EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

9 February 2021

(Testing proposal – Extended one-generation reproductive toxicity study – Error of assessment – Third-party consultation – Animal welfare – Proportionality)

Case number	A-015-2019
Language of the case	English
Appellant	Polynt S.p.A., Italy
Representatives	Claudio Mereu and Sandra Sáez Moreno Fieldfisher (Belgium) LLP, Belgium
Contested Decision	TPE-D-2114483466-38-01/F of 4 September 2019 adopted by the European Chemicals Agency (the 'Agency') pursuant to Article 40 of 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; the 'REACH Regulation')

THE BOARD OF APPEAL

composed of Antoine Buchet (Chairman and Rapporteur), Andrew Fasey (Technically Qualified Member) and Ángel M. Moreno (Legally Qualified Member)

Registrar: Alen Močilnikar

gives the following

Decision

Background to the dispute

1. The Appellant is a registrant of the substance hexahydro-4-methylphthalic anhydride (EC number 243-072-0, CAS number 19438-60-9; the 'Substance'). The Appellant registered the Substance at the 1 000 tonnes or more per year tonnage band.

2. The Appellant's registration dossier included a testing proposal for an '*extended one-generation reproductive toxicity [study] – basic test design (Cohorts 1A and 1B without extension)'*. According to the Appellant's testing proposal, the need for the extension of Cohort 1B, inclusion of Cohort 2A and 2B and/or Cohort 3, would be '*determined from the findings of studies on similar cyclic anhydrides'* and the results of a repeated dose 90-day oral toxicity study in rats (OECD test guideline ('TG') 408; the 'sub-chronic toxicity study') to be conducted by the Appellant. The sub-chronic toxicity study had been requested by the Agency in a compliance check decision on the Substance of 28 November 2014 addressed to the Appellant (CCH-D-2114289309-36-01/F).

3. On 19 October 2016, the Board of Appeal dismissed an appeal by the Appellant against the compliance check decision referred to in the previous paragraph and required the Appellant to submit information on the sub-chronic toxicity study by 28 October 2018 (see Case A-004-2015, *Polynt*, Decision of the Board of Appeal of 19 October 2016). Following the Board of Appeal's Decision, the Appellant updated its registration dossier with the results of the sub-chronic toxicity study.

4. Between 28 February and 16 April 2018, the Agency conducted a public consultation on the testing proposal for the extended one-generation reproductive toxicity study (the 'EOGRTS'), pursuant to Article 40(2) of the REACH Regulation (all references to Recitals, Articles and Annexes hereinafter concern the REACH Regulation unless stated otherwise). The Agency received the following response from a third party:

   '*The substance is a known respiratory sensitiser and has a harmonised classification under CLP for respiratory sensitisation. Respiratory sensitisers are potentially considered to constitute equivalent level of concern to CMRs under Article 57(f) […] due to their potential to cause serious irreversible health effects. [The Agency] further consider[s] that it is not possible to derive a safe concentration for respiratory sensitisers as it is difficult to establish the thresholds for the induction and elicitation of sensitisation. Consequently, occupational exposure to respiratory sensitisers is minimised through the use of [risk management measures] including engineering controls and personal protective equipment. Furthermore, according to read-across data presented in the Registration Dossier, other acid anhydrides have been investigated for reproductive toxicity and are shown not to raise any concerns. Given the very low potential for exposure based on the toxicological properties of the substance and its uses, testing for reproductive toxicity in an EOGRTS as proposed would appear to be neither scientifically justified or in the interests of animal welfare. The outcome of any study would not provide any useful information of relevance to the human risk assessment.*'

5. On 5 December 2018, the Agency notified the draft decision to the Appellant for its comments. According to the draft decision:

   '*Your testing proposal is modified and you are requested to carry out:*

   Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the [Substance] specified as follows:

   - *Ten weeks premating exposure duration for the parental (P0) generation;*
   - *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; and*
   - *Cohort 3 (Developmental immunotoxicity)*.'

6. On 25 January 2019, the Appellant submitted comments on the draft decision.

7. On 27 February 2019, the Appellant updated its dossier with the full report of the sub-chronic toxicity study and the historical control data for that study.

8. On 4 September 2019, 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).

9. According to the Contested Decision:

'*Your testing proposal is modified and you are requested to carry out:*

Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the [Substance] specified as follows:

- *Ten weeks premating exposure duration for the parental (P0) generation;*
- *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; and*
- *Cohort 3 (Developmental immunotoxicity)*.

You have to submit the requested information in an updated registration dossier by 13 September 2021. You also have to update the chemical safety report, where relevant.'

Procedure before the Board of Appeal

10. On 4 December 2019, the Appellant lodged this appeal.

11. On 10 February 2020, the Agency lodged its Defence.

12. On 11 March 2020, Cruelty Free Europe ('CFE') was granted leave to intervene in support of the Appellant.

13. On 21 May 2020, CFE informed the Board of Appeal that it no longer wished to intervene in the case.

14. On 9 June 2020, the Appellant lodged its observations on the Defence.

15. On 31 August 2020, the Agency lodged its observations on the Appellant's observations on the Defence.

16. On 31 August 2020, Ángel M. Moreno, alternate member of the Board of Appeal, was designated to act as a legally qualified member of the Board of Appeal in this case, in accordance with the second subparagraph of Article 3(2) of 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; the 'Rules of Procedure').

17. On 4 November 2020, a hearing took place at the Appellant's request. The hearing was held by video-conference in accordance with Article 13(7) of the Rules of Procedure. At the hearing, the Parties made oral submissions and answered questions from the Board of Appeal.

Form of order sought

18. The Appellant requests the Board of Appeal to annul the Contested Decision. In the alternative, the Appellant requests the partial annulment of the Contested Decision insofar as it requires the EOGRTS to include Cohort 3 (developmental immunotoxicity).

19. The Appellant also requests the Board of Appeal to order the Agency to pay the costs of the appeal proceedings.

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

Reasons

21. The Appellant raises the following pleas in law:

    1. The Agency made an error of assessment and breached Section 8.7. of Annex X by requiring the Appellant to carry out an EOGRTS (first plea);

    2. The Agency made an error of assessment in requiring the inclusion of Cohort 3 in the requested EOGRTS (second plea);

    3. The Agency breached Article 40(2) regarding the public consultation on the Appellant's testing proposal (third plea); and

    4. The Agency breached Article 13 of the Treaty on the Functioning of the European Union ('TFEU'), Article 25 of the REACH Regulation, and '*the principle of proportionality/animal welfare/sound administration*' (fourth group of pleas).

1. The Agency made an error of assessment and breached Section 8.7. of Annex X by requiring the Appellant to carry out an EOGRTS

Relevant legislation

22. Column 1 ('*standard information required'*) of Section 8.7.3. of Annex X provides:

    '*[EOGRTS] (B.56 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 443), basic test design (cohorts 1A and 1B without extension to include a F2 generation), one species, most appropriate route of administration, having regard to the likely route of human exposure, unless already provided as part of Annex IX requirements.*'

23. Column 2 ('*specific rules for adaptation from Column 1*') of Section 8.7. of Annex X concerning reproductive toxicity provides:

    '*The [reproductive toxicity] studies need not be conducted if:*

    - *the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or*
    - *the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or*
    - *the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.*

    If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for developmental toxicity must be considered.

    If a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.'

24. Article 57(f) provides:

    '*The following substances may be included in Annex XIV in accordance with the procedure laid down in Article 58:*
    […]

(f) substances — such as those having endocrine disrupting properties or those having persistent, bioaccumulative and toxic properties or very persistent and very bioaccumulative properties, which do not fulfil the criteria of points (d) or (e) — for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59.'

Arguments of the Parties

25. First, the Appellant argues that, based on the first indent of Column 2 of Section 8.7. of Annex X, it is not necessary for the Appellant to conduct an EOGRTS for registration purposes. This is because the Substance is '*of equivalent concern to carcinogen, mutagen and reproductive toxic substances ("CMR substances")*'.

26. The Appellant argues that the Substance is classified as a skin sensitiser Category 1 and has been identified as a substance of very high concern ('SVHC') under Article 57(f). The Appellant argues that, according to the European Court of Justice, the identification of a substance under Article 57(f) presupposes that two cumulative criteria are met. Those two criteria are (i) that it is probable that the substance concerned has serious effects on human health or the environment, and (ii) that those effects '*give rise to an equivalent level of concern'* to those of other substances listed in Article 57(a) to (e) (judgment of 15 March 2017, *Polynt* v *ECHA*, C-323/15 P, EU:C:2017:207, paragraph 24 and judgment of 15 March 2017, C-324/15 P, *Hitachi Chemical Europe and Polynt* v *ECHA*, EU:C:2017:208, paragraph 40).

27. The Appellant argues that the SVHC assessment for the Substance carried out by the Agency concluded that the Substance is of equivalent concern to CMR substances.

28. The Appellant argues that substances which are of equivalent concern to CMR substances '*are elevated to the rank of CMR substances*'. Therefore, according to the Appellant, the specific rules in Column 2 of Section 8.7. of Annex X exempting registrants from conducting studies should also apply, provided that appropriate risk management measures are in place.

29. The Appellant argues that appropriate risk management measures are in place for the Substance to ensure worker protection as the Substance is a respiratory sensitiser which is considered to give rise to an equivalent level of concern to CMR substances.

30. Second, the Appellant states that, based on the third indent of Column 2 of Section 8.7. of Annex X, a registrant is not required to conduct an EOGRTS if the substance is of low toxicological activity, it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure, and there is no or no significant human exposure. The Appellant argues that, in view of this specific adaptation, the Agency made an error of assessment and breached Section 8.7. of Annex X by requiring the Appellant to carry out an EOGRTS.

31. The Agency disputes the Appellant's arguments.

Findings of the Board of Appeal

32. Under Article 10(a)(ix), registration dossiers must include a technical dossier containing '*proposals for testing where listed in Annexes IX and X*'.

33. The Appellant registered the Substance at the 1 000 tonnes or more per year tonnage band. Therefore, in accordance with Section 8.7.3. of Annex X, an EOGRTS is a standard information requirement for the Appellant's registration of the Substance.

34. The specific rules for adaptation contained in Column 2 of Section 8.7. of Annex X (see paragraph 23 above) provide that studies on reproductive toxicity, including the EOGRTS required by Section 8.7.3. of Annex X, need not be conducted if certain conditions are met.

35. The Appellant argues that the Agency made an error of assessment in requiring the EOGRTS. This is because, under the specific rules for adaptation contained in the first and third indents of Column 2 of Section 8.7. of Annex X, the EOGRTS is not necessary.

36. In assessing the Appellant's plea that the Agency made an error of assessment, it is necessary to examine whether the arguments put forward by the Appellant are capable of demonstrating that the Agency made an error in requesting the Appellant to carry out the EOGRTS (see, by analogy, judgment of 20 September 2019, *BASF Grenzach* v *ECHA*, T-125/17, EU:T:2019:638, paragraph 89). It is necessary to examine whether the Agency has examined carefully and impartially all the relevant facts of the individual case, and whether those facts support the conclusions that the Agency drew from them (see, by analogy, judgment of 19 January 2012, *Xeda International and Pace International* v *Commission*, T-71/10, EU:T:2012:18, paragraph 71; see also Case A-006-2017, *Climax Molybdenum*, Decision of the Board of Appeal of 11 December 2018, paragraph 38).

1.1. First indent of Column 2 of Section 8.7. of Annex X

37. According to the first indent of Column 2 of Section 8.7. of Annex X, an EOGRTS would not need to be conducted if, first, the Substance is known to be a genotoxic carcinogen and, second, appropriate risk management measures are implemented.

38. By Decision of 18 December 2012 (ED/169/2012), the Agency decided that, due to its respiratory sensitising properties, the Substance raises an '*equivalent level of concern*' to a substance with CMR properties. The Agency therefore identified the Substance as an SVHC in accordance with Articles 57(f) and 59.

39. The first indent of Column 2 of Section 8.7. of Annex X refers to substances which are known to be genotoxic carcinogens. That provision does not refer to substances of '*equivalent level of concern*' to a substance with CMR properties.

40. The purpose of registration is to obtain information on every registered substance. Column 1 of each of Annexes VII to X contains a list of the standard information needed for registration purposes. Column 2 to each of those Annexes contains a series of specific adaptation rules that apply to the standard information requirements. Some of those specific adaptation rules allow for the standard information required in the Column 1 to be omitted if the conditions set out in Column 2 are fulfilled. As they constitute an exception from the legal obligation to provide standard information, the specific adaptation rules in Column 2 must be interpreted restrictively as regards the conditions under which the standard information referred to in Column 1 could be omitted (see, to this effect and by analogy, judgment of 10 November 2016, *Baštová*, C-432/15, EU:C:2016:855, paragraph 59, and judgment of 27 September 2017, *Puškár*, C-73/16, EU:C:2017:725, paragraph 38; see also Case A-006-2016, *SI Group UK and Others*, Decision of the Board of Appeal of 6 June 2018, paragraph 64).

41. Column 2 of Section 8.7. of Annex X (see paragraph 23 above) contains a closed list of conditions which, if fulfilled, relieve registrants of the obligation to conduct studies on reproductive toxicity (see Case A-004-2015, *Polynt*, cited in paragraph 3 above, paragraph 87 of the Decision).

42. Column 2 of Section 8.7. of Annex X does not make provision for omitting studies on reproductive toxicity on the basis that a substance has been identified as an SVHC due to its respiratory sensitising properties. Indeed, the fact that the Substance has respiratory sensitising properties gives no indication as to its reproductive toxicity and therefore cannot justify the omission of a requirement to provide standard information on the Substance's potential to cause reproductive toxicity (see Case A-004-2015, *Polynt*, cited in paragraph 3 above, paragraphs 88 and 89 of the Decision).

43. As a consequence, the requirement to perform the EOGRTS in the present case cannot be omitted under the first indent of Column 2 of Section 8.7. of Annex X simply on the basis that the Substance is a respiratory sensitiser.

44. The conclusion in the previous paragraph is not called into question by the Appellant's argument that the Substance has already been identified as a SVHC and stringent risk management measures are in place to protect users from the sensitisation hazard (see *Polynt*, cited in paragraph 3 above, paragraphs 91 to 95 of the Decision).

45. In accordance with Recital 19, the objective of the registration provisions under the REACH Regulation is to '*require manufacturers and importers to generate data on the substances they manufacture or import, to use these data to assess the risks related to these substances and to develop and recommend appropriate risk management measures*'. It is clear from Column 2 of Section 8.7. of Annex X, read in light of Recital 19, that the fact that stringent risk management measures are in place to protect users from the sensitisation hazard does not affect the Appellant's obligation to provide information on other endpoints, assess all the risks related to the Substance, and develop appropriate risk management measures with regard to all those risks, and not only to respiratory sensitisation.

46. In the absence of standard information on all endpoints there is uncertainty as to whether the respiratory sensitisation potential of the Substance poses the greatest risk. Data derived from an EOGRTS may, in principle, lead to or affect authorisation and restriction decisions regarding the Substance or may lead to different risk management measures being required.

47. The fact that the Substance is identified as a SVHC due to its respiratory sensitising properties therefore does not relieve the Appellant of the obligation to provide standard information for the various other endpoints required by the REACH Regulation, including for reproductive toxicity.

48. The European Court of Justice has confirmed that a substance has different properties which may give rise to risks of a different nature and that it is possible that the intrinsic properties of a substance may come under several of the grounds set out in Article 57(a) to (f). The Agency is therefore empowered to supplement existing entries in the candidate list of substances with new grounds within the meaning of Article 57 (see, judgment of 23 January 2019, *Deza a.s.* v *ECHA*, C-419/17 P, EU:C:2019:52, paragraphs 34 to 39).

49. During the present appeal proceedings, the Appellant argued that the Board of Appeal's Decision in Case A-004-2015, *Polynt,* cited in paragraph 3 above, must be distinguished from the present case. This is because the Decision in Case A-004-2015, *Polynt,* was adopted before the judgment of the Court of Justice in C-324/15 P, *Hitachi Chemical Europe and Polynt* v *ECHA* and the present case concerns a testing proposal decision rather than a compliance check decision. For the following reasons, those arguments must be rejected.

50. First, the Court of Justice's judgment in C-324/15 P, *Hitachi Chemical Europe and Polynt* v *ECHA* concerned the legality of the Agency's decision of 18 December 2012 (ED/169/2012) to include the Substance on the candidate list because of its respiratory sensitising properties. That judgment did not concern the interpretation of the specific adaptation rules listed in Column 2, Section 8.7. of Annex X.

51. Second, Column 2 of Section 8.7. of Annex X sets out specific rules for adaptation from the standard information required for registration purposes. The compliance check procedure under Article 41 and the testing proposal procedure under Article 40 are both dossier evaluation procedures. Both procedures aim to ensure that the registration dossier for the substance at issue contains the standard information set out in the REACH Regulation or an acceptable adaptation. The specific adaptation rules in Column 2 of Section 8.7. of Annex X apply equally to the compliance check procedure and to the testing proposal procedure. Furthermore, the scope and content of those specific adaptation rules do not vary depending on whether they are applied in a testing proposal procedure or a compliance check procedure. In addition, adaptations may, depending on their content, be examined under both Article 40(3) and Article 41(1)(b) (see Case A-005-2016, *Cheminova*, Decision of the Board of Appeal of 30 January 2018, paragraph 53).

52. The first indent of Column 2 of Section 8.7. of Annex X does not allow for an EOGRTS to be omitted on the ground that a substance is of an '*equivalent level of concern*' to substances '*known to be a genotoxic carcinogen*'. In the present case, it is therefore irrelevant for the purposes of omitting the EOGRTS under Column 2 of Section 8.7. of Annex X whether

'*appropriate risk management measures are implemented*' regarding the respiratory sensitising properties of the Substance.

53. In view of paragraphs 37 to 52 above, the Appellant's argument that, based on the first indent of Column 2 of Section 8.7. of Annex X, the EOGRTS can be omitted because the Substance is '*of equivalent concern to CMR substances*' must be rejected.

1.2. Third indent of Column 2 of Section 8.7. of Annex X

54. In order to rely successfully on the specific adaptation rule set out in the third indent of Column 2 of Section 8.7. of Annex X, cited in paragraph 23 above, a registrant must demonstrate the following:

    (i) The substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available);

    (ii) It can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and

    (iii) There is no, or no significant, human exposure.

55. The Appellant refers to the wording of the third indent of Column 2 of Section 8.7. of Annex X in its Notice of Appeal. However, although the Appellant presents some arguments regarding the level of human exposure to the Substance, it does not attempt to justify why the Agency made an error of assessment in requesting the EOGRTS in view of the remaining conditions of that adaptation. Although the Appellant refers in its Notice of Appeal to the comment of the third-party regarding low toxicological activity (see paragraph 4 above), it did not attempt to demonstrate that there is '*no evidence of toxicity seen in any of the tests available*'. In addition, the Appellant did not provide '*toxicokinetic data that no systemic absorption occurs via relevant routes of exposure'.* The Appellant limited itself to arguing that '*there is no systemic absorption via relevant exposure*'.

56. The Appellant did not therefore substantiate its argument that the conditions in the third indent of Column 2 of Section 8.7. of Annex X were met. Furthermore, the effects observed in the sub-chronic toxicity study, such as the decreased thymus weight and reduced white blood cell counts, show both that the Substance is absorbed via the relevant route of exposure and that there is evidence of toxicity in the tests available.

57. The Appellant's arguments that, under the third indent of Column 2 of Section 8.7. of Annex X, the Appellant was not required to provide information on an EOGRTS are therefore unsubstantiated and must be rejected.

1.3. Conclusion on the Appellant's first plea

58. In view of paragraphs 32 to 57 above, the Appellant's plea that the Agency made an error of assessment and breached Section 8.7. of Annex X by requiring the Appellant to carry out an EOGRTS must be dismissed.

2. The Agency made an error of assessment in requiring the inclusion of Cohort 3 in the requested EOGRTS

Relevant legislation

59. The second and third subparagraphs of Column 2 of Section 8.7.3. of Annex X provide:

    '*An [EOGRTS] including cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, in case of particular concerns on (developmental) neurotoxicity or (developmental) immunotoxicity justified by any of the following:*

- *existing information on the substance itself derived from relevant available* in vivo *or non-animal approaches (e.g. abnormalities of the CNS, evidence of adverse effects on the nervous or immune system in studies on adult animals or animals exposed prenatally), or*
- *specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity and/or (developmental) immunotoxicity (e.g. cholinesterase inhibition or relevant changes in thyroidal hormone levels associated to adverse effects), or*
- *existing information on effects caused by substances structurally analogous to the substance being studied, suggesting such effects or mechanisms/modes of action.*

Other studies on developmental neurotoxicity and/or developmental immunotoxicity instead of cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) of the [EOGRTS] may be proposed by the registrant in order to clarify the concern on developmental toxicity.'

Arguments of the Parties

60. The Appellant argues that the Agency committed an error of assessment in requiring Cohort 3 to be included in the EOGRTS. This is because the studies submitted by the Appellant, including the sub-chronic toxicity study, demonstrate that there is no concern for developmental immunotoxicity justified by any of the criteria in Column 2 of Section 8.7.3. of Annex X.

61. The Appellant argues that the Agency failed to show that the inclusion of Cohort 3 is based on a concern specific to developmental immunotoxicity and which demonstrates a certain level of severity as indicated in the Agency's Guidance on information requirements and chemical safety assessment on reproductive toxicity (version 6.0, July 2017, Chapter R.7.6.; the 'Agency Guidance').

62. The Appellant argues that, contrary to the conclusion in the Contested Decision, the results observed in the sub-chronic toxicity study did not demonstrate the need to include Cohort 3 in the EOGRTS. The Appellant argues that the reduction in thymus weight and decreased white blood cell counts observed in the sub-chronic toxicity study were not attributable to immunotoxic effects of the Substance, as claimed by the Agency, but '*is an apparent effect occurring as a result of individual variation and clustering leading to statistically significant differences in the data set*'.

63. The Appellant argues that the Agency misinterpreted the findings of the WHO Concise International Chemical Assessment Document 75 on '*Cyclic acid anhydrides: Human health aspects*' (2009; the 'WHO 2009 document'). The Appellant argues that the Agency limited its use of the WHO 2009 document to a description of respiratory sensitisation and mode of action of cyclic acid anhydrides in humans. However, the evaluation of health effects in that document is more relevant to the necessity of conducting a reproductive toxicity study in the present case.

64. The Appellant argues that, according to the Agency Guidance, the identification of the Substance as an SVHC based on its classification as skin and respiratory Category 1 may only be used as a supportive factor to justify the inclusion of the developmental immunotoxicity cohort; it cannot be used as a particular concern in itself to justify the inclusion of Cohort 3.

65. The Agency disputes the Appellant's arguments.

Findings of the Board of Appeal

66. In assessing the Appellant's plea that the Agency made an error of assessment, it is necessary to examine whether the arguments put forward by the Appellant are capable of demonstrating that the Agency made an error in concluding that there is a concern for immunotoxicity justifying the inclusion of Cohort 3 (see, by analogy, *BASF Grenzach* v *ECHA*, cited in paragraph 36 above, paragraph 89 of the judgment). It is necessary to examine whether the Agency has examined carefully and impartially all the relevant facts of the individual case, and whether those facts support the conclusions that the Agency drew from them (see, by analogy, *Xeda International and Pace International* v *Commission*, cited in paragraph 36 above, paragraph 71 of the judgment; see also Case A-006-2017, *Climax Molybdenum*, cited in paragraph 36 above, paragraph 38 of the Decision).

67. The Agency considered that existing information on the Substance demonstrated that there was a concern for immunotoxicity justifying the inclusion of Cohort 3 in the EOGRTS. This concern for immunotoxicity was based primarily on the results of the sub-chronic toxicity study submitted by the Appellant. According to the Contested Decision, in the sub-chronic toxicity study, '*[in] the absence of changes in body weight, statistically significant reduction in thymus weight was noted in low dose (-19%) and high dose (-21%) males at termination of treatment, and also in the recovery group (-22%) males. Decreased white blood cell counts were noted in females (all dose groups) and males (low and mid dose groups). No increased adrenal or decreased spleen weights […] were noted indicating stress-related thymic atrophy and hence [the Agency] considers that these adverse effects (i.e. reduced thymus weight and decreased white blood cell counts, could be attributed to the immunotoxic effects of the [Substance]*'.

68. The Agency clarified during the present proceedings that, although there were other supporting factors, such as the decreased white blood cell counts in the sub-chronic toxicity study, the thymus weight reduction observed in the sub-chronic toxicity study was the main factor justifying the inclusion of Cohort 3 in the EOGRTS.

69. Specifically, the Agency relied on the finding in the sub-chronic toxicity study that a statistically significant reduction in thymus weight in males was noted at low (-19 %) and high doses (-21 %). There was also a statistically significant reduction in thymus weight in recovery group (-22 %) males suggesting that the animals did not recover following exposure.

70. The Appellant has not demonstrated that the Agency made an error of assessment in finding that the decreased thymus weights in the low and high dose group males after treatment with the Substance and following a recovery period are a sign of potential immunotoxicity. In addition, there was an absence of body weight changes in the study and, as stated in the Contested Decision, '*[n]o increased adrenal or decreased spleen weights (spleen weights were actually increased up to 15 % in male recovery group) were noted indicating stress-related thymic atrophy*'. Those elements have not been rebutted by the Appellant who, rather, has shown a difference of interpretation of, and scientific opinion on, the results of the sub-chronic toxicity study. The Appellant has therefore not demonstrated that the Agency made an error of assessment in finding that the reduced thymus weight may be attributable to the immunotoxic effects of the Substance.

71. The fact that no similar effects (thymus weight reduction) were observed in females in the sub-chronic toxicity study does not mean that those effects in males should be disregarded. It is not disputed by the Parties that there can be sex specific differences that explain differences in immune mediated responses.

72. The Appellant argues that the Agency's conclusion that effects were observed in the sub-chronic toxicity study is based on '*minor statistical variations in various parameters*'. However, this argument is not capable of demonstrating that the Agency made an error of assessment in finding that there is a concern for immunotoxicity. The Appellant raised similar arguments in its comments on the draft decision and the Agency responded to those arguments in the Contested Decision. During the present proceedings, the Appellant did not raise new arguments and demonstrate that the Agency made an error of assessment in

concluding that there were effects observed in the sub-chronic toxicity study which indicate a concern for immunotoxicity and justify the inclusion of Cohort 3. The Appellant, rather, has shown a difference of interpretation of, and scientific opinion on, the results.

73. The Appellant and the Agency also disagree on whether the results of the sub-chronic toxicity study are sufficiently severe within the meaning of the Agency Guidance to indicate a concern for immunotoxicity justifying the inclusion of Cohort 3 in the EOGRTS. The Appellant itself acknowledged at the hearing that there was a difference of scientific opinion in this respect. The existence of a diverging scientific opinion is not, in itself, sufficient for the purposes of demonstrating the existence of an error vitiating the Contested Decision (see, by analogy, *BASF Grenzach* v *ECHA*, cited in paragraph 36 above, paragraph 458 of the judgment).

74. In view of paragraphs 66 to 73 above, the Appellant has not demonstrated that the Agency made an error of assessment in requiring the inclusion of Cohort 3 in the EOGRTS based on the reduction in thymus weight observed in the sub-chronic toxicity study. As a result, it is not necessary to examine the Appellant's arguments on the findings in the Contested Decision regarding the WHO 2009 document and the decreased white blood cell counts observed in the sub-chronic toxicity study (see paragraphs 62 and 63 above). The Appellant's plea must therefore be rejected.

3. Breach of Article 40(2) regarding the public consultation on the Appellant's testing proposal

Relevant legislation

75. Article 40(2) provides:

'*Information relating to testing proposals involving tests on* vertebrate *animals shall be published on the Agency website. The Agency shall publish on its website the name of the substance, the hazard end-point for which vertebrate testing is proposed, and the date by which any third party information is required. It shall invite third parties to submit, using the format provided by the Agency, scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal, within 45 days of the date of publication. All such scientifically valid information and studies received shall be taken into account by the Agency in preparing its decision in accordance with paragraph 3.*'

Arguments of the Parties

76. The Appellant argues that the Agency breached Article 40(2) '*by ignoring or improperly disregarding information submitted by a third party*' following the public consultation on the Appellant's testing proposal (see paragraph 4 above).

77. The Appellant argues that the Agency breached Article 40(2) '*by requiring that the scientific information submitted by third parties* "prove[s]" *or* "fulfils" *information requirements in a registration dossier*'.

78. The Agency disputes the Appellant's arguments.

Findings of the Board of Appeal

79. In response to the public consultation held pursuant to Article 42(2), the Agency received the third-party comments set out in paragraph 4 above.

80. According to the Contested Decision, the information provided by the third party '*is not sufficient to fulfil this information requirement*'. The Contested Decision also states that '*the third party did not prove that no systemic absorption occurs via relevant routes of exposure and that the substance is of low toxicological activity*'.

81. Under Article 40(2), third parties may submit scientifically valid information and studies that address the relevant substance and hazard endpoint within 45 days of the date of publication of the testing proposal. The Agency must take into account any such scientifically valid information and studies received. Contrary to the wording used in the Contested Decision, this does not mean that the information received from the third-party consultation under Article 40(2) must '*fulfil*' the information requirement or '*prove*' that the information requested is not necessary. Although a requirement that the information provided by the third party must '*fulfil*' or '*prove*' the information requirement would go beyond the requirements of Article 40(2), the Agency did not breach Article 40(2) in the present case.

82. Specifically, for the following reasons, the Appellant has not demonstrated that the Agency failed to take into account the third party's observations as required by Article 40(2).

83. The majority of the points raised by the third party are addressed explicitly in the Contested Decision, including in Section 1(b) ('*Consideration of the information received during third party consultation*'). The issue of read-across under Section 1.5. of Annex XI mentioned by the third-party is also addressed at a general level in the Contested Decision which states that it is the Appellant's '*responsibility to consider and justify in the registration dossier any adaptation of the information requirements in accordance with Annex X, Section 8.7., column 2, or Annex XI*' (emphasis added).

84. In the present case, the third party provided the Agency with observations or statements only, rather than '*scientifically valid information and studies'* as referred to in Article 40(2). The third-party comments set out in paragraph 4 above were not substantiated or accompanied by any documentation, scientific or otherwise, or references to documentation. Since the third party's observations were not substantiated or documented, the Agency was not required to respond to them in detail in the Contested Decision. In addition, it is not necessary for the reasoning in an Agency decision to go into all the relevant facts and points of law. In particular, the Agency is not required to adopt a position on all the arguments relied on by the parties concerned, but it is sufficient if it sets out the facts and the legal considerations having decisive importance in the context of the decision (see, for example, Case A-023-2015, *S.A. Akzo Nobel Chemicals and Others*, Decision of the Board of Appeal of 13 December 2017, paragraph 172). The fact that the Agency did not specifically address in detail in the Contested Decision all the statements made by the third party does not mean that the Agency failed to take those statements into account.

85. The Agency notified the third party's comments to the Appellant together with the draft decision. Within the time-limit set out in Article 50(1), the Appellant could have updated its registration dossier with relevant information to support the claims in the third-party consultation, if it considered them to be relevant. However, the Appellant did not withdraw its testing proposal or update its dossier with an adaptation. The Appellant's registration dossier did not, at any point, contain an adaptation concerning the EOGRTS in Section 8.7.3. of Annex X. In this respect, it must be noted that it is not the task of the Agency to develop or improve an adaptation on a registrant's behalf (see, for example, Case A-006-2018, *Emerald Kalama Chemical and Others*, Decision of the Board of Appeal of 24 March 2020, paragraph 61). Similarly, the Agency does not have a legal obligation, under either Article 40 or Article 41, to wait for the Appellant to improve the justification for its adaptation (see Case A-005-2016, *Cheminova*, cited in paragraph 51 above, paragraph 49 of the Decision).

86. In view of paragraphs 79 to 85 above, the Appellant's plea that the Agency breached Article 40(2) must be rejected.

4. The Agency breached Article 13 of the TFEU, Article 25 of the REACH Regulation, and '*the principle of proportionality/animal welfare/sound administration*'

Arguments of the Parties

87. The Appellant argues that the Agency breached Article 13 of the TFEU, Article 25 of the REACH Regulation, and '*the principle of proportionality/animal welfare*' for the following reasons:

- The Agency failed to consider alternatives to animal testing,
- The Agency required the Appellant to carry out an EOGRTS despite the fact that the Substance is a known respiratory sensitiser of equivalent level of concern to CMR substances,
- The Agency required the inclusion of Cohort 3 in the EOGRTS even though there is no particular concern based on the results of the sub-chronic toxicity study,
- There is no systemic absorption via relevant exposure and the Substance has low toxicological activity, and
- More uses of the Substance than previously thought are as an intermediate; '*[t]his will not only reduce the volume of the [Substance] significantly, but it would put it in a lower tonnage band*'.

88. The Appellant argues that the Agency breached the principle of sound administration, as set out in Article 41 of the Charter of Fundamental Rights, because the Agency did not carefully examine all relevant aspects of the present case.

89. The Agency disputes the Appellant's arguments.

90. The Agency also argues that the Appellant's arguments related to the breach of the principle of sound administration are inadmissible pursuant to Article 12(2) of the Rules of Procedure as they were raised after the first exchange of written submissions in the present proceedings.

Findings of the Board of Appeal

4.1. Breach of the principle of sound administration

91. The Appellant raised the plea of the Agency's breach of the principle of sound administration in the Notice of Appeal. That plea cannot therefore be considered a new plea within the meaning of Article 12(2) of the Rules of Procedure as claimed by the Agency.

92. In the Notice of Appeal, the Appellant did not substantiate its plea that the Agency breached the principle of good administration. However, in its observations on the Defence, the Appellant provided arguments in support of its plea by referring essentially to certain of the arguments it presented to support its first, second and third pleas which were examined in paragraphs 22 to 86 above. Since the first, second and third pleas, and the arguments presented by the Appellant to support them, have been rejected, the Appellant's plea that the Agency breached the principle of sound administration must also be rejected for the same reasons.

4.2. The Agency breached Article 13 of the TFEU, Article 25 of the REACH Regulation as well as the '*principles of proportionality/animal welfare*'

93. Article 13 of the TFEU provides, amongst other things, that in formulating and implementing the European Union's internal market policies, the Union and the Member States shall, since animals are sentient beings, pay full regard to the welfare requirements of animals. The REACH Regulation contains a number of provisions which take into account the welfare of animals. This includes, for example, Article 25(1) (see, for example, Case A-006-2012, *Momentive Specialty Chemicals*, Decision of the Board of Appeal of 13 February 2014, paragraph 96).

94. In order to respect the principle of proportionality, measures adopted by the European Union institutions and agencies must not exceed the limits of what is appropriate and necessary in order to achieve the objectives legitimately pursued by the measure in question. When there is a choice between several appropriate measures recourse must be had to the least onerous, and the disadvantages caused must not be disproportionate to the aims pursued (judgment of 21 July 2011, *Etimine*, C-15/10, EU:C:2011:504, paragraph 124; Case A-004-2017, *3v Sigma*, Decision of the Board of Appeal of 15 January 2019, paragraph 34).

95. The Contested Decision includes a section entitled '*Considerations of alternatives*'. According to that section of the Contested Decision, the Appellant provided '*considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed*'. In the present proceedings, the Appellant did not suggest any alternatives to the EOGRTS – a standard information requirement – other than arguing that it should not be conducted at all or that that study should not include Cohort 3.

96. To support its pleas based on Article 13 of the TFEU, Article 25 of the REACH Regulation as well as the '*principles of proportionality/animal welfare'*, the Appellant raises similar arguments to those raised to support its first, second and third pleas which were examined in paragraphs 22 to 86 above. In essence, the Appellant argues that, since the EOGRTS, or at least the extension to include Cohort 3, is not necessary, the Agency breached Article 13 of the TFEU, Article 25 of the REACH Regulation as well as the '*principles of proportionality/animal welfare*'.

97. Since the Appellant's first, second and third pleas, and the arguments presented by the Appellant to support them, have been rejected, the Appellant's plea that the Agency breached Article 13 of the TFEU, Article 25 of the REACH Regulation, and the '*principles of proportionality/animal welfare*' must also be rejected for the same reasons.

98. This conclusion is not affected by the Appellant's argument that the tonnage band at which the Substance is registered could be reduced in the future and therefore the EOGRTS may not remain necessary (see paragraph 87 above). In the present case, it is sufficient to note that the Substance was registered at the 1 000 tonnes or more per year tonnage band and remains registered at that tonnage band. The Agency was not required to wait for a potential dossier update reducing the tonnage band at which the Substance is registered before adopting the Contested Decision.

4.3. Conclusion on the Appellant's fourth group of pleas

99. In view of paragraphs 91 to 98 above, the Appellant's plea that the Agency breached Article 13 of the TFEU, Article 25 of the REACH Regulation, and '*the principle of proportionality/animal welfare/sound administration*' must be rejected.

Conclusion on the appeal

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

Claim for the reimbursement of costs

101. In the Notice of Appeal, the Appellant requests the Board of Appeal to order the Agency to pay the costs of these proceedings.

102. The Rules of Procedure do not provide for the reimbursement of costs that are not, as provided in Articles 17 and 21(1)(h) thereof, related to the taking of evidence. Furthermore, Article 17*a* of the Rules of Procedure provides that the parties shall bear their own costs.

103. Consequently, and as in the present case no costs arose in relation to the taking of evidence, the Appellant's request for reimbursement of costs is rejected.

Refund of the appeal fee

104. Pursuant to Article 10(4) of 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), if an appeal is dismissed the appeal fee is not refunded. As this appeal is dismissed, the appeal fee is not refunded.

Effects of the Contested Decision

105. The Contested Decision, upheld in the present case, required the Appellant to submit information on the EOGRTS by 13 September 2021 which is two years and nine days from the date of that Decision.

106. Pursuant to Article 91(2), an appeal has suspensive effect. The deadline set in the Contested Decision to provide the EOGRTS must therefore be calculated starting from the date of notification of the present decision of the Board of Appeal to the Parties.

107. The Appellant must therefore provide the EOGRTS in the form required by the Contested Decision by 20 February 2023.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Dismisses the appeal.**

2. **Decides that the EOGRTS in the form required by the Contested Decision must be submitted by 20 February 2023.**

3. **Rejects the claim for the reimbursement of costs incurred in these proceedings.**

4. **Decides that the appeal fee is not refunded.**

Antoine Buchet
Chairman of the Board of Appeal

Alen Močilnikar
Registrar of the Board of Appeal