EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

12 January 2021

(Substance evaluation – Error of assessment – Potential risk – Improved risk management measures – Proportionality – Article 25)

Case number	A-007-2019
Language of the case	English
Appellant	Chemours Netherlands B.V., the Netherlands
Representatives	Ruxandra Cana and Filippo Mattioli Steptoe & Johnson LLP, Belgium
Interveners	(I) The Ministry of Infrastructure and Water Management of the Kingdom of the Netherlands (II) PETA International Science Consortium Ltd, United Kingdom
Contested Decision	Decision of 20 February 2019 on the substance evaluation of ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoate adopted by the European Chemicals Agency (the 'Agency') pursuant to Article 46 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 Agency included ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoate (EC No 700-242-3, CAS No 62037-80-3; the 'Substance') in the Community rolling action plan for substance evaluation in 2017. This was on the basis of an opinion of the Member State Committee and due to initial grounds for concern relating to suspected persistent, bioaccumulative and toxic (PBT)/very persistent and very bioaccumulative (vPvB) properties of the Substance and exposure of the environment. The Community rolling action plan including the Substance was published on the Agency's website on 21 March 2017 in accordance with Article 44(2) of the REACH Regulation (all references to Articles and Annexes hereinafter concern the REACH Regulation unless stated otherwise). The Competent Authorities of the Netherlands and Germany were appointed as the evaluating Member State Competent Authorities (the 'eMSCAs').

2. In the course of the evaluation, the eMSCAs identified additional concerns regarding '*human health hazard relating to carcinogenicity and bioaccumulation*'.

3. On 20 March 2018, following the substance evaluation of the Substance, the eMSCAs submitted a draft decision (the 'initial draft decision') to the Agency. The initial draft decision required the Appellant to submit information on:

   - A carcinogenicity study in mice via oral route (OECD test guideline ('TG') 451); and
   - A human biomonitoring study in workers at the manufacturing site.

4. According to the initial draft decision, the Appellant's registration dossier includes one carcinogenicity study with rats (the 'Rae *et al.* (2015) study'[1]). That study '*demonstrated induction of adenoma/carcinoma in the pancreas in males, induction of hepatocellular adenomas and carcinomas in females, and increased incidence (but not statistically significant) in Leydig cell tumors in the testes*'.

5. The initial draft decision also addresses the assertions made by the Appellant in its registration dossier that the effects observed in the Rae *et al.* (2015) study are not relevant to humans because those effects are induced by the peroxisome proliferator-activated receptor alpha ('PPARα') mode of action. According to the initial draft decision, '*the tumors observed may be considered relevant for humans*'. The initial draft decision further states that this conclusion is supported by information on another substance - perfluorooctanoic acid ('PFOA') – which shows that '*tumor formation via other mode of action (MoA) than PPARα also cannot be excluded*'.

6. On 9 April 2018, the Agency notified the initial draft decision to the Appellant and invited it to provide comments pursuant to Article 50(1).

7. On 14 May 2018, the Appellant provided comments to the Agency on the initial draft decision. Amongst other things, the Appellant contested the Agency's reliance on information on PFOA to support its conclusion that there is a concern for carcinogenicity. The Appellant argued that, whilst both substances are PPARα agonists, they are structurally and chemically different.

8. The Appellant also argued that there is sufficient data on the Substance to conclude that the tumours observed in the Rae *et al.* (2015) study included in the Appellant's dossier are caused by the PPARα mode of action and are therefore not relevant to humans. Consequently, according to the Appellant, '*there is no basis for [a] carcinogenicity concern in humans and no credible basis for classification [of the Substance] as a human carcinogen*'.

[1] J.M. Caverly Rae *et al.* '*Evaluation of chronic toxicity and carcinogenicity of ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate Sprague-Dawley rats*', Toxicology Reports 2 (2015) pp. 939-949.

9. On 30 August 2018, the eMSCAs notified an amended version of the draft decision (the 'amended draft decision') and the Appellant's comments on the initial draft decision to the competent authorities of the other Member States and the Agency in accordance with Article 52(1).

10. Some of the competent authorities of the Member States and the Agency submitted proposals for amendment to the revised draft decision in accordance with Article 51(2).

11. On 5 October 2018, the Agency notified the Appellant of the proposals for amendment and a further revised draft decision (the 'revised draft decision'). The Appellant was invited, pursuant to Article 51(5), to provide comments on the proposals for amendment.

12. On 19 October 2018, the Appellant submitted comments on the proposals for amendment.

13. The revised draft decision was discussed at the Member State Committee meeting of 10 to 14 December 2018. The Member State Committee reached unanimous agreement on the revised draft decision at that meeting.

14. On 20 February 2019, the Agency adopted the Contested Decision and notified it to the Appellant.

15. The Contested Decision requires the Appellant to update its registration dossier by 28 November 2022 with the following information on the Substance: '*Carcinogenicity study in mice via oral route; test method, OECD [TG] 451'* (the 'carcinogenicity study in mice').

16. According to the Contested Decision, the Rae *et al.* (2015) study demonstrated in rats statistically significant induction of hepatocellular adenomas and carcinomas in the liver of females, statistically significant induction of adenomas/carcinomas in the pancreas in males and increased incidence of Leydig cell tumours in the testes. Further, the Contested Decision states, that '*it cannot be excluded that these tumours are induced by a mode of action (MoA) other than peroxisome proliferator-activated receptor alpha (PPARα) activation and are therefore considered relevant for humans*'. As a result, '*a carcinogenicity study in mice is requested to further evaluate the carcinogenic potential of the [Substance] and to determine if/which further action is needed, for example risk management measures to be taken*'.

17. According to the Contested Decision, '*when comparing the [Substance] to [PFOA], it is concluded that the tumours observed [in the Rae et al. (2015) study] may be considered relevant for humans. Published reviews on the carcinogenicity of PFOA indicate that PFOA-induced carcinogenicity should be considered relevant for humans, because [modes of action] other than via PPARα cannot be excluded'.* According to the Contested Decision, the Substance '*is used as a replacement of PFOA and its ammonium salt (APFO) for the production of Teflon. A comparison of the toxicological properties of both ammonium salts (the [Substance] and APFO) is considered relevant. The substances have many similarities […]. They show similarities in toxicological profiles. They show comparable effects in the liver and induce the same tumours […]*'.

18. The Contested Decision also states that '*there is a potential risk for workers and the general population to be clarified' and 'there is a potential risk for the environment and humans via the environment*'.

19. The Contested Decision also requires the Appellant to update its registration dossier by 1 March 2021 with the following information on the Substance: '*Human biomonitoring study in volunteering workers at the manufacturing site*'.

Procedure before the Board of Appeal

20. On 17 May 2019, the Appellant filed this appeal.

21. On 22 July 2019, the Agency filed its Defence.

22. On 24 September 2019, the Ministry of Infrastructure and Water Management of the Kingdom of the Netherlands (the 'Dutch Ministry') was granted leave to intervene in support of the Agency.

23. On 9 October 2019, PETA International Science Consortium Ltd. ('PISC') was granted leave to intervene in support of the Appellant.

24. On 11 October 2019, the Board of Appeal rejected the application to intervene submitted by Cruelty Free Europe.

25. On 8 November 2019, the Appellant filed its observations on the Defence.

26. On 27 November 2019, the Dutch Ministry filed its statement in intervention.

27. On 13 December 2019, the Agency filed observations on the Appellant's observations on the Defence.

28. On 18 December 2019, PISC filed its statement in intervention.

29. On 14 February 2020, the Appellant and the Agency submitted their respective observations on the statements in intervention lodged by the Dutch Ministry and PISC.

30. On 2 March 2020, the Appellant and the Agency replied to questions from, and provided documents requested by, the Board of Appeal.

31. On 26 March 2020, the Agency submitted its replies to questions from the Board of Appeal.

32. On 25 May 2020, Ángel M. Moreno, alternate member of the Board of Appeal, was designated to replace Sari Haukka in this case, in accordance with the first 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').

33. On 15 September 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 Appellant, the Agency and the Interveners made oral submissions and answered questions from the Board of Appeal.

Form of order sought

34. The Appellant, supported by PISC, requests the Board of Appeal to annul the Contested Decision insofar as it requires the Appellant to conduct the carcinogenicity study in mice.

35. The Appellant also requests the Board of Appeal to order the refund of the appeal fee and to take any other or further measures as justice may require.

36. The Agency, supported by the Dutch Ministry, requests the Board of Appeal to dismiss the appeal as unfounded.

Reasons

37. The Appellant raises the following pleas in law:

    1. The Agency made an error of assessment:

        1.1. By concluding that there is a carcinogenicity concern based on the available information on the Substance;
        1.2. By concluding that there are similarities between the Substance and PFOA capable of justifying a concern; and
        1.3. By concluding that the carcinogenicity study in mice would provide information capable of leading to improved risk management measures.

    2. The Agency breached Article 25; and
    3. The Agency breached the principle of proportionality.

1. The Agency made an error of assessment

38. It is settled case-law that in order to request information under substance evaluation, the Agency must establish that:

    - there are grounds for considering that, based on a combination of exposure and hazard information, a substance constitutes a potential risk to human health or the environment,
    - the potential risk needs to be clarified, and
    - the requested information, needed to clarify the concern, has a realistic possibility of leading to improved risk management measures (see, for example, Case A-008-2018, *Taminco and Performance Additives Italy*, Decision of the Board of Appeal of 29 January 2020, paragraphs 45 and 46; see also judgment of 20 September 2019, *BASF Grenzach* v *ECHA*, T-125/17, EU:T:2019:638, paragraph 276).

39. The Appellant claims that the Agency made three separate errors of assessment in relation to the three criteria defined in the previous paragraph. Each of the alleged errors of assessment will be examined in turn below.

40. In assessing the Appellant's pleas that the Agency made errors 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 the Substance constitutes a potential carcinogenicity concern and whether the carcinogenicity study in mice has a realistic possibility of leading to improved risk management measures (see, by analogy, *BASF Grenzach* v *ECHA*, cited in paragraph 38 above, paragraph 89 of the judgment). In this respect, 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 Case A-006-2017, *Climax Molybdenum*, Decision of the Board of Appeal of 11 December 2018, paragraph 38).

1.1. The Agency made an error of assessment by concluding that there is a carcinogenicity concern based on the available information on the Substance

Arguments of the Parties and the Interveners

41. The Appellant, supported by PISC, argues that the available information does not demonstrate a concern for carcinogenicity. The Agency made an error in its assessment of the available data to substantiate the concern. As a result, the carcinogenicity study in mice is not justified.

42. The Appellant argues that the adenomas and carcinomas in the liver in females, the adenomas and carcinomas in the pancreas in males, and the Leydig cell tumours in the testes observed in the Rae *et al.* (2015) study are caused by a PPARα mode of action (see also paragraph 5 above). The Appellant argues that the Thompson *et al.* (2019) study[2] and Wang *et al.* (2017)[3] study show that the liver tumours were caused by a PPARα mode of action.

43. The Appellant argues that the PPARα mode of action is relevant to rats and mice, but not to humans. As the effects observed in the Rae *et al.* (2015) study are not relevant to humans, they cannot be considered to be the basis of a concern for carcinogenicity.

44. The Appellant argues that the effects identified in the pancreas and Leydig cells in the Rae *et al.* (2015) study are not statistically significant. Consequently, those effects '*are not relevant to draw any conclusions*'.

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[2] Thompson *et al. 'Development of an oral reference dose for the perfluorinated compound GenX'*. J. Appl. Toxicol., 2019; 39(9):1267-1282.

[3] Wang, *et al.*, '*RNA-sequencing analysis reveals the hepatotoxic mechanism of perfluoroalkyl alternatives, HFPO2 and HFPO4, following exposure in mice*'. J. Appl. Toxicol., 2017 37:436-444.

45. The Agency, supported by the Dutch Ministry, disputes the Appellant's and PISC's arguments.

Findings of the Board of Appeal

46. According to the Contested Decision there is a concern for carcinogenicity. The concern for carcinogenicity is based primarily on the results of the Rae *et al.* (2015) study. In that study, tumours were observed in the liver, in the pancreas and in Leydig cells.

47. As stated in paragraph 38 above, the demonstration of a potential risk is based on a combination of exposure and hazard information.

48. In the present case, there is clear and uncontested evidence of potential exposure to the Substance for the environment, the general population and workers. However, the Appellant claims that the Agency made an error of assessment in concluding that there is a carcinogenicity concern based on the available information on the Substance. Specifically, the Appellant claims that the Agency committed an error of assessment in concluding that the effects observed in the Rae *et al.* (2015) study in the liver, in the pancreas and in Leydig cells are relevant for humans (Section 1.1.1. below).

49. The Appellant also claims that the effects observed in the pancreas and Leydig cells are not statistically significant and therefore '*are not relevant to draw any conclusions*' (Section 1.1.2. below).

1.1.1. Human relevance of the effects in the liver, in the pancreas and in Leydig cells observed in the Rae *et al.* (2015) study

50. The Appellant argues that the tumours in the liver, in the pancreas and in Leydig cells observed in the Rae *et al.* (2015) study are not relevant for humans. This is because the tumours are caused through the PPARα mode of action which the Appellant considers is not relevant to humans. The Agency therefore made an error of assessment in concluding that there is a carcinogenicity concern based on the available information on the Substance.

51. According to the Contested Decision, '*[the Substance] induced tumours in a two-year carcinogenicity study in rats [the Rae* et al*. (2015) study]. It cannot be excluded that these tumours are induced by a mode of action (MoA) other than peroxisome proliferator-activated receptor alpha (PPARα) activation and are therefore considered relevant for humans*'.

52. Section 3.6.1.1. of Annex I to 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; the 'CLP Regulation') provides:

'*Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans*' (emphasis added).

53. It is undisputed between the Parties that the Rae *et al.* (2015) study is a well performed experimental study on animals within the meaning of Section 3.6.1.1. of Annex I to the CLP Regulation. It is also undisputed that the results of the Rae *et al.* (2015) study show that the Substance has induced '*benign and malignant tumours'* in rats within the meaning of Section 3.6.1.1. of Annex I to the CLP Regulation.

54. Therefore, the presumption that the benign and malignant tumours induced by the Substance are relevant to humans applies. Consequently, for the Appellant's plea to succeed, and rebut that presumption, there must be '*strong evidence*' that the modes of action linked to the tumour formation observed in the Rae *et al.* (2015) study are not relevant for humans.

55. The Parties' arguments on the human relevance of the effects observed in the Rae *et al.* (2015) study will be examined, first, with regard to the liver (Section 1.1.1.1. below) and, second, with regard to the pancreas and Leydig cells (Section 1.1.1.2. below).

1.1.1.1. Human relevance of the effects in the liver

56. It is undisputed between the Parties that the PPARα mode of action is relevant in the formation of the liver tumours observed in the Rae *et al.* (2015) study. It is also undisputed that liver tumours in rodents caused solely by the PPARα mode of action are not relevant to humans.

57. However, whether PPARα is the sole mode of action in the formation of the liver tumours observed in the Rae *et al.* (2015) study is disputed. In the Contested Decision, the Agency argues that for PPARα agonists, such as the Substance, there may be more than one mode of action linked to carcinogenic effects in the liver. The Appellant contests this.

58. For the following reasons, the Appellant has not provided sufficient evidence capable of demonstrating that the Agency made an error of assessment in concluding that there may be modes of action, other than the PPARα mode of action, related to the tumour formation in the liver observed in the Rae *et al.* (2015) study and that those modes of action may be relevant to humans.

59. First, during the Member State Committee meeting at which a draft of the Contested Decision was discussed in the presence of the Appellant (see paragraph 13 above), the Appellant confirmed that '*no studies with regard to carcinogenic mode of action had been carried out on the [Substance]*'.

60. Second, although the Rae *et al.* (2015) study report discusses the PPARα mode of action, that study does not investigate whether the PPARα mode of action is the sole mode of action linked to the formation of tumours in the liver. The absence of an investigation of other possible modes of action in the Rae *et al.* (2015) study does not demonstrate that no other modes of action are relevant. The primary purpose of the Rae *et al.* (2015) study, a study conducted according to OECD TG 453, was not to investigate the modes of action for carcinogenicity. Although an OECD TG 453 study may, amongst other things, provide data to test hypotheses regarding mode of action, one of its main objectives is to observe test animals for a major portion of their life span for the development of neoplastic lesions during or after exposure to various doses of a test substance by an appropriate route of administration.

61. Third, the Appellant argues that the Thompson *et al.* (2019) study and the Wang *et al.* (2017) study show that the liver tumours were caused by a PPARα mode of action.

62. At the outset, it must be noted that, since the Thompson *et al.* (2019) study was published only after the adoption of the Contested Decision, it was not possible for the Agency to take that study into account. Nonetheless, although showing that PPARα is one likely mode of action, neither the Thompson *et al.* (2019) study nor the Wang *et al*. (2017) study demonstrate that PPARα is the sole mode of action linked to the tumours observed in the liver.

63. Fourth, the fact that the Agency did not identify in the Contested Decision any other possible modes of action linked to the tumour formation in the Rae *et al.* (2015) study does not mean that no other relevant modes of action exist. Contrary to the Appellant's arguments, the Agency is not obliged to identify modes of action which may be linked to the tumour formations observed in a carcinogenicity study such as the Rae *et al.* (2015) study.

64. In view of paragraphs 56 to 63 above, whether PPARα is the sole mode of action in the formation of the liver tumours observed in the Rae *et al.* (2015) study is the subject of scientific disagreement between the Parties. 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 38 above, paragraph 458 of the judgment). The Appellant's claims that

the Agency committed an error of assessment in concluding that the effects observed in the liver are relevant for humans must therefore be rejected.

1.1.1.2. Human relevance of the effects in the pancreas and Leydig cells

65. The Appellant argues that the tumours observed in the pancreas and in Leydig cells in the Rae *et al.* (2015) study are caused by the PPARα mode of action which is not relevant to humans. According to the Appellant, the Agency therefore made an error of assessment in concluding that there is a carcinogenicity concern based on the available information on the Substance. This argument is contested by the Agency.

66. The Appellant's arguments must be rejected for the following reasons.

67. First, the Appellant did not develop arguments capable of demonstrating that the tumours observed in the pancreas and in Leydig cells in the Rae *et al.* (2015) study were caused by the PPARα mode of action, or that the Agency's findings in the Contested Decision are vitiated by error in this regard. The mode of action causing the tumours observed in the pancreas and in Leydig cells is subject to a scientific disagreement. 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 38 above, paragraph 458 of the judgment).

68. The existence of a scientific disagreement is confirmed by the findings of the Klaunig *et al.* (2003) study[4] submitted by the Appellant. Although it does not contain information specifically on the Substance, that study concludes that there is insufficient evidence to establish which mode or modes of action cause tumours in the pancreas and in Leydig cells following exposure to PPARα agonists, a class of substances to which the Substance itself belongs.

69. Second, even if the tumours observed in the Rae *et al.* (2015) study in the pancreas and in Leydig cells were caused via the PPARα mode of action and this is not relevant to humans, the Appellant has not demonstrated that the PPARα mode of action is the sole mode of action linked to the formation of tumours in the pancreas and in Leydig cells. Consequently, there might be different modes of action causing the tumours in the pancreas and in Leydig cells, some of which might be relevant to humans.

70. In view of paragraphs 65 to 69 above, the Appellant has not established the mode or modes of action that caused the tumours observed in the pancreas and in Leydig cells in the Rae *et al.* (2015) study. Without establishing the mode or modes of action causing the tumour formation, it is not possible to conclude that they are not relevant to humans. As a result, the Appellant has not provided '*strong evidence*' within the meaning of Section 3.6.1.1. of Annex I to the CLP Regulation that the modes of action that caused the tumours observed in the pancreas and in Leydig cells in the Rae *et al.* (2015) study are not relevant to humans.

71. The Appellant's claim that the Agency committed an error of assessment in concluding that the effects observed in the Rae *et al.* (2015) study in the pancreas and in Leydig cells are relevant for humans must therefore be rejected.

1.1.2. Statistical significance of the effects observed in the pancreas and in Leydig cells

72. According to Section 3.6.2.2.3. of Annex I to the CLP Regulation, '*[s]trength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance*.'

[4] Klaunig JE *et al.* '*PPAR agonist-induced rodent tumors: modes of action and human relevance'*. Crit. Rev. Toxicol., 2003; 33(6): 655-780.

73. According to the Contested Decision, the Rae *et al.* (2015) study '*demonstrated statistically significant induction of adenomas/carcinomas in the pancreas in males, statistically significant induction of hepatocellular adenomas and carcinomas in females, and increased incidence of Leydig cell tumours in the testes*'.

74. The Appellant argues that the effects identified in the pancreas and in Leydig cells in the Rae *et al.* (2015) study were not statistically significant. Consequently, according to the Appellant, those effects '*are not relevant to draw any conclusions*'. It is undisputed that the effects observed in the liver are statistically significant.

75. Pursuant to Article 46, it is not necessary for the Agency to demonstrate an '*actual risk*', only a '*potential risk*'. The aim of requesting additional information under substance evaluation is to clarify whether the '*potential risk*' is an '*actual risk*' (see *BASF Grenzach* v *ECHA*, cited in paragraph 38 above, paragraphs 272 and 273 of the judgment, and Case A-023-2015, *Akzo Nobel Chemicals and Others*, Decision of the Board of Appeal of 13 December 2017, paragraph 99).

76. This approach is consistent with the European Union Courts' interpretation of the precautionary principle according to which '*a preventive measure may be taken only if the risk, although the reality and extent thereof have not been 'fully' demonstrated by conclusive scientific evidence, appears nevertheless to be adequately backed up by the scientific data available at the time the measure was taken*' (see judgment of 11 September 2002, *Pfizer Animal Health SA* v *Council*, T-13/99, EU:T:2002:209, paragraph 144).

77. In the Contested Decision, the Agency did not examine the available information in order to clarify whether there is an actual risk for carcinogenicity and the appropriate classification for the Substance. The Agency rather examined the available information and concluded that there was a potential risk for carcinogenicity which would justify requesting additional information aimed at clarifying the carcinogenicity concern.

78. Furthermore, it has not been demonstrated that the effects observed in the Rae *et al.* (2015) study in the liver, in the pancreas and in Leydig cells are not relevant for humans (see Section 1.1.1. above). This is sufficient in the present case, coupled with the undisputed potential exposure to the Substance for the environment, the general population and workers, to demonstrate a potential risk for the purposes of requesting information under substance evaluation. In this respect, even effects observed in studies that are not statistically significant but biologically relevant may indicate a concern (see Case A-010-2018, *Symrise*, Decision of the Board of Appeal of 18 August 2020, paragraph 149).

79. In view of paragraphs 72 to 78 above, the Appellant's claim that the effects observed in the pancreas and in Leydig cells are not statistically significant and that the Agency therefore made an error of assessment in concluding that those effects are relevant must be rejected.

1.1.3. Conclusion on plea that the Agency made an error of assessment in concluding that there is a concern on the basis of the available information on the Substance

80. In view of paragraphs 46 to 79 above, the Appellant's plea that the Agency made an error of assessment in concluding that there is a carcinogenicity concern based on the available information on the Substance must be rejected.

1.2. Error of assessment in concluding that there are similarities between the Substance and PFOA capable of justifying a concern

Arguments of the Parties and the Interveners

81. The Appellant, supported by PISC, argues that the Agency committed an error of assessment in concluding that additional information is required on the basis of information available on another substance, PFOA. The Appellant argues that the

Agency made an error of assessment in assuming that the Substance is toxicologically and kinetically the *'same'* as PFOA.

82. The Appellant argues that, had the Agency assessed the Substance on the basis of the available information on the Substance, instead of the data on PFOA, the Contested Decision would have not been adopted. This is because the information on the Substance is not sufficient on its own to justify the request for the carcinogenicity study in mice.

83. The Agency, supported by the Dutch Ministry, disputes the Appellant's and PISC's arguments.

Findings of the Board of Appeal

84. As stated in paragraph 46 above, the concern for carcinogenicity is based primarily on the results of the Rae *et al.* (2015) study.

85. The Agency relied on information on PFOA to rebut the Appellant's arguments, and address the comments made by a competent authority of a Member State during the decision-making procedure, related to the mode of action relevant to the tumour formation observed in the Rae *et al.* (2015) study. In particular, information on PFOA is used to support the Agency's argument that there may be more than one mode of action at work in the formation of tumours and that the results from the Rae *et al.* (2015) study may be relevant to humans.

86. As shown in Section 1.1. above, the Agency demonstrated the existence of a potential risk based on the results of the Rae *et al.* (2015) study and potential exposure to the Substance. That information, on its own, is sufficient to justify the request for the carcinogenicity study in mice. The arguments in the Contested Decision on the structural similarity of the Substance and PFOA are only a secondary element in establishing a concern; they are used by the Agency to support its argument that there may be more than one mode of action linked to the tumour formation observed in the Rae *et al.* (2015) study. Even without this information, the fact remains that the Appellant has not demonstrated that the formation of liver, pancreas and Leydig cell tumours in rats observed in the Rae *et al.* (2015) study following exposure to the Substance is not relevant to humans.

87. The Appellant's argument that the available information on the Substance is not sufficient on its own to justify the request for the carcinogenicity study in mice (see paragraph 82 above) must therefore be dismissed as unfounded.

88. Since the information from the Rae *et al.* (2015) study and the potential exposure to the Substance are sufficient to justify the request for the carcinogenicity study in mice it is not necessary to examine the Appellant's arguments related to the structural similarity of the Substance and PFOA.

89. The Appellant's plea that the Agency committed an error of assessment in concluding that additional information is required on the basis of information available on PFOA must therefore be rejected as unfounded.

1.3. Error of assessment in concluding that the carcinogenicity study in mice would provide information capable of leading to improved risk management measures

Arguments of the Parties and the Intervener

90. The Appellant, supported by PISC, argues that conducting the carcinogenicity study in mice will not improve the risk management measures currently applicable to the Substance.

91. The Appellant argues that the carcinogenicity study in mice will not provide information on the relevant mode of action and therefore will not be relevant for the classification of the Substance as carcinogen Category 1B or 2.

92. The Appellant argues that the exposure of workers to the Substance is extremely low since it is used in manufacturing processes in '*very high containment conditions*'. Even if the carcinogenicity study in mice is conducted, this could not have the effect of protecting workers to a higher extent than they already are. The derived no-effect level currently applied is sufficiently low to protect workers against potential carcinogenicity effects.

93. The Agency, supported by the Dutch Ministry, disputes the Appellant's and PISC's arguments.

Findings of the Board of Appeal

94. As stated in paragraph 38 above, in order to request the carcinogenicity study in mice the Agency must demonstrate, amongst other things, that that study has a realistic possibility of leading to improved risk management measures.

95. In the Contested Decision, the possible improvements in risk management measures are set out as follows:

'In case of sufficient evidence for carcinogenicity, further regulatory action may be needed to guarantee safety of workers and the general population.

In addition, there is a potential risk for the environment and humans via the environment associated to persistence and bioaccumulation, and the requested data will also contribute to the PBT assessment. The registered substance is currently self classified as STOT RE 2, based on hepatotoxic effects. However, the evidence for harmonised classification as STOT RE is borderline and therefore it is questionable whether the T criterion of PBT is fulfilled based on this endpoint. The current data for the [Substance] are not sufficient to conclude whether classification for carcinogenicity is triggered, and to differentiate between a carcinogenicity classification in CLP Cat. 1B or Cat. 2. Harmonised classification for Carc. Cat. 1B may impact occupational exposures through the Carcinogens and Mutagens Directive (CMD). It will also make the [Substance] a candidate for SVHC according to [Article] 57(a), be of influence for granting industrial emission permits under the Industrial Emissions Directive (IED) and will fulfil the T criterion for PBT identification according to Article 57(d) of REACH. The potential bioaccumulation is addressed by the request of a human biomonitoring study in this decision.

In comparison, harmonised classification for Carc. Cat. 2 will not trigger any regulatory risk management measures for workers nor any emission reduction under IED. It will not be sufficient to meet the criteria for SVHC under Article 57(a) and will not be sufficient to meet the T criterion for PBT identification according to Article 57(d).'

96. According to the CLP Regulation, a Category 1B classification for carcinogenicity ('*presumed to have carcinogenic potential for humans*') is based on the strength of evidence together with additional considerations. According to Section 3.6.2.2.3. of Annex I to the CLP Regulation, when looking at the strength of evidence of carcinogenicity using evidence on experimental animals, it is necessary to establish '*sufficient evidence of carcinogenicity*' (emphasis added). That Section of the CLP Regulation provides:

'*Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms 'sufficient' and 'limited' have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows:*

[…]

(b) Carcinogenicity in experimental animals

[…] The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

— *sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites;*

— *limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs*' (emphasis added).

97. Currently, there is one carcinogenicity study in rats on the Substance: the Rae *et al.* (2015) study. The Agency therefore has '*limited evidence*' only regarding the carcinogenic potential of the Substance. To have '*sufficient evidence of carcinogenicity*', and therefore the possibility to classify the Substance as Category 1B carcinogen, there would need to be, at least, two studies.

98. The Appellant argues that the requested study will not resolve the question of the mode of action and human relevance. The Appellant argues that the test will simply confirm the results of the Rae *et al.* (2015) study, that the Substance may cause cancer in rodents via the PPARα mode of action. These arguments must be rejected for the following reasons.

99. First, for the reasons set out in Section 1.1. above, it has not been demonstrated that the PPARα mode of action is the sole mode of action related to the tumour formations observed in the Rae *et al.* (2015) study.

100. Second, the determination of the mode of action is not a regulatory requirement in itself. The main purpose of the carcinogenicity study in mice requested in the Contested Decision is not to determine the relevant mode of action but to clarify the carcinogenic properties of the Substance. The carcinogenicity study in mice will be the second study that is required to draw a conclusion on the carcinogenic potential of the Substance.

101. Third, even if the carcinogenicity study in mice does not provide any additional information regarding the mode or modes of action and their human relevance, according to Section 3.6.1.1. of Annex I to the CLP Regulation, there is a presumption that '*[s]ubstances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanisms of tumour formation is not relevant for humans*.'

102. In view of paragraphs 94 to 101 above, the carcinogenicity study in mice is necessary to decide on whether the Substance should be classified for carcinogenicity and, in particular, whether it can be classified as a Category 1B carcinogen. Furthermore, there is a realistic possibility that the latter classification will lead to the risk management measures identified by the Agency in the Contested Decision (see paragraph 95 above).

103. For example, under Article 57(a), if the results of the carcinogenicity study in mice, coupled with the existing evidence, lead to a classification of the Substance in the hazard class carcinogenicity Category 1B, the Substance may subsequently be included in Annex XIV ('*List of substances subject to authorisation*'). Substances included in Annex XIV may be subject to the authorisation process leading to controls on their use and eventually they may be phased out.

104. In addition, prior to inclusion in Annex XIV, the Substance would need to be included on the candidate list of substances of very high concern under Article 59. The identification of a substance as being of very high concern serves to improve information for the public and professionals as to the risks incurred. Consequently, such identification must be regarded as a means of enhancing the protection of human health and the environment (judgment of 7 March 2013, *Rütgers Germany and Others* v *ECHA*, T-96/10, EU:T:2013:109, paragraph 137). Inclusion on the candidate list is therefore an improved risk management measure in itself. Consequently, there is a realistic possibility that at least one of the possible improved risk management measures identified in the Contested Decision (see paragraph 95 above) may result from the carcinogenicity study in mice. It is therefore not necessary to examine the other possible risk management measures put forward by the Agency in the Contested Decision.

105. In view of paragraphs 94 to 104 above, the Appellant's plea that the Agency committed an error of assessment in concluding that the requested information would provide information capable of leading to improved risk management measures is rejected.

2. Breach of Article 25 and the principle of proportionality

Arguments of the Parties and the Interveners

106. The Appellant, supported by PISC, argues that the Rae *et al.* (2015) study provides sufficient information to conclude on the carcinogenicity of the Substance. Conducting the carcinogenicity study in mice is neither necessary nor appropriate and will not contribute to the protection of workers or of the general population.

107. The Appellant argues that '*the Agency could and should have considered less onerous studies, such as short-term toxicogenomic studies capable of measuring changes in multiple pathways simultaneously that could aid in identifying the mode of action*' at issue in the Rae *et al.* (2015) study. The Agency therefore did not ensure that testing on animals was undertaken only as a last resort.

108. The Agency, supported by the Dutch Ministry, disputes the Appellant's and PISC's arguments.

Findings of the Board of Appeal

109. 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).

110. Article 25(1) provides *'[i]n order to avoid animal testing, testing on vertebrate animals for the purposes of [the REACH] Regulation shall be undertaken only as a last resort […]*'.

111. In Section 1 above, it has been found that the Agency has demonstrated a potential concern for carcinogenicity that needs to be clarified. Contrary to the Appellant's claims, the Agency does not currently have sufficient evidence to conclude on the concern. The carcinogenicity study in mice is necessary to clarify the carcinogenicity concern and has a realistic possibility of leading to improved risk management measures (see Section

1.3. above). The Appellant's claim that the required information is not necessary must therefore be rejected.

112. Under the REACH Regulation, the Agency has an obligation to consider animal welfare in its decision-making. Where the Agency requires additional testing under substance evaluation it must ensure that vertebrate animals are used only as a last resort (see Case A-023-2015, *S.A. Akzo Nobel Chemicals*, Decision of the Board of Appeal of 13 December 2017, paragraph 271). Similarly, under the principle of proportionality, the Agency must ensure that, where there is a choice of appropriate measures, the least onerous measure is chosen.

113. In the present case, it is evident from the wording of the Contested Decision itself that alternatives to the carcinogenicity study in mice were considered by the Agency. The Agency concluded that there were no less onerous measures and that animal testing was necessary to clarify the concern for carcinogenicity. The Agency concluded in the section '*Consideration of alternative approaches*' of the Contested Decision that '*for determining the carcinogenicity of a substance, the cancer bioassay is the only study available*.'

114. The Appellant has not demonstrated that there are less onerous alternatives available which are capable of clarifying the carcinogenicity concern and that would avoid animal testing.

115. The Appellant argues that less onerous studies such as short-term toxicogenomic studies could have been requested to clarify the mode of action relevant to the tumour formation observed in the Rae *et al.* (2015) study. In the Contested Decision, the Agency states that '*alternatives or further examination of the mechanism would not be appropriate as several [modes of action] may be involved and need to be investigated, and the tumorigenesis involves multiple organs (not only liver). Hence, further examination of the mechanism would require even more testing and use of more animals, which is considered not proportionate*'. The Appellant has not provided reasons capable of refuting the Agency's arguments.

116. The alternative proposed by the Appellant may help to clarify whether the effects observed in the liver are associated with the PPARα mode of action. However, this would not help to clarify the carcinogenicity concern for the pancreas and Leydig cells. In addition, test methods for toxicogenomic studies to assess carcinogenic mechanisms and modes of action have not yet been internationally validated.

117. In view of paragraphs 109 to 116 above, the Appellant's pleas that the Agency breached Article 25 and the principle of proportionality must be rejected.

Conclusion on the appeal

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

Refund of the appeal fee

119. In accordance with 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), 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.

Effects of the Contested Decision

120. The Contested Decision, upheld in the present appeal proceedings, required the Appellant to submit the carcinogenicity study in mice by 28 November 2022 which is three years, nine months and eight days from the date of that Decision.

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

122. The Appellant must therefore provide the information on the carcinogenicity study in mice required by the Contested Decision by 21 October 2024.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Dismisses the appeal.**
2. **Decides that the carcinogenicity study in mice requested in the Contested Decision must be submitted to the Agency by 21 October 2024.**
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