRTS will not generate any additional information.

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[9] See paragraph 37 above.

[10] This concerns both the male and female animals, although the Appellant challenges the decision only with regard to the male animals.

62. However, a registrant who relies on an adaptation must set out clearly, in the relevant part of its registration dossier, the provision of Annexes VII to XI on which the adaptation is based, the grounds for the adaptation, and the scientific information which substantiates those grounds.[11] The Appellant did not include in its registration dossier, together with the results of the EOGRTS, any adaptation for the histopathological investigations at issue.

63. In addition, contrary to the Appellant's argument, Column 1 of Section 8.7.3. of Annex X does not allow registrants to forgo elements of an EOGRTS based on a 90-day study carried out under Section 8.6.2. of Annex IX. Column 1 of Section 8.7.3. of Annex X states that an EOGRTS is required '*unless [the information was] already provided as part of Annex IX requirements*'. This means only that if a registrant has already carried out an EOGRTS under Annex IX it is not obliged to repeat the same EOGRTS under Annex X.

64. Finally, there are certain differences between the investigations which are required from the Appellant as part of its EOGRTS, and those which were conducted as part of the 90-day study. In particular, the number of animals per dose group is higher in the EOGRTS than in the 90-day study, so that the EOGRTS carries a higher statistical power; the treatment period of the animals in the P0 generation in the EOGRTS is longer than the treatment period of the animals in the 90-day study; and the age of the animals at the start of the study differs, the males being younger in the 90-day study than in the EOGRTS. Those differences justify the Agency's conclusion that the information derived from the 90-day study is not sufficient to fill the data gap identified in the compliance check decision of 29 October 2018.

65. It follows that Contested Decision is not vitiated by an error insofar as it finds that the Appellant was not entitled to omit the histopathological investigations of organs of male animals in the P0 generation at the low and mid-doses in the EOGRTS based on the results of the 90-day study.

66. The second plea must consequently be rejected.

5. Result

67. As both of the Appellant's pleas are rejected, the appeal must be dismissed.

6. The Appellant's request to rule that the deadlines set in the Contested Decision should run from the date of the decision of the Board of Appeal

68. By the fourth point of its form of order, the Appellant requests the Board of Appeal to rule, in the event that the appeal should be dismissed, that the deadlines set in the Contested Decision should run from the date of the decision of the Board of Appeal.

69. Article 91(2) provides that an appeal has suspensive effect. The deadlines set in a contested decision are consequently suspended during the appeal proceedings. That suspension ends with the notification of the final decision of the Board of Appeal. Where a contested decision sets a deadline, the Board of Appeal sets a new deadline in its decision if it dismisses the appeal.[12]

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[11] Decision of the Board of Appeal of 6 June 2023, *Cytec Engineered Materials*, A-001-2022, paragraph 59.

[12] See, to that effect, judgment of 22 November 2023, *Symrise* v *ECHA*, T-655/20, EU:T:2023:736, paragraph 244.

70. The Contested Decision, as a follow-up decision under Article 42(1), does not contain any new or further requests for information and does not prescribe any deadlines.[13] The Appellant's request that the Board of Appeal should rule that the deadlines set in the Contested Decision should run from the date of the decision of the Board of Appeal must therefore be rejected.

7. Refund of the appeal fee

71. Under Article 10(4) of the Fee Regulation[14] the appeal fee is refunded if the appeal is decided in favour of an appellant. As the appeal is dismissed, the appeal fee is not refunded.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Dismisses the appeal.**
2. **Rejects the request to rule that the deadlines set in the Contested Decision should run from the date of the decision of the Board of Appeal.**
3. **Decides that the appeal fee is not refunded.**

Antoine BUCHET
Chairman of the Board of Appeal

Alen MOČILNIKAR
Registrar of the Board of Appeal

[13] See paragraph 27 above.

[14] Commission Regulation (EC) No 340/2008 on the fees and charges payable to the European Chemicals Agency pursuant to the REACH Regulation (OJ L 107, 17.4.2008, p. 6).