EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

21 June 2023

(Dossier evaluation – Compliance check – Sections 8.7.2. and 8.7.3. of Annex IX – Mode of administration for PNDT study and EOGRTS – Dose level setting – Right to be heard – Animal welfare – Time limit to submit the requested information)

Case number	A-004-2022
Language of the case	English
Appellant	Symrise AG, Germany Represented by Ruxandra Cana and Hannah Widemann Steptoe & Johnson LLP, Belgium
Intervener	Cruelty Free Europe, Belgium Represented by David Thomas Advocates for Animals Ltd, United Kingdom
Contested Decision	Decision of 14 January 2022 on a compliance check of the registration for the substance (E)-anethole, adopted by the European Chemicals Agency under Article 41 of the REACH Regulation The Contested Decision was notified to the Appellant under annotation number CCH-C-2114591506-41-01/F

THE BOARD OF APPEAL

composed of Antoine Buchet (Chairman), Nikolaos Georgiadis (Technically Qualified Member), and Marijke Schurmans (Legally Qualified Member and Rapporteur)

Registrar: Alen Močilnikar

gives the following

Decision

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1. Background to the dispute

1. The appeal concerns a compliance check of the registration for the substance (E)-anethole (the **Substance**).[1]

2. In 2013, the Appellant registered the Substance at the tonnage band of 100 to 1 000 tonnes per year, which corresponds to the volume of manufacture or import referred to in Annex IX to the REACH Regulation.[2]

3. On 14 August 2020, the Agency initiated a compliance check of the registration for the Substance in accordance with Article 41.

4. On 5 August 2021, in accordance with Articles 41(3) and 50(1), the Agency notified a draft decision to the Appellant. In the draft decision, the Agency stated that the Appellant's registration had several data-gaps, including under Sections 8.7.2. and 8.7.3. of Annex IX.

5. On 12 September 2021, the Appellant submitted comments on the draft decision in accordance with Article 50(1). The Agency considered the Appellant's comments but did not amend the requests contained in the draft decision.

6. On 28 October 2021, the Agency notified the draft decision to the competent authorities of the Member States in accordance with Articles 50(1) and 51(1).

7. On 14 January 2022, as no proposals for amendment were submitted by the competent authorities of the Member States, the Agency adopted the Contested Decision in accordance with Article 51(3).

2. Contested Decision

8. The Contested Decision requires the Appellant to submit, by 21 October 2024, information on:

*'1. Transgenic rodent somatic and germ cell ['**TGR**'] gene mutation assays (Annex IX, Section 8.4., column 2; test method: OECD TG 488) in transgenic mice or rats, oral route, on the following tissues: liver and glandular stomach; germ cells and duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.*

OR

In vivo mammalian alkaline Comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum

*2. Pre-natal developmental toxicity ['**PNDT**'] study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral gavage, in one species (rat or rabbit)*

*3. Extended one-generation reproductive toxicity study ['**EOGRTS**'] (triggered by Annex IX, Section 8.7.3., column 1; test method: OECD TG 443) by oral gavage, in rats, specified as follows:*

- *Ten weeks premating exposure duration for the parental (P0) generation;*

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1 EC number 224-052-0.

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 Recitals, Articles or Annexes hereinafter concern the REACH Regulation unless stated otherwise.

- *Dose level setting shall aim to induce systemic toxicity at the highest dose level;*
- *Cohort 1A (Reproductive toxicity);*
- *Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.'*

3. Procedure before the Board of Appeal

9. On 14 April 2022, the Appellant filed this appeal.

10. On 20 June 2022, the Agency filed its Defence.

11. On 8 July 2022, Cruelty Free Europe (**CFE**) and PETA Science International E.V. (**PSCI**) were both granted leave to intervene in support of the Appellant.

12. On 31 August 2022, the Appellant filed its observations on the Defence.

13. On 27 September 2022, PSCI informed the Board of Appeal that it no longer wished to intervene in this case.

14. On 30 September 2022, CFE submitted its statement in intervention.

15. On 7 October 2022, the Agency filed its observations on the Appellant's observations on the Defence.

16. On 3 November 2022, the Appellant and the Agency submitted their observations on the statement in intervention.

17. On 7 March 2023, a hearing was held at the Appellant's request. At the hearing, the Parties and the Intervener made oral submissions and responded to questions from the Board of Appeal.

4. Form of order sought

18. The Appellant requests the Board of Appeal to:

- annul the Contested Decision insofar as it requires the PNDT study to be carried out via oral administration by gavage,
- annul the Contested Decision insofar as it requires the EOGRTS;
- in the event that the information requirement for the EOGRTS is maintained, annul the Contested Decision insofar as (i) it requires the EOGRTS to be carried out via oral administration by gavage, and (ii) sets out requirements for dose level setting,
- annul the Contested Decision insofar as it sets out a time limit which requires the Appellant to carry out the studies requested in the Contested Decision in parallel by 21 October 2024,
- order the refund of the appeal fee, and
- take such other or further measures as justice may require, including an extension of the time limit to allow sequential testing.

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

5. Assessment of the case

20. The Appellant raises four pleas, alleging that the Agency:

- erred in its assessment, exceeded its competences, breached Sections 8.7.2. and 8.7.3. of Annex IX and Article 25 by requesting the PNDT study and the EOGRTS to be carried out via oral administration by gavage (**first plea**),
- erred in its assessment, exceeded its competences, breached Section 8.7.3. of Annex IX, Article 25 and the Appellant's right to be heard by requesting the EOGRTS (**second plea**),
- erred in its assessment, exceeded its competences and breached Section 8.7.3. by requesting the dose level setting for the EOGRTS (**third plea**), and
- erred in its assessment and breached the relevant sections of Annex IX and Article 25 by requesting the studies required by the Contested Decision to be carried out in parallel and submitted by 21 October 2024 (**fourth plea**).

5.1. First plea: The Agency committed an error of assessment, exceeded its competences, breached Sections 8.7.2. and 8.7.3. of Annex IX and Article 25 by requesting the PNDT study and the EOGRTS to be carried out via oral administration by gavage

Arguments of the Parties and the Intervener

21. The first plea of the Appellant consists of two parts.

22. First, the Appellant argues that the Agency exceeded its competences by requiring the PNDT study and the EOGRTS to be carried out via oral administration by gavage, and not allowing the Appellant to apply the most scientifically appropriate method.

23. In support of the first part of the first plea, the Appellant argues that the Agency's competence under Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX is limited to the choice of route of administration (i.e. oral, dermal or inhalation) as explicitly mentioned in those provisions, and that the Agency is not allowed to prescribe which mode of administration (e.g. oral administration by gavage or oral administration through the diet) is to be applied.

24. The Appellant further argues that it should be allowed to carry out the required studies via oral administration through the diet because (i) testing at the higher dose can be achieved equally via oral administration through the diet and (ii) with proper monitoring of the studies, clear conclusions on the administered doses and uptake of the Substance via oral administration through the diet can be achieved. In that case the artificial effects of the bolus dose caused by the oral administration by gavage can be excluded.

25. Second, the Appellant argues that the Agency erred in its assessment that oral administration by gavage is necessary and appropriate.

26. In support of the second part of the first plea, the Appellant argues that the use of oral administration by gavage could lead to stress in the test animals causing systemic toxicity effects which are not related to the Substance.

27. The Appellant further argues that the Agency cannot request the PNDT study and the EOGRTS to be carried out via oral administration by gavage since humans cannot be exposed to the Substance via oral administration by gavage.

28. In addition, the Appellant argues that the Agency misinterpreted the existing information because the two reproductive toxicity studies available in the Appellant's registration dossier, namely a PNDT study in a first species (rat) from 1992 carried out via oral administration by gavage (the **1992 study**), and a four-generation study from 1971 carried out via oral administration through the diet (the **1971 study**) are not comparable due to different study designs and testing conditions. Therefore, the Agency could not have relied on the comparison to justify why oral administration by gavage must be used for the PNDT study and the EORGTS.

29. The Appellant further argued, at the hearing, that although the studies show reduced palatability of the Substance, this issue can be overcome by micro-encapsulation and proper monitoring of the studies.

30. Last, the Appellant argues that based on the available information on the Substance the requirement to use oral administration by gavage instead of oral administration through the diet is not in line with Article 25. According to the Appellant, oral administration through the diet is less stressful for the test animals compared to oral administration by gavage. The latter is also in conflict with the general principle of replacing, reducing and refining vertebrate animal testing set out in Recital 47 (the **3Rs principle**).

31. The Intervener supports the Appellant's arguments and argues that the oral administration of a substance by gavage is the method of oral administration which is most stressful for the test animals and most technically demanding. According to the Intervener, the stress and distress from the use of oral administration by gavage can confound the results of a study.

32. The Intervener further argues that the sixth introductory paragraph to Annex IX, which was introduced by Commission Regulation (EU) 2021/979[3] and which confers on the Agency new powers for imposing requirements on study design, was applicable only from 8 January 2022, which is six days before the date of the Contested Decision. Therefore, according to the Intervener the Agency breached (i) the principle of legal certainty and/or similar principles, (ii) the principle of legitimate expectations and (iii) the principle of non-retroactivity by applying the sixth introductory paragraph to Annex IX during the decision-making procedure leading to the Contested Decision.

33. The Agency disputes the merits of the Appellant's and the Intervener's arguments.

34. The Agency further argues that the arguments raised by the Intervener concerning the sixth introductory paragraph to Annex IX constitute different pleas than the ones raised by the Appellant in its Notice of Appeal and therefore alter the subject matter of the case. According to the Agency, the Intervener's arguments concerning the sixth introductory paragraph to Annex IX are therefore inadmissible.

Findings of the Board of Appeal

5.1.1. Admissibility of the Intervener's arguments concerning the sixth introductory paragraph to Annex IX

35. Under Article 8 of the Rules of Procedure[4] an intervener may submit a statement in intervention which contains, amongst other information, the pleas in law and the arguments of fact relied on.

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[3] Commission Regulation (EU) 2021/979 of 17 June 2021 amending Annexes VII to XI to the REACH Regulation (OJ L 216, 18.6.2021, p. 121–132).

[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).

36. An intervener may raise new pleas insofar as they are not entirely unconnected to the pleas raised by the main party and do not modify the subject matter of the case.[5]

37. In the present case, the arguments of the Intervener concerning the sixth introductory paragraph to Annex IX were not raised by the Appellant in its Notice of Appeal.

38. However, the arguments of the Intervener are not entirely unconnected with the issue underlying the dispute, as they relate to the plea raised by the Appellant regarding the limits of the competences of the Agency to prescribe a specific mode of administration of the substance to be tested.

39. In its Notice of Appeal, the Appellant argues that the Agency exceeded its competences by requiring the Appellant to carry out the PNDT study and the EOGRTS via oral administration by gavage. In its statement in intervention, the Intervener argues that the Agency erroneously based the requirement to use oral administration by gavage on the competence conferred on the Agency by the sixth introductory paragraph to Annex IX. The Intervener's arguments are therefore closely connected to the Appellant's first plea and do not alter the subject matter of the case.

40. Furthermore, the Agency did not bring any other element demonstrating how the Intervener's arguments concerning the sixth introductory paragraph to Annex IX would modify the subject matter of the case.

41. The Agency's inadmissibility claim must therefore be rejected.

5.1.2. Substance of the first plea

42. The Appellant does not contest that the Agency is empowered to require registrants to perform a PNDT study and an EOGRTS using the oral route of administration. However, the Appellant argues that the Agency's competence under Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX is limited to the route of administration (i.e. oral, dermal or inhalation) and does not extend to the mode of administration.

43. The first plea consists of two parts, which will be examined separately. To that end, it is necessary to examine whether the Agency (a) has the competence to require the use of a specific mode of administration in the PNDT study and the EOGRTS, and (b) made an error of assessment in requiring the use of oral administration by gavage in the PNDT study and the EOGRTS.

(a) The Agency has competence to require the use of a specific mode of administration in the PNDT study and the EOGRTS (first part of the first plea)

44. Under Article 41(1)(a) the Agency has competence to examine whether any registration complies with the requirements set out in Articles 10, 12, 13 and Annexes III and VI to X.

45. Article 41(3) empowers the Agency to request from a registrant any information that is needed to bring the registration into compliance with the information requirements set out in the REACH Regulation.[6]

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[5] See, to that effect and by analogy, judgment of 14 March 2013, *Fresh Del Monte Produce* v *Commission*, T-587/08, EU:T:2013:129, paragraph 537. See also intervention decision of the Board of Appeal of 15 December 2017, *Climax Molybdenum (Plansee)*, A-006-2017, paragraph 23.

[6] Decision of the Board of Appeal of 25 April 2023, *BASF Lampertheim and Metall-Chemie*, A-002-2022 and A-003-2022, paragraph 36.

46. Under the first subparagraph of Article 13(3), where tests on substances are required to generate information on the intrinsic properties of substances, those tests must be carried out in accordance with the test methods laid down in the Test Methods Regulation[7] or in accordance with other international test methods recognised by the Commission or the Agency as being appropriate.

47. Under Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX[8] a PNDT study and an EOGRTS examining the reproductive toxicity properties of a substance must be carried out using the '*most appropriate route of administration, having regard to the likely route of human exposure*'.

48. The main routes of administration are identified in the REACH Regulation as oral, dermal and inhalation. The Annexes to the REACH Regulation consistently refer to these main routes of administration. However, the REACH Regulation makes no reference to modes of administration. In particular, as regards the oral route of administration, the Annexes do not distinguish between oral administration through the diet and oral administration by gavage.

49. The fact that Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX only mentions the route of administration does not mean that the Agency is legally precluded from verifying or requiring other elements of the study design in accordance with Article 41(1)(a) and (3) in conjunction with the first subparagraph of Article 13(3). The mere mention of the route of administration in Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX cannot be interpreted as limiting the competence of the Agency in a compliance check decision under Article 41 to define certain elements of the study design, if those elements are set out in the respective test methods.

50. Furthermore, Article 41(1)(a) empowers the Agency to examine whether the registration complies not only with the specified Annexes, but also with, amongst other provisions, Article 13(3).

51. Under Article 13(3) the information requirements set out in Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX must be read in conjunction with the applicable test methods for a PNDT study and an EOGRTS. The respective test methods are set out in the Test Methods Regulation as EU test method B.31 (corresponding to OECD test guideline (**TG**) 414) and EU test method B.56 (corresponding to OECD TG 443).

52. The test methods describe how the study can be carried out[9] and may include several options on some elements of the study which can depend, amongst other things, on the properties of the substance that is being tested.[10]

53. The test methods are not only addressed to the registrants for carrying out the reproductive studies, but also to the Agency, which may verify the compliance of registration dossiers under Article 41(1)(a) and may require information under Article 41(3) to fill data-gaps that have been identified in those registration dossiers.

54. Both OECD TG 414 and OECD TG 443 contain several options regarding the route and mode of administration of the substance to be tested, including oral administration by gavage and oral administration through the diet.

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[7] Commission Regulation (EC) No 440/2008 laying down test methods pursuant to the REACH Regulation (OJ L 142, 31.5.2008, p. 1).

[8] In the version applicable at the time of the adoption of the Contested Decision.

[9] Paragraph 2 of OECD TG 443.

[10] Paragraph 4 of OECD TG 414.

55. Paragraph 18 of OECD TG 414 (PNDT study) provides:

'*The test chemical or vehicle is usually administered orally by intubation. If another route of administration is used, the tester should provide justification and reasoning for its selection, and appropriate modifications may be necessary*' (emphasis added).

56. Paragraph 18 of OECD TG 443 (EOGRTS) provides:

'*Selection of the route should take into consideration the route(s) most relevant for human exposure. Although the protocol is designed for administration of the test chemical through the diet, it can be modified for administration by other routes (drinking water, gavage, inhalation, dermal), depending on the characteristics of the compound and the information required*' (emphasis added).

57. Irrespective of whether the test method describes oral administration by gavage as a route or a mode of administration and irrespective of whether the test method sets a preference or a default or not, both OECD TG 414 and TG 443 recognise oral administration by gavage and oral administration through the diet as ways in which a substance can be administered to the test animals.

58. Both test guidelines allow for flexibility and specific modifications in individual cases on the basis of specific knowledge on e.g. physicochemical or toxicological properties of the test chemical. Such modifications are acceptable when convincing scientific evidence suggests that the modification will lead to a more informative test.[11]

59. When the relevant OECD test guideline provides for the flexibility referred to in paragraphs 52 and 58 above, in a compliance check under Article 41 the Agency may require the registrants to carry out the respective study by using a specific mode of administration, if this mode of administration is possible under the applicable test guideline and necessary to obtain meaningful information on the intrinsic properties of the substance in question.

60. This is consistent with the powers conferred on the Agency in the evaluation of testing proposals. Article 40(3)(b) and (d) states that following an examination of a testing proposal the Agency can modify the conditions under which the test is to be carried out or take a decision rejecting the testing proposal.

61. That conclusion is not called into question by the wording '*the likely route of human exposure*' in Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX for two reasons.

62. First, the likely route of human exposure is only considered in the REACH Regulation as one of the elements to select the most appropriate route of administration (i.e. oral, dermal or inhalation). Therefore, it does not restrict the Agency from deciding on a specific mode of administration if it is foreseen in the applicable test guideline.

63. Second, the objective of the standard information requirements under the REACH Regulation, such as the PNDT study and the EOGRTS under Sections 8.7.2. and 8.7.3. of Annex IX respectively, is to examine the intrinsic properties of a substance, not the exposure to that substance or the potential risks that result from the exposure.[12] Therefore, the Agency can require oral administration by gavage even if humans under normal conditions are not exposed to the Substance in that way.

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[11] Paragraph 4 of OECD TG 414, and paragraph 16 of OECD TG 443.

[12] Decision of the Board of Appeal of 8 September 2017, *Envigo and DJChem*, A-026-2015, paragraph 110, and decision of the Board of Appeal of 24 March 2020, *Emerald Kalama Chemical and Others*, A-006-2018, paragraph 69.

64. It follows from the reasons set out in paragraphs 44 to 63 above that the Agency was competent to require the use of oral administration by gavage for the PNDT study and the EORGTS in accordance with the applicable test guidelines.

65. For the following reasons, this conclusion is not called into question by the Intervener's argument that the Agency erroneously applied Commission Regulation (EC) 2021/979, which introduced the sixth introductory paragraph to Annex IX, in the decision-making procedure leading to the Contested Decision.[13]

66. First, the Contested Decision makes no reference to Commission Regulation 2021/979. The Intervener did not demonstrate that this regulation was either decisive or essential at the time of the adoption of the Contested Decision.

67. Second, the power of the Agency to require registrants to carry out a study by using a specific mode of administration is inherent in its competences under Article 41 and therefore predates the entry into force of Regulation 2021/979.[14]

68. Consequently, contrary to the Intervener's arguments the Agency did not apply the sixth introductory paragraph to Annex IX in the decision-making procedure leading to the Contested Decision.

69. It follows that the Agency has not exceeded its power to examine and require a mode of administration in accordance with Articles 41(3) and 13, and the applicable test guidelines.

70. The first part of the first plea must therefore be rejected.

(b) The Agency did not make an error of assessment in requiring the use of oral administration by gavage in the PNDT study and the EOGRTS (second part of the first plea)

71. By the second part of the first plea, the Appellant argues that the Agency erred in its assessment that oral administration by gavage is necessary and appropriate.

72. Both OECD TG 414 and TG 443 recognise oral administration by gavage and oral administration through the diet as a way to administer the substance to be tested. If another method is chosen than the one on the basis of which the test guideline is designed, justification needs to be provided.[15]

73. As explained in paragraphs 52 and 58 above, both test guidelines allow for flexibility and specific modifications in individual cases on the basis of specific knowledge on e.g. physicochemical or toxicological properties of the test chemical. Such a modification is acceptable when convincing scientific evidence suggests that the modification will lead to a more informative test.

74. When such a discretion is exercised, whether by the registrant or the Agency, all the necessary information should be taken into account and Article 25 should be adhered to.[16]

75. The second part of the first plea must be examined in the light of those considerations.

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[13] See paragraph 32 above.

[14] See paragraph 59 above.

[15] Paragraph 18 of OECD TG 414, and paragraph 18 of OECD TG 443.

[16] See, to that effect and by analogy, decision of the Board of Appeal of 29 April 2013, *Honeywell*, A-005-2011, paragraphs 90 to 110; see also judgment of 21 January 2021, *Germany* v *Esso Raffinage*, C-471/18 P, EU:C:2021:48, paragraph 132.

76. In the Contested Decision, the Agency explained that the requirement to use oral administration by gavage in the PNDT study and the EOGRTS in the present case is based on the findings in (i) the existing studies, (ii) the palatability of the Substance and (iii) the regulatory means.

- *Existing studies*

77. The Agency explained in the Contested Decision that the use of oral administration by gavage for both the PNDT study and EORGTS is necessary as more severe effects (increase in average gestation length, increase in stillborn pups and decrease in pup viability index) were observed in the 1992 study carried out via oral administration by gavage than in the 1971 study carried out via oral administration through the diet.[17]

78. The Appellant argues that these two reproductive studies are not comparable due to different study designs and testing conditions.[18]

79. The Agency explained in the Contested Decision that in the 1992 study and the 1971 study are comparable. Despite the differences in protocols and study design, in both studies the exposure to the Substance of female rats covered the full gestation period and (part of) the postnatal period. According to the Agency, these periods are critical for the assessment of reproductive and developmental toxicity.

80. The Contested Decision further states that more severe reproductive and developmental toxicity effects were observed in the 1992 study than in the 1971 study. This indicates that oral administration by gavage may cause more severe reproductive and developmental toxicity than oral administration through the diet.

81. The Appellant did not establish that the Agency committed an error as regards the assessment of these existing studies.

- *Palatability of the Substance*

82. The Agency explained in the Contested Decision that due to the reduced palatability of the Substance there is a risk that the doses achieved via oral administration through the diet are not sufficiently high. The reduced palatability and the difficulties in achieving and maintaining sufficiently high dose levels via oral administration through the diet were observed in the 1971 study and in a 90-day repeated dose toxicity study performed in 1997 according to OECD TG 408 (the **1997 study**).[19]

83. The Appellant does not contest that those studies show reduced palatability. However, the Appellant argues that the issue can be overcome by using micro-encapsulation for the oral administration of the Substance through the diet and proper monitoring of the studies.[20]

84. Whilst the Appellant argued in the present appeal proceedings that the micro encapsulation may help to address the reduced palatability of the Substance and ensure that sufficiently high doses are achieved and maintained, it did not provide any information or evidence to demonstrate that this technique would overcome the reduced palatability of the Substance in the present case.

85. It follows that the Appellant has not established that the Agency committed an error as regards the assessment of the palatability of the Substance.

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[17] See pages 7, 8 and 12 of the Contested Decision.

[18] See paragraph 28 above.

[19] See pages 7 and 8 of the Contested Decision.

[20] See paragraph 29 above.

- *Regulatory means (adequacy for hazard and risk assessment)*

86. The Parties agree that the data generated under the REACH Regulation need to be adequate for hazard identification, classification and risk assessment.

87. The Appellant, supported by the Intervener, argues that if the relevant test guidelines allow for flexibility regarding the mode of administration of the substance to be tested, the Agency should have taken Article 25 and the 3Rs principle into account when deciding that the requested studies should be carried out via oral administration by gavage.[21] Had the Agency done so, the Agency would not have required the use of oral administration by gavage because this could lead to stress in the test animals causing systemic toxicity effects which are not related to the Substance.[22] Moreover, even if the oral administration by gavage is better, according to the Intervener, this does not render the oral administration through the diet less adequate.

88. In the present case, neither the Appellant nor the Intervener demonstrated that the Agency made an error of assessment in requiring the requested information via oral administration by gavage for the following reasons.

89. First, the 3Rs principle was already taken into account by the European Commission when EU test methods B.31 and B.56, which correspond to the OECD test guidelines 414 and 443, were inserted in the Annex to the Test Methods Regulation.[23]

90. The use of oral administration by gavage is recognised as one of the modes of administration both in the OECD TG 414/EU test method B.31 and the OECD TG 443/EU test method B.56, the legality of which cannot be contested before the Board of Appeal.[24]

91. Second, Article 25 requires both the registrants and the Agency to ensure that, in complying with the relevant information requirements, registrants do not carry out unnecessary vertebrate animal testing.[25] If a vertebrate animal study cannot be avoided on the basis of existing information, the Agency is – in accordance with Article 25 – empowered and required to ensure that a vertebrate animal study requested in a compliance check decision is carried out in a way that maximises the likelihood of obtaining useful results[26] and minimises the risk of having to duplicate that study.

92. In the context of reproductive toxicity, as in the present case, testing must be performed at appropriately high dose levels in order to provide adequate information on the reproductive toxicity properties of the Substance and to ensure that the data generated are adequate for hazard identification, classification and risk assessment.

93. In the present case, the Agency considered the existing studies, the palatability of the Substance and the regulatory means (adequacy for hazard and risk assessment) in order to determine the mode of administration. According to the Contested Decision, on the basis of existing information and the palatability of the Substance there is a risk that the doses achieved by the oral administration through the diet

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[21] See paragraphs 30 and 31 above.

[22] See paragraph 26 above.

[23] See Recital 5 of the Test Methods Regulation, and Article 13(2) of the REACH Regulation.

[24] See, to that effect, decision of the Board of Appeal of 10 May 2022, *Lanxess Deutschland and Schirm*, A-002-2021, paragraph 79.

[25] See, to that effect and by analogy, decision of the Board of Appeal of 29 April 2013, *Honeywell*, A-005-2011, paragraphs 90 to 110; judgment of 21 January 2021, *Germany* v *Esso Raffinage*, C-471/18 P, EU:C:2021:48, paragraph 132.

[26] Decision of the Board of Appeal of 18 August 2020, *Symrise*, A-009-2018, paragraph 173.

are not sufficiently high for proper hazard identification and risk assessment. Furthermore, the existing information shows that oral administration by gavage compared to oral administration through the diet allows a better control of the administered doses and a more precise characterisation of the dose-response relationship, which is necessary for hazard identification and risk assessment.[27] As explained above, the Appellant has not demonstrated that the choice made by the Agency is inadequate on the basis of existing information.

94. Furthermore, the use of control groups is part of the test protocol in both the PNDT study and the EOGRTS. The use of control groups will allow to differentiate whether potential stress caused by the use of oral administration by gavage affected the animals. The Appellant's argument that the use of oral administration by gavage could lead to stress in the test animals causing effects which are not related to the Substance must therefore be rejected.

95. The Appellant, supported by the Intervener, did also not demonstrate that the choice made by the Agency is inadequate insofar it would lead to duplication of studies.[28]

96. Third, the use of micro-encapsulation in oral administration through the diet, presented by the Appellant and the Intervener at the hearing as being adequate for hazard and risk assessment, has not been supported by any evidence.

97. Finally, the Appellant's argument that the Contested Decision precludes it from applying the most scientifically appropriate method must be rejected. The Contested Decision requires the Appellant to carry out the PNDT study and the EOGRTS by using oral administration of the Substance by gavage. Based on the information available at the time of the adoption of the Contested Decision, and after having fulfilled its duties under Article 25, the Agency did not make an error in requiring the oral administration of the Substance by gavage, which is a binding element of the Contested Decision.

98. However, this does not preclude the Appellant from fulfilling the information requirements set out in the Contested Decision, when in the present case the OECD test guidelines allow for such flexibility and in view of the 3Rs principle, by alternative scientifically justified means (other than the ones requested in the context of the studies required by the Contested Decision). In particular, the Appellant might decide to carry out those studies by having recourse to innovative scientific methods which the Agency could not assess at the time of the adoption of the Contested Decision, provided that the Appellant fills the data-gaps of its registration and takes due account of the objections identified in the Contested Decision as regards the existing studies, the palatability of the Substance and the need to generate adequate data for hazard identification, classification and risk assessment.[29]

99. It follows that the Appellant has not established that the Agency committed an error as regards the assessment of regulatory means (adequacy for hazard and risk assessment).

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[27] See page 8 of the Contested Decision.

[28] See to that effect Article 25 and Recital 49.

[29] See, to that effect, Recital 1 of Commission Regulation (EU) 2015/282 amending Annexes VIII, IX and X to the REACH Regulation as regards the Extended One-Generation Reproductive Toxicity Study (OJ L 50, 21.2.2015, p. 1); see also, to that effect and by analogy, judgments of 29 March 2023, *Nouryon Industrial Chemicals and Others* v *Commission*, T-868/19, EU:T:2023:168, paragraph 146, and of 21 January 2021, *Germany* v *Esso Raffinage*, C-471/18 P, EU:C:2021:48, paragraph 132.

- *Conclusion on the second part of the first plea*

100. It follows from the reasons set out in paragraphs 71 to 99 above that, based on existing studies, the palatability of the Substance and the regulatory means (adequacy for hazard and risk assessment), the Agency did not make an error in its assessment that oral administration by gavage is necessary and appropriate.

101. The second part of the first plea must therefore be rejected.

5.1.3. Conclusion on the first plea

102. As both parts of the first plea are unfounded, the first plea must be rejected.

5.2. Second plea: The Agency committed an error of assessment, exceeded its competences, breached Section 8.7.3. of Annex IX, Article 25 and the Appellant's right to be heard by requesting the EOGRTS

Arguments of the Parties and the Intervener

103. By the second plea the Appellant, supported by the Intervener, argues that the requirement for an EOGRTS under Column 1 of Section 8.7.3. of Annex IX is not triggered in the present case. According to the Appellant, the available studies do not indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity study.

104. First, according to the Appellant, the potential fertility effects were sufficiently addressed in the 1971 study and all the remaining reproductive toxicity concerns will be investigated in the PNDT study. Therefore, according to the Appellant, there is no need for the EOGRTS.

105. Second, in its comments on the draft decision the Appellant claimed that in the 1992 study the adverse effects were observed at massive systemic toxic doses causing lethality and that the increase in gestation lengths is likely due to delayed development of the pups following reduced feed consumption and body weight gain as well as systemic toxicity in the dams. In the Contested Decision the Agency held that as the Appellant had not provided more detailed individual/numerical data to support this argument it was not possible to conclude on the cause of the adverse effects. The Appellant argues that the Agency breached its right to be heard by not specifically requesting such data before adopting the Contested Decision.

106. The Agency disputes the Appellant's and the Intervener's arguments.

Findings of the Board of Appeal

107. The second plea consists of two parts, which will be examined separately.

5.2.1. Trigger for the EOGRTS (first part of the second plea)

108. Under Column 1 of Section 8.7.3. of Annex IX an EORGTS with basic test design (cohorts 1A and 1B without extension to include a F2 generation) is triggered as a standard information requirement if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.

109. In the Contested Decision, the Agency requested an EOGRTS with the basic study design. The Agency found that the EOGRTS was needed because an increase in average gestation length, a statistically significant increase in the number of stillborn pups and a statistically significant decrease in pup viability index were observed in the 1992 study and various gross histopathological findings in the uterus of female rats in the 1997 study.

110. The Appellant contests the Agency's reliance on the uterus findings of the 1997 study, arguing that uterus findings were not observed in any other studies with longer exposure and are not confirmed by histopathological findings in the study. The Appellant does not contest the findings of the 1992 study as the trigger for the EOGRTS as such but argues that carrying out an EOGRTS will not provide any information other than information which is already available or would be obtained as a result of the PNDT study. Those arguments must be rejected for the following reasons.

111. First, the 1992 study showed a statistically significant increase in the number of stillborn pups and a statistically significant decrease in pup viability index. Contrary to the Appellant's arguments, the fact that those effects were observed at high dose does not mean that those effects should be disregarded. As the Agency explained in the Contested Decision, the main signs of maternal toxicity reported at the high dose of 350 mg/kg bw/day were significantly reduced mean body weight and feed consumption, with no details provided on the percentage of decrease that would support the Appellant's claim of massive systemic toxic doses. The Contested Decision further states that one test animal died in the high-dose group on gestation day 20 but, from the limited information available, it is unclear whether death is related to the treatment or not, since this was the only mortality reported and the cause of death was congested lungs.[30] The Agency did not make an error in finding that the high doses used in the 1992 study should be considered and that the results of the study were relevant for establishing a fertility concern.

112. Second, contrary to the Appellant's argument, the 1971 study is incapable of clarifying the effects observed in the 1992 study, due to its significant deficiencies as identified in the Contested Decision.

113. Third, contrary to the Appellant's argument, when the conditions set out in Column 1 of Section 8.7.3. of Annex IX are fulfilled, an EOGRTS is a standard information requirement which is distinct from the requirement to carry out a PNDT study under Column 1 of Section 8.7.2. of Annex IX. Therefore, when the conditions for triggering an EOGRTS at Annex IX level are fulfilled, the EOGRTS cannot be adapted on the basis that some of the properties of the respective substance might be examined in a PNDT study as well. Moreover, as stated in the Contested Decision, a PNDT study will not provide information on fertility, reproductive performance and developmental toxicity manifested shortly after birth, or toxicity to the offspring after birth up to adulthood (including reproductive toxicity and systemic toxicity) as foreseen to be investigated in an EOGRTS.

114. The first part of the second plea must therefore be rejected as unfounded.

5.2.2. Right to be heard (second part of the second plea)

115. In its comments on the draft decision the Appellant claimed that in the 1992 study the adverse effects were observed in the high-dose group and were a result of reduced feed consumption and body weight gain as well as systemic toxicity in the dams. The Appellant did not provide detailed data to substantiate this claim.

[30] See page 9 of the Contested Decision.

116. In the Contested Decision the Agency found that in the absence of supporting information (i.e. more detailed individual/numerical data) the Appellant's claim was unsubstantiated and could not rebut the concern on the reproductive toxicity.

117. The Appellant argues that the Agency breached its right to be heard as the Contested Decision was adopted without first requesting the Appellant to substantiate its claim with additional information.

118. It is the sole responsibility of the registrants to generate, gather and submit to the Agency the information that they consider will fulfil the information requirements of the REACH Regulation.[31]

119. In the present case, the Agency correctly limited its examination to the information submitted by the Appellant in its registration and during the decision-making procedure leading to the Contested Decision.

120. It was for the Appellant to provide all the necessary information to rebut the Agency's finding in the draft decision that an EOGRTS is triggered. The Agency was not required to request the Appellant to provide further information when it considered that the claim made by the Appellant in its comments on the draft decision was unsubstantiated.

121. Even assuming that the Appellant had been requested to submit the necessary supporting data, it could not have done so since the Appellant, as it confirmed at the hearing, was (and still is) not in possession of the full study report of the 1992 study and therefore not able to provide detailed information to support its claim. Therefore, the Appellant's argument on the breach of its right to be heard remains speculative.

122. The second part of the second plea must therefore be rejected as unfounded.

5.2.3. Conclusion on the second plea

123. As both parts of the second plea are unfounded, the second plea must be rejected.

5.3. Third plea: The Agency committed an error of assessment, exceeded its competences and breached Section 8.7.3. by requesting the dose level setting for the EOGRTS

Arguments of the Parties and the Intervener

124. By the third plea the Appellant, supported by the Intervener, argues that the Agency committed an error of assessment, exceeded its competences and breached Section 8.7.3. of Annex IX by requesting the dose level setting for the EOGRTS.

125. First, the Appellant argues that the REACH Regulation does not allow the Agency to impose detailed dose setting requirements which are set out in the Contested Decision.

126. Second, the Appellant argues that the requirement of the Contested Decision to base the dose level selection on fertility effects is misleading. The Appellant argues that when the Contested Decision requires the dose level to be set based on fertility effects it is unclear if doses beyond 1000 mg/kg bw/day should be tested in cases where no systemic toxicity is detected.

127. Third, the Appellant argues that due to the low toxicity of the Substance it may not be technically possible to fulfil the requirements of the Contested Decision as regards the dose level setting.

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[31] Decision of the Board of Appeal of 29 June 2021, *SNF*, A-001-2020, paragraph 47.

128. The Agency disputes the Appellant's and the Intervener's arguments.

Findings of the Board of Appeal

129. The Contested Decision states that for the study to be compliant and not be rejected due to excessively low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon fertility effects.[32]

130. First, the Appellant argues that the REACH Regulation does not allow the Agency to set out such requirements for the dose setting.

131. As regards the requirement that the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, the Contested Decision merely repeats paragraph 21 of OECD TG 443.

132. As regards the indication that the dose level selection should be based on fertility effects, the Agency is competent in a compliance check decision under Article 41 to define certain elements of the study design within the flexibility allowed by the applicable test guideline and under the conditions set out in that guideline.[33]

133. OECD TG 443, which sets out the test method for the EOGRTS, provides for flexibility as regards the setting of dose levels. In order to maximise the likelihood of obtaining useful results from the requested study it may be necessary for the Agency to set out requirements for the dose level setting.[34]

134. Therefore, the Agency did not exceed its competences by setting out requirements for dose level setting in the Contested Decision.

135. Second, the Appellant argues that the requirement of the Contested Decision to base the dose level selection on fertility effects is misleading. It is unclear if doses beyond 1000 mg/kg bw/day should be tested in cases where no systemic toxicity is detected.

136. Contrary to the Appellant's argument, the Contested Decision does not require the Appellant to go beyond a limit dose of 1000 mg/kg bw/day if no systemic toxicity is observed up to that dose.

137. Indeed, as the Agency confirmed at the hearing, according to paragraph 25 of OECD TG 443 if there is no evidence of toxicity at a dose of at least 1000 mg/kg bw/day, a study using several dose levels may not be necessary, but the EOGRTS can instead be carried out at a single dose of at least 1000 mg/kg bw/day. The Contested Decision does not preclude the Appellant from carrying out a limit test within the meaning of paragraph 25 of OECD TG 443 if the conditions set out in that paragraph are met.

138. Third, the Appellant argues that due to the low toxicity of the Substance it may not be technically possible to fulfil the requirements of the Contested Decision as regards the dose level setting. However, the Appellant did not provide any concrete evidence to support this claim. Therefore, the Appellant's claim that it may not be technically possible to fulfil the requirements of the Contested Decision as regards the dose level setting due to the low toxicity of the Substance is unsubstantiated.

139. As a result, the third plea must be rejected as unfounded.

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[32] See page 11 of the Contested Decision.

[33] See paragraphs 44 to 63 above.

[34] Decision of the Board of Appeal of 11 December 2018, *Climax Molybdenum*, A-006-2017, paragraphs 78 to 84; see also, to that effect and by analogy, decisions of the Board of Appeal of 18 August 2020, *Symrise*, A-009-2018, paragraphs 165 to 175, and of 18 August 2020, *Symrise*, A-010-2018, paragraphs 164 to 174.

5.4. Fourth plea: The Agency committed an error of assessment and breached the relevant sections of Annex IX and Article 25 by requesting the studies required by the Contested Decision to be carried out in parallel and submitted by 21 October 2024

Arguments of the Parties and the Intervener

140. By the fourth plea, the Appellant, supported by the Intervener, argues that the Agency made an error of assessment and breached Section 8.7. of Annex IX and Article 25 by setting too short a time limit (33 months and one week) for fulfilling the three information requirements set out in the Contested Decision.

141. Although the Appellant does not contest as such the first information requirement in the Contested Decision (TGR gene mutation assays or *in vivo* mammalian alkaline Comet assay), the Appellant argues that the time limit set in the Contested Decision is inadequate because it does not allow to carry out the three requested studies in sequence.

142. Moreover, the Appellant argues that the time limit is in breach of Article 25 because the TGR gene mutation assay could lead to adapting the PNDT study and the EOGRTS on the basis of Column 2 of Section 8.7. of Annex IX.

143. In addition, the Appellant argues that the PNDT study should be carried out before carrying out the EOGRTS as the PNDT study will provide relevant additional information on the endpoints for reproductive toxicity and may lead to the possibility of adapting the EOGRTS.

144. Last, the Appellant argues that the time limit is in any case based on too short an estimate of the respective duration of the three studies. At the hearing the Appellant explained that, considering the limitations in the current capacity of contract research organisations, the sequential conduct of the three studies would take 58 to 61 months.

145. The Agency disputes the Appellant's and the Intervener's arguments.

Findings of the Board of Appeal

146. The arguments of the Appellant that the time limit of 33 months and one week specified in the Contested Decision breaches Section 8.7. of Annex IX and Article 25 must be rejected for the following reasons.

147. Under Article 41(3) the Agency must specify an adequate time limit allowing the registrant concerned to bring its registration dossier into compliance, that is to say to fill the data-gaps identified by the Agency in a compliance check decision. For each data-gap identified in such a compliance check decision, the registrant concerned must submit information on the study requested or, alternatively, an acceptable adaptation.[35]

148. In the present case, the Contested Decision requires the Appellant to submit information on one of two mutagenicity studies (TGR gene mutation assays or *in vivo* mammalian alkaline Comet assay), information on a PNDT study, and information on an EOGRTS. The Contested Decision specifies a time limit of 33 months and one week for submitting information on all the three studies, i.e. 21 October 2024.

[35] Decision of the Board of Appeal of 9 November 2021, *Polynt*, A-009-2020, paragraph 44.

149. Column 2 of Section 8.7. of Annex IX lays down specific rules for adaptation from Column 1 of that section (reproductive toxicity). That provision states, amongst other things, that studies do not need to be carried out if a substance is known to be a germ cell mutagen meeting the criteria for classification for germ cell mutagenicity (category 1A or 1B) and appropriate risk management measures are implemented.

150. The results of the first information requirement in the Contested Decision (TGR gene mutation assays or *in vivo* mammalian alkaline Comet assay) might open the possibility to submit an adaptation instead of carrying out the PNDT study and/or the EOGRTS, which both concern reproductive toxicity, and could avoid unnecessary vertebrate animal testing in line with Article 25.

151. Column 2 of Section 8.7. of Annex IX[36] also prescribes that, if a substance is known to cause reproductive toxicity meeting the criteria for classification as toxic for reproductive category 1A or 1B for sexual function and fertility and/or for developmental toxicity and the available data are adequate to support a robust risk assessment, then no further vertebrate animal testing for sexual function and fertility and/or developmental toxicity respectively is necessary.

152. In the present case, the time limit of 33 months and one week provided by the Agency is adequate to meet the three information requirements addressed in the Contested Decision.

153. First, the Appellant does not contest the first information requirement in the Contested Decision (TGR gene mutation assays or *in vivo* mammalian alkaline Comet assay) in itself. This means that the Appellant agreed either to carry out one of the two mutagenicity studies or to develop an adaptation in accordance with Annex XI to comply with the information requirement set out in Column 2 of Section 8.4. of Annex IX.

154. Second, irrespective of any time limit, it is for the Appellant to take appropriate measures following the adoption of the Contested Decision to start carrying out a mutagenicity study or developing an adaptation if it considered that it could lead to the possibility of adapting the PNDT study and the EOGRTS. The Appellant has not only the right but also the obligation to do so in order to avoid unnecessary vertebrate animal testing under Article 25 whenever possible.[37]

155. Third, the time limit of 33 months and one week allows the Appellant to carry out first a mutagenicity study and then, in the event that the results of that study would not lead to a possibility to adapt the information requirements on reproductive toxicity, based on Column 2 of Section 8.7 of Annex IX, to carry out the PNDT study and the EOGRTS. If the Agency had required parallel testing it would have specified a shorter time limit than the one set out in the Contested Decision.

156. Fourth, insofar the Appellant contests that the time limit does not allow sequential testing because of practical issues in the implementing stage of the testing, the Agency does not have to consider practicalities of which the Agency is not aware of. Should a registrant face difficulties in the implementing stage, it should raise those issues with supporting evidence to the Agency during the decision-making process leading to the adoption of the Contested Decision. The Appellant did not raise any comment during the decision-making in this regard. It is only at the hearing that the Appellant clarified that it plans to fulfil the first information requirement in the Contested Decision by carrying out the TGR gene mutation assays in the last quarter

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[36] As amended by Commission Regulation (EU) 2021/979.

[37] See, to that effect, judgments of 21 January 2021, *Germany* v *Esso Raffinage*, C-471/18 P, EU:C:2021:48, paragraph 132, and of 29 March 2023, *Nouryon Industrial Chemicals and Others* v *Commission*, T-868/19, EU:T:2023:168, paragraph 139.

of 2024, without supporting evidence.

157. Fifth, the Appellant has not demonstrated that the PNDT study could impact the study design of the EOGRTS, or *vice versa*, on the basis of the available repeated dose toxicity study that is considered to be relevant for the study design.

158. It follows from the reasons set out in paragraphs 140 to 157 above that the Appellant did not demonstrate that the Agency committed an error in imposing the time limit set in the Contested Decision. As a result, the fourth plea must be rejected as unfounded.

6. Result

159. As all the Appellant's pleas have been rejected, the appeal must be dismissed.

7. Effects of the Contested Decision

160. The contested part of the Contested Decision, which is upheld in the present appeal proceedings, required the Appellant to submit the requested information requirements by 21 October 2024, which is 33 months and one week from the date of that decision.

161. Under Article 91(2), an appeal has suspensive effect. The time limit set in the Contested Decision must therefore be calculated starting from the date of notification of the present decision of the Board of Appeal to the Parties.

162. The Appellant must consequently provide the information on the PNDT study and the EOGRTS by 29 March 2026.

8. Refund of the appeal fee

163. Under Article 10(4) of the Fee Regulation,[38] the appeal fee must be refunded if the appeal is decided in favour of an appellant. As the appeal is dismissed, the appeal fee is not refunded.

[38] 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).

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Dismisses the appeal.**
2. **Decides that the information on the PNDT study and the EOGRTS as prescribed in the Contested Decision must be provided by 29 March 2026.**
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