EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

29 August 2023

(Dossier evaluation – Compliance check – Section 8.7.3. of Annex IX – EOGRTS – Investigation of the effects of a substance on the gut microbiome)

Case number	A-006-2022
Language of the case	English
Appellants	Symrise AG, Germany ADEKA Europe GmbH, Germany Evonik Dr. Straetmans GmbH, Germany CBW Chemie GmbH, Germany Represented by Ruxandra Cana, Hannah Widemann, and Tom Gillett Steptoe & Johnson LLP, Belgium
Contested Decision	Decision of 13 April 2022 on a compliance check of the registration for the substance Octane-1,2-diol, adopted by the European Chemicals Agency under Article 41 of the REACH Regulation

THE BOARD OF APPEAL

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

Registrar: Alen Močilnikar

gives the following

Decision

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1. Background to the dispute

1. This appeal concerns a compliance check of the registration for the substance octane-1,2-diol (the Substance*).*[1]

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

3. On 8 June 2021, the Agency initiated a compliance check under Article 41.

4. On 16 November 2021, the Agency notified to the Appellants a draft decision in accordance with Articles 41(3) and 50(1). The draft decision required the Appellants to submit information on, amongst others, an extended one-generation reproductive toxicity study (EOGRTS) under Column 1 of Section 8.7.3. of Annex IX.

5. On 28 December 2021, ADEKA Europe GmbH, in its capacity as lead registrant, submitted on behalf of all the Appellants comments on the draft decision in accordance with Article 50(1). On 7 January 2022, Symrise AG also submitted comments on the draft decision. The Agency took the Appellants' comments into account and did not amend its request to submit information on an EOGRTS.

6. On 3 March 2022, 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 13 April 2022, as no proposals for amendment were submitted to the Agency by the competent authority of a Member State, the Agency adopted the Contested Decision in accordance with Article 51(3).

2. Contested Decision

8. The Contested Decision requires the Appellants to submit, by 19 July 2024, information on, among others, an EOGRTS under Column 1 of Section 8.7.3. of Annex IX (test method: Organisation for Economic Co-Operation and Development (OECD) test guideline (TG) 443), to be performed on rats, by oral route, with the following specifications:

   - ten weeks premating exposure duration for the parental generation,
   - the highest dose level in parental animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths as specified in Appendix 1 to the Contested Decision, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels ('EOGRTS Testing Conditions'),
   - cohort 1A (reproductive toxicity), and
   - cohort 1B (reproductive toxicity) without extension to mate the cohort 1B animals to produce the F2 generation.

9. In the Contested Decision, the Agency found that the available studies involving repeated administration of the Substance indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation to reproductive toxicity, such as (i) reduced survival index of the offspring in the 2013 screening study for

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1 EC No 214-254-7; CAS No 1117-86-8.

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 or Annexes hereinafter concern the REACH Regulation unless stated otherwise.

reproductive/developmental toxicity in rats (OECD TG 421; screening study)[3] and (ii) reduced gravid uterine weights and reduced body weight of offspring in the 2013 developmental toxicity study in rats (OECD TG 414; PNDT study).[4] According to the Agency, those indications on the potential reproductive toxicity properties of the Substance must be therefore further investigated in an EOGRTS.

3. Procedure before the Board of Appeal

10. On 12 July 2022, the Appellants filed this appeal.

11. On 13 September 2022, the Agency submitted its Defence.

12. On 17 October 2022, the Appellants submitted their observations on the Defence.

13. On 9 December 2022, the Agency submitted its observations on the Appellants' observations on the Defence.

14. On 19 April 2023, a hearing was held as the Board of Appeal considered it necessary in accordance with Article 13(1) of the Rules of Procedure[5]. The hearing was held at the Agency's premises. At the hearing, the Parties made oral submissions and responded to questions from the Board of Appeal.

4. Form of order sought

15. The Appellants request the Board of Appeal to:

- annul the Contested Decision insofar as it requires the EOGRTS.
- in the alternative, the Appellants request the Board of Appeal to exercise its powers under Article 93(3), for example by amending the Contested Decision to:
  (a) allow for 36 months for the Appellants to submit the EOGRTS, and
  (b) remove from Appendix 1 to the Contested Decision the following specification: '*Regarding the highest dose level, it is important to ensure that sufficient severity of toxicity in both female and male animals is achieved to ensure that potential effects on sexual function and fertility in either gender is not overlooked*',
- order the refund of the appeal fee, and
- take such other or further measures as justice may require.

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

5. Assessment of the case

17. The Appellants raise two pleas, alleging that the Agency:

- erred in its assessment and failed to take relevant information into account by requesting information on an EOGRTS without taking into account the prior necessary investigation of the effects of the Substance on the gut microbiome (first plea), and

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[3] Reproduction / developmental toxicity screening test of 71868 in Wistar rats by oral route. Advinus Therapeutic Ltd study no. G8504, dated 30 August 2013.

[4] Prenatal developmental toxicity study of 71868 in Wistar rats by oral route. Advinus Therapeutic Ltd study no. G8505, dated 5 July 2013.

[5] 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).

- erred in its assessment, failed to take relevant information into account, exceeded its competences, breached Articles 13(3) and 25, and breached the principles of legal certainty and the protection of legitimate expectations by requesting the Appellants to generate information on an EOGRTS with the EOGRTS Testing Conditions (second plea).

5.1. First plea: Error of assessment and failure to take relevant information into account by requesting information on an EOGRTS without taking into account the prior necessary investigation of the effects of the Substance on the gut microbiome

Arguments of the Parties

18. In support of their first plea, the Appellants raise the following arguments.

19. First, the Appellants – as confirmed at the hearing – do not dispute the Agency's conclusion that the available information on the Substance triggers the requirement to carry out an EOGRTS under Column 1 of Section 8.7.3. of Annex IX. However, the Appellants argue that the Agency erred by requesting information on an EOGRTS without taking into account the need to investigate the effects of the Substance on the gut microbiome before starting the EOGRTS.

20. Specifically, the Appellants argue that the prior investigation of the effects of the Substance on the gut microbiome is scientifically necessary to plan the study design of the EOGRTS in order to perform an adequate hazard assessment. According to the Appellants, that investigation would allow the dose regime and the appropriate mode of administration for the EOGRTS to be determined. With regard to the mode of administration, the Appellants argue that the effects observed in the available studies on the Substance are not relevant because those studies were carried out via oral gavage and used high doses of the Substance to which humans would never be realistically exposed.

21. Second, the Appellants argue that the data obtained from the prior investigation of the effects of the Substance on the gut microbiome would allow a differentiation to be made between generic systemic toxicity effects and specific effects of reproductive toxicity. As a result, according to the Appellants, that data could result in classification of the Substance for target organ toxicity repeated exposure ('STOT RE') – instead of for reproductive toxicity – under the CLP Regulation[6]. Specifically, according to the Appellants, that investigation would allow them to identify the concentration of the Substance at which the gut microbiome activity of the test animals is inhibited and how many of them were affected.

22. Moreover, the Appellants argue that the Agency erroneously disregarded the fact that the prior investigation on the gut microbiome is required to obtain meaningful information on the intrinsic properties of the Substance and ultimately to ensure that the data generated in the EOGRTS are adequate for hazard identification and assessment. According to the Appellants, the generation and submission of information on the effects of the Substance on the gut microbiome would require 9 to 12 months, while the EOGRTS would require at least 24 months. Therefore, the time limit set in the Contested Decision is inadequate because it does not allow the investigation of the effects of the Substance on the gut microbiome and the EOGRTS to be carried out in sequence.

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[6] Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1).

23. The Agency disputes the merits of the Appellants' arguments.

24. The Agency also objects to the admissibility of the argument raised by the Appellants in their observations on the Defence according to which the reduced gravid uterine weights observed in the PNDT study do not provide indications of adverse effects triggering the requirement to provide information on an EOGRTS, and that the effects observed in the screening study are attributable to the antimicrobial activity of the Substance. According to the Agency, this argument is new and therefore inadmissible under Article 12(2) of the Rules of Procedure because it is not based on new matters of law and fact which came to light in the course of the proceedings.

Findings of the Board of Appeal

5.1.1. Admissibility of the Appellants' argument in their observations on the Defence

25. As explained in paragraph 24 above, according to the Agency, the Appellants raised a new argument in the observations on the Defence which should be dismissed as inadmissible. The Agency argues that the Appellants should have raised that argument in the Notice of Appeal and not in the observations on the Defence.

26. Under Article 12(2) of the Rules of Procedure, no new plea in law may be introduced after the first exchange of written pleadings unless the Board of Appeal decides that it is based on new matters of law or of fact that come to light in the course of the proceedings.

27. For the following reasons, the Appellants' argument referred to in paragraph 24 above is not a new plea in law.

28. First, that argument merely substantiates and confirms an argument already raised in the Notice of Appeal, namely that it is necessary to investigate the effects of the Substance on the gut microbiome before starting the EOGRTS.

29. Second, as confirmed by the Appellants at the hearing, the Appellants do not dispute the Agency's conclusion that the available information on the Substance triggers the requirement to carry out an EOGRTS under Column 1 of Section 8.7.3. of Annex IX. The argument referred to in paragraph 24 above does not enlarge the scope of the first plea.

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

5.1.2. Examination of the first plea

31. The Appellants argue in essence that the time limit set in the Contested Decision prevents them from investigating the effects of the Substance on the gut microbiome before starting the EOGRTS. The Appellants argue that the prior investigation of the gut microbiome is necessary both from a legal and scientific point of view.

32. In order to decide on the first plea, it is therefore necessary to examine (a) whether the Agency was legally required to extend the time limit set in the Contested Decision as the investigation of the effects of the Substance on the gut microbiome is a legal prerequisite for conducting the EOGRTS under Column 1 of Section 8.7.3. of Annex IX and (b) whether the investigation of the effects of the Substance on the gut microbiome is scientifically necessary for an adequate hazard assessment.

(a) The Agency was not legally required to extend the time limit set in the Contested Decision as the investigation of the effects of the Substance on the gut microbiome is not a legal prerequisite for conducting the EOGRTS under Column 1 of Section 8.7.3. of Annex IX

33. Under Article 41, the Agency can assess the quality and adequacy of information submitted in a registration dossier in order to determine whether that information satisfies the information requirements set out in the REACH Regulation.[7]

34. Under Column 1 of Section 8.7.3. of Annex IX, information on an EOGRTS is a standard information requirement if the available repeated dose toxicity studies (for example 28-day or 90-day studies, OECD TG 421 or OECD TG 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation to reproductive toxicity. The Parties agree that in the present case the available information on the Substance triggers the requirement to carry out an EOGRTS under Column 1 of Section 8.7.3. of Annex IX.[8]

35. Column 1 of Section 8.7.3. of Annex IX makes no reference to studies aimed at investigating the effects of a substance on the gut microbiome. That provision only mentions repeated dose toxicity studies (for example 28-day or 90-day studies, OECD TG 421 or OECD TG 422 screening studies) as the source of information on concerns which may justify the need to carry out an EOGRTS.[9] It is clear from that provision that the investigation of the effects of the Substance on the gut microbiome is not a standard information requirement for registration purposes.

36. Furthermore, as confirmed by the Appellants at the hearing, the investigation of the effects of the Substance on the gut microbiome is not a preliminary dose-range finding study aimed at determining the appropriate dose for the main study. That investigation is rather a specific study for the Substance seeking to establish the concentration at which the gut microbiome activity is inhibited.

37. The Agency was therefore entitled to require the Appellants to submit information on an EOGRTS without extending the time limit set in the Contested Decision to allow for the investigation of the effects of the Substance on the gut microbiome. The Agency was not obliged to wait for the Appellants to generate information not falling within the scope of the information requirements set out in the testing Annexes.[10]

38. The Appellants' first line of argument must therefore be rejected.

(b) The investigation of the effects of the Substance on the gut microbiome is not scientifically necessary for an adequate hazard assessment

39. According to the sixth introductory paragraph to Annex IX, the choices made in relation to the study design of the EOGRTS must ensure that the data generated through that study are adequate for hazard identification and risk assessment. The same objective is set out in Recital 7 of Commission Regulation (EU) 2015/282[11] and paragraph 22 of OECD TG 443.

40. The Appellants argue that the effects observed in the available studies on the

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[7] See decision of the Board of Appeal of 11 December 2018, *Climax Molybdenum*, A-006-2017, paragraph 40.

[8] See paragraph 19 above.

[9] See Recital 10 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).

[10] See, to that effect and by analogy, decision of the Board of Appeal of 22 March 2022, *Campine Belgium*, A-003-2020, paragraphs 115 and 116.

[11] See reference to the Regulation in footnote 9 above.

Substance[12] are secondary to the imbalanced nutrition of the parental test animals which in turn was caused by the antimicrobial activity that the Substance may have exerted on their gut microbiome. According to the Appellants, the data resulting from the investigation of the effects of the Substance on the gut microbiome are necessary to adequately design the EOGRTS (with respect to dose regime and mode of administration)[13] so that the results of that study will enable an adequate hazard assessment. That argument must be rejected for the following reasons.

41. First, during the present appeal proceedings the Appellants provided scientific articles related to antibiotics used in human drugs, to aspects of microbiome disruption, to the herbicide metribuzin, to the fungicide isoflucypram, and a feed-deprivation study. However, that literature has no bearing on the present case since it does not relate to the Substance and does not investigate the gut microbiome. The Appellants therefore failed to establish that there could be a direct causation between effects observed in the available studies and the antimicrobial activity of the Substance.

42. Second, even assuming that the investigation of the effects of the Substance on the gut microbiome could be useful – as acknowledged also by the Agency at the hearing – to demonstrate a specific maternally-mediated mechanism, it cannot nevertheless exclude on its own that other factors might have caused the effects observed in the available studies. In their Notice of Appeal, the Appellants themselves state explicitly that a palatability screening study is part of their testing strategy. In particular, it will reduce the uncertainties of the potential palatability effects of the Substance, should the Appellants opt for the administration of the Substance through the diet.

43. Third, lowering the doses to a level where no antimicrobial effects are detected runs the risk of not achieving sufficient exposure to the Substance for the parental animals and the developing embryo and foetuses and therefore of overlooking potential effects on sexual function and fertility.

44. Fourth, it is clear from Article 13(3) read in conjunction with Column 1 of Section 8.7.3. of Annex IX that the method to be followed to carry out the EOGRTS is set out in OECD TG 443, to which the Contested Decision refers.[14] OECD TG 443 recognises both oral administration by gavage and through the diet as ways to administer the substance to be tested.[15] By not imposing any specific mode of administration, the Contested Decision gives the Appellants the discretion to decide whether to carry out the EOGRTS via oral administration through the diet.

45. In addition, the Agency correctly based its conclusions on the information contained in the Appellants' registration at the time of the adoption of the Contested Decision. The Agency also correctly found in the Contested Decision that the Appellants' argument '*relies on data which is yet to be generated, therefore no conclusion on the robustness of your [the Appellants'] argument regarding the secondary nature of the findings can currently be made*'. It was therefore not possible for the Agency to assess or take into account information that is not available to it.

46. If the Appellants are convinced of the necessity to investigate the effects of the

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[12] See paragraph 9 above.

[13] See paragraph 21 above.

[14] See pages 17 to 19 of the Contested Decision.

[15] Decision of the Board of Appeal of 21 June 2023, *Symrise AG*, A-004-2022, paragraphs 57 and 72.

Substance on the gut microbiome for the study design of the EOGRTS, it remains their sole responsibility to generate, gather and submit to the Agency the information that they consider that will fulfil the information requirements of the REACH Regulation. As stated above, the Agency correctly limited its examination to the information submitted by the Appellants in their registration, in accordance with the relevant provisions of the REACH Regulation (Articles 10(a)(vii) and 14(1), and Annex I).[16]

47. In any event, under Article 42(1), the Agency is required to examine any information submitted in consequence of the Contested Decision. The Appellants may therefore present, by the deadline set in the Contested Decision, an updated registration with information on both the requested EOGRTS and the effects of the Substance on the gut microbiome, if they so wish.

(c) Conclusion on the first plea

48. It follows from the reasons set out in paragraphs 33 to 47 above that the first plea must be rejected.

5.2. Second plea: Error of assessment, failure to take relevant information into account, exceeding competence, breaches of Articles 13(3) and 25, and breaches of the principles of legal certainty and the protection of legitimate expectations by requesting information on an EOGRTS with the EOGRTS Testing Conditions

5.2.1. The contested parts of the Contested Decision as regards the dose level setting of the EOGRTS

49. The second plea consists of the following seven parts: (i) error of assessment, (ii) failure to take relevant information into account, (iii) exceeding competence, (iv) breach of Article 13(3), (v) breach of Article 25, (vi) breach of principle of legal certainty, and (vii) breach of the principle of protection of legitimate expectations.

50. The Appellants argue that the Agency committed several errors in setting out, in the Contested Decision, requirements for the dose level setting of the EOGRTS. Specifically, the Appellants argue that the Agency erred in requiring the highest dose level to be determined based on clear evidence of an adverse effect on sexual function and fertility (see paragraph 8 above). The Appellants also argue that the Agency erred in requiring the doses to be '*sufficiently high*' (paragraph 109 of the Contested Decision) and the highest dose to be '*as high as possible*' (paragraph 110 of the Contested Decision).

51. In order to decide on the second plea, the Board of Appeal will firstly examine the third part, secondly the first, second, and fourth parts together, thirdly the fifth part, and, finally, the sixth and seventh parts together.

5.2.2. Third part of the second plea: Exceeding competence

Arguments of the Parties

52. By the third part of the second plea, the Appellants argue that the Agency exceeded its competences by requesting information on an EOGRTS with the EOGRTS Testing Conditions referred to in paragraph 8 above.

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[16] See, to that effect, decision of the Board of Appeal of 29 June 2021, *SNF SA*, A-001-2020, paragraph 47.

53. The Agency disputes the Appellants' argument.

Findings of the Board of Appeal

54. The Appellants do not support by any justification or evidence their claim that the Agency exceeded its competences in requesting the EOGRTS with the Testing Conditions specified in the Contested Decision. This part of the second plea is therefore unsubstantiated and must be rejected.

5.2.3. First, second, and fourth parts of the second plea: Error of assessment, failure to take relevant information into account, and breach of Article 13(3)

Arguments of the Parties

55. By the first, second, and fourth parts of the second plea, the Appellants argue that, by requesting information on an EOGRTS with the EOGRTS Testing Conditions, the Agency committed an error of assessment, failed to take relevant information into account, and breached Article 13(3). According to the Appellants, the specifications on the dose level setting of the EOGRTS – as they are established in the parts of the Contested Decision referred to in paragraph 50 above – are in breach of, and go beyond the scope of, OECD TG 443.

56. Specifically, the Appellants argue that, by requiring the highest dose level to be determined based on clear evidence of an adverse effect on sexual function and fertility, the Agency breached OECD TG 443. According to the Appellants, OECD TG 443 merely requires the highest dose to be chosen with the aim to induce some systemic toxicity[17] and not, as stated in the Contested Decision, specific toxicity (i.e. developmental or reproductive toxicity).

57. The Appellants also argue that, based on the results of the available PNDT study, conducting an EOGRTS with the EOGRTS Testing Conditions and without the prior investigation of the effects of the Substance on the gut microbiome runs the risk that the differentiation between effects related to systemic toxicity and those related to specific toxicity (i.e. developmental or reproductive toxicity) would no longer be possible.

58. The Agency disputes the Appellants' arguments.

Findings of the Board of Appeal

59. The Contested Decision requires the Appellants to provide information on an EOGRTS in accordance with OECD TG 443. The operative part of the Contested Decision states that the legal basis for this request is Article 41 in conjunction with Column 1 of Section 8.7.3. of Annex IX. The latter provision explicitly refers to the OECD TG 443.

60. At the outset, the relevant part of the Contested Decision laying down the requirements for the dose level setting for the EOGRTS is section 6.3.3. ('Dose-level setting') of that Decision[18] and not the paragraphs of the Contested Decision mentioned by the Appellants.[19] Specifically, section 6.3.3. ('Dose-level setting') of the Contested Decision states:

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[17] Paragraph 21 of OECD TG 443.

[18] See page 18 of the Contested Decision.

[19] See paragraph 50 above.

'*122. The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, para. 22; OECD GD 151, para. 28; Annex I Section 1.0.1. of REACH and Recital 7, Regulation 2015/282) […]*'

123. To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Section 3.7.2.4.4 of Annex I to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, para. 18) in the P0 animals.

124. In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.'

61. For the following reasons, contrary to the Appellants' arguments, the Agency committed no error in requiring in the Contested Decision that the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility.

62. First, paragraph 21 of OECD TG 443 states that '*the highest dose should be chosen with the aim to induce some systemic toxicity, but not death or severe suffering of the animals*'. The expression '*some systemic toxicity*' must be read in light of Article 10 in conjunction with Column 1 of Section 8.7., according to which registrants at Annex IX level are required to submit, in their registration, information on the reproductive toxicity properties of the substance they intend to register. That information is to be generated by conducting the studies indicated in Column 1 of Sections 8.7.2. and 8.7.3. of Annex IX. Article 13(3) read in conjunction with Column 1 of Section 8.7.3. of Annex IX provides that the method to be followed on how to conduct the EOGRTS is set out in the OECD TG 443.[20]

63. Paragraph 21 of OECD TG 443 must be read also in conjunction with paragraph 22 of that test guideline. Paragraph 22 of OECD TG 443 provides: '*In the dose selection the investigator should also consider and ensure that data generated is adequate to fulfil the regulatory requirements across OECD countries as appropriate (e.g., hazard and risk assessment, classification and labelling, ED assessment, etc.)*'. One of the purposes of data generation is therefore to ensure that the data is adequate for hazard assessment and fulfils the requirements set out in the CLP Regulation.

64. Section 3.7.1.1. of Annex I to the CLP Regulation provides that '*Reproductive toxicity means adverse effects on sexual function and fertility*'. It is also apparent from Section 3.7.2.1.1. of Annex I to the CLP Regulation that, for the purpose of classification as a reproductive toxicant, data from animal studies must provide '*clear evidence of an adverse effect on sexual function and fertility*'.

65. Recital 7 of Commission Regulation (EU) 2015/282 provides that an EOGRTS under Column 1 of Section 8.7.3. of Annex IX should allow an '*assessment of possible effects on fertility. The […] dose selection should be appropriate to meet risk assessment and classification and labelling purposes as required by [the REACH Regulation] and [the CLP Regulation]*'.

[20] See paragraph 44 above.

66. The sixth introductory paragraph to Annex IX provides that '*Where a test method offers flexibility in the study design, for example in relation to the choice of dose levels, the chosen study design shall ensure that the data generated are adequate for hazard identification and risk assessment. To this end, testing shall be performed at appropriately high dose levels […]*'.

67. It follows from paragraphs 62 to 66 above that under paragraph 21 of OECD TG 443 the doses inducing '*some systemic toxicity*' have to be set at appropriately high levels so as to ensure adequate identification of a potential hazard of the concerned substance in relation to its effects on sexual function and fertility.

68. Therefore, the Agency did not breach Article 13(3) or the relevant provisions of OECD TG 443 in requiring in the Contested Decision that the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility.

69. Second, in laying down the requirements for the dose level setting for the EOGRTS, the Agency took into account the relevant information on sexual function and fertility resulting from the available studies on the Substance.[21] The Agency committed no errors in that regard.

70. It follows from the reasons set out in paragraphs 62 to 69 above that the Agency did not commit an error of assessment, did not fail to take relevant information into account, and did not breach Article 13(3). The first, second, and fourth parts of the second plea must therefore be rejected.

5.2.4. Fifth part of the second plea: Breach of Article 25

Arguments of the Parties

71. By the fifth part of the second plea, the Appellants argue that by requesting information on an EOGRTS with the EOGRTS Testing Conditions the Agency breached Article 25. According to the Appellants, the administration of the highest dose will likely cause animal suffering and lead to massive systemic toxicity. In addition, the Appellants argue that the imposition of legally uncertain and undefined dose levels increases the risk of the study having to be duplicated.

72. The Agency disputes the Appellants' arguments.

Findings of the Board of Appeal

73. According to Article 25, the aim of Title III of the REACH Regulation is to ensure that testing on vertebrate animals for the purposes of that Regulation is undertaken only as a last resort and to avoid the duplication of such testing.

74. In the present case, the Agency concluded that the Appellants' registration dossier has a data-gap under Column 1 of Section 8.7.3. of Annex IX. As confirmed by the Appellants at the hearing, that finding is not disputed by the Appellants.

75. The consequences of the existence of a data-gap flow directly from the REACH Regulation. Under Article 10(a)(vi), read in conjunction with Section 8.7. of Annex IX and Annex XI, the Appellants are obliged to submit either information on an OECD TG 443 study or, alternatively, an acceptable adaptation in accordance with the specific adaptation rules in Column 2 of Section 8.7.3. of Annex IX or the general adaptation rules in Annex XI. In the present case, the Appellants did not provide an acceptable adaptation based on Column 2 of Section 8.7.3. of Annex IX, or an adaptation under the general rules for adaptation set out in Annex XI.

[21] See paragraph 9 above.

76. Therefore, the Agency was neither required nor empowered to consider whether it is consistent with Article 25 for the Appellants to be required to submit this information[22].

77. It follows from the reasons set out in paragraphs 73 to 76 above that the Agency did not breach Article 25. The fifth part of the second plea must therefore be rejected.

5.2.5. Sixth and seventh parts of the second plea: Breach of the principles of legal certainty and the protection of legitimate expectations

Arguments of the Parties

78. The Appellants argue that the Agency breached the principle of legal certainty by using vague and entirely undefined terms in the Contested Decision. Specifically, the Appellants refer to wording such as '*sufficient severity of toxicity*', '*[…] highest dose should be as high as possible […]*', and '*highest possible dose*' which, according to the Appellants, do not enable them to ascertain unequivocally what their rights and obligations are.

79. The Appellants further argue that they had a legitimate expectation, based on the Agency's guidance document *'Advice on dose-level selection for the conduct of reproductive toxicity studies (OECD TGs 414, 421/422 and 443) under REACH'*[23] that they would not be required to provide information on an EOGRTS with the EOGRTS Testing Conditions.

80. According to the Appellants, the Contested Decision deviates from that guidance document which sets out that the selection of the highest dose should (i) *'aim to induce some systemic toxicity but no death or severe suffering'*, and (ii) *'take regulatory requirements in the EU into account (see, for example paragraph 22 of OECD TG 443), i.e. its applicability for being able to achieve conclusive decisions on classification and labelling'*.

81. The Agency disputes the Appellants' arguments.

Findings of the Board of Appeal

82. The principle of legal certainty requires that every act of the administration which produces legal effects should be clear and precise so that the person concerned is able to know without ambiguity what his rights and obligations are and to take steps accordingly. As part of the principle of legal certainty, registrants must be able to rely on the most recent instruction issued by the Agency being up-to-date and correct.[24]

83. The right to rely on the principle of the protection of legitimate expectations presupposes that precise, unconditional and consistent assurances originating from authorised, reliable sources have been given to the person concerned by the

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[22] See, to that effect and by analogy, judgment of 28 June 2023, *Polynt* v *ECHA*, T-207/21, EU:T:2023:361, paragraph 110. See also decision of the Board of Appeal of 4 May 2020, *Clariant Plastics & Coatings*, A-011-2018, paragraphs 94 to 96.

[23] European Chemicals Agency, *Advice on dose-level selection for the conduct of reproductive toxicity studies (OECD TGs 414, 421/422 and 443) under REACH*, January 2022, available at https://www.echa.europa.eu/documents/10162/17220/211221_echa_advice_dose_repro_en.pdf/27159fb1-c31c-78a2-bdef-8f423f2b6568?t=1640082455275 (last accessed on 25.08.2023).

[24] See decision of the Board of Appeal of 9 April 2019, *BrüggemannChemical, L. Brüggemann*, A-001-2018, paragraphs 44 and 50.

competent authorities of the European Union. That right applies to any individual in a situation in which a European Union institution, body or agency, by giving that person precise assurances, has led that individual to entertain well-founded expectations. Precise, unconditional and consistent information, in whatever form it is given, constitutes such an assurance.[25]

84. The arguments of the Appellants as regards the Agency's breach of those two principles must be rejected for the following reasons.

85. First, in the present case, the Contested Decision requires the Appellants to submit information on an EOGRTS under Column 1 of Section 8.7.3. of Annex IX. Section 6.3.3. ('Dose-level setting') of the Contested Decision[26] lays down the requirements for the dose level setting for the EOGRTS by merely replicating, as set out in paragraphs 60 to 68 above, the wording of the provisions and test guidelines applicable to this information requirement.

86. Further, the requirements for the dose level setting for the EOGRTS are clearly explained in paragraphs 122 to 127 of the Contested Decision[27] in such a way that the Appellants are able to carry out the requested EOGRTS. The Appellants are able to know, without ambiguity, what their obligations are and to take steps accordingly.

87. Second, the Agency's guidance referred to by the Appellants makes reference to paragraphs 21 and 22 of OECD TG 443. As explained in paragraphs 64 to 67 above, those paragraphs of OECD TG 443 must be read in conjunction with the sixth introductory paragraph to Annex IX, Recital 7 of Commission Regulation (EU) 2015/282, and the other relevant provisions of the CLP Regulation. There is therefore no inconsistency between the Agency's guidance and the EOGRTS Testing Conditions specified in the Contested Decision.

88. It follows from the reasons set out in paragraphs 85 to 87 above that by requesting information on an EOGRTS with the EOGRTS Testing Conditions the Agency did not breach the principles of legal certainty and protection of legitimate expectations. The sixth and seventh parts of the second plea must therefore be rejected.

5.2.6. Conclusion on the second plea

89. It follows from the reasons set out in paragraphs 52 to 88 above that in requesting information on an EOGRTS with the EOGRTS Testing Conditions the Agency did not commit an error of assessment, did not fail to take relevant information into account, did not exceed its competence, did not breach Articles 13(3) and 25, and did not breach the principles of legal certainty and the protection of legitimate expectations. The second plea must therefore be rejected.

6. Result

90. As all the Appellants' pleas have been rejected, the appeal must be dismissed.

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[25] See judgment of 13 June 2013, *HGA and Others* v *Commission*, C-630/11 P to C-633/11 P, EU:C:2013:387, paragraph 132; see also decision of the Board of Appeal of 30 January 2018, *Cheminova*, A-005-2016, paragraph 179.

[26] See paragraph 60 above.

[27] See pages 18 and 19 of the Contested Decision.

7. Effects of the Contested Decision

91. The Contested Decision, upheld in the present appeal proceedings, required the Appellants to submit information on the EORGTS by 19 July 2024, which is 2 years, 3 months and 6 days from the date of that decision.

92. Under Article 91(2), an appeal has suspensive effect. The deadline 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.

93. The Appellants must consequently provide the information on the EOGRTS by 5 December 2025.

8. Refund of the appeal fee

94. Under Article 10(4) of the Fee Regulation[28], 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.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Dismisses the appeal.**
2. **Decides that information on an EOGRTS must be provided by 5 December 2025.**
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

[28] 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).