EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL
OF THE EUROPEAN CHEMICALS AGENCY

19 October 2016

(Compliance check – Read-across – Right to be heard – Animal welfare – Proportionality – Legitimate expectations)

Case number	A-004-2015
Language of the case	English
Appellant	Polynt S.p.A., Italy
Representative	Claudio Mereu Fieldfisher LLP, Belgium
Contested Decision	CCH-D-2114289309-36-01/F of 28 November 2014 adopted by the European Chemicals Agency pursuant to Article 41(3) 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; corrected by OJ L 136, 29.5.2007, p. 3; hereinafter the 'REACH Regulation')

THE BOARD OF APPEAL

composed of Mercedes Ortuño (Chairman), Andrew Fasey (Technically Qualified Member) and Sari Haukka (Legally Qualified Member and Rapporteur)

Registrar: Alen Močilnikar

gives the following

Decision

Summary of the dispute

1. The Appellant is a registrant of the substance hexahydro-4-methylphthalic anhydride (EC No 243-072-0, CAS No 19438-60-9, hereinafter '4-MHHPA' or the 'Substance'). The present appeal is directed against a compliance check decision requiring inter alia the submission of:

   - a sub-chronic toxicity study (90-day) on the Substance in rats, oral route, pursuant to Section 8.6.2 of Annex IX to the REACH Regulation (hereinafter the 'sub-chronic toxicity study'), conducted in accordance with OECD test guideline (hereinafter 'TG') 408, and
   - a pre-natal developmental toxicity study on the Substance in rats or rabbits, oral route, pursuant to Section 8.7.2 of Annex IX to the REACH Regulation (hereinafter the 'pre-natal developmental toxicity study' or 'PNDT study'), conducted in accordance with OECD TG 414.

2. The Appellant requests the Board of Appeal to:

   - partially annul the Contested Decision in so far as it requires the sub-chronic toxicity study and the PNDT study to be conducted on the Substance, and
   - order the Agency to pay the costs of these proceedings.

Background of the dispute

3. On 21 October 2010, the Appellant submitted a registration dossier for the Substance. In its registration dossier, the Appellant sought to adapt the information requirements for inter alia sub-chronic toxicity and pre-natal developmental toxicity. For the sub-chronic toxicity endpoint the Appellant provided a study record for a repeated dose 28-day oral toxicity study on the Substance (OECD TG 407). In addition, the Appellant referred to sub-acute and sub-chronic data for other cyclic anhydrides, substances that the Appellant considers to have similar structures and toxicological properties to 4-MHHPA. In relation to the pre-natal developmental toxicity endpoint, the Appellant sought to adapt this information requirement by reference to a reproduction/pre-natal developmental toxicity screening test on the Substance (OECD TG 421), during which no effects regarding pre-natal developmental toxicity were observed, and by reference to data for other cyclic anhydrides.

4. On 16 July 2013, the Agency initiated a compliance check of the Appellant's registration dossier.

5. On 5 November 2013, the Agency notified a draft decision (hereinafter the 'Draft Decision') to the Appellant and invited it to provide comments within 30 days in accordance with Article 50(1) of the REACH Regulation (all references to Recitals, Articles and Annexes hereinafter concern the REACH Regulation unless stated otherwise). The Draft Decision rejected the proposed adaptations and requested the Appellant to submit a sub-chronic toxicity study (90-day), oral route in rats, and a pre-natal developmental toxicity study in rats or rabbits, oral route. The Draft Decision

also requested the Appellant to submit a two-generation reproductive toxicity study or, alternatively, an extended one-generation reproductive toxicity study (hereinafter 'EOGRTS').

6. With respect to sub-chronic toxicity, the Draft Decision explained that the repeated dose 28-day oral toxicity study initially submitted by the Appellant '*does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower*' resulting in reduced sensitivity. In addition, '*no robust study summary was provided*' for the data to which the Appellant referred in the justification of the adaptation, and '*therefore, this information cannot be evaluated*'. Moreover, according to the Draft Decision, the Appellant did not provide and document '*a read-across justification assessing the structural similarity and a systematic comparison of toxicological properties and thus, the requirements in Annex XI, Section 1.5. have not been fulfilled*'.

7. With respect to pre-natal developmental toxicity, the Draft Decision noted that the screening test provided by the Appellant '*does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations*'. In addition, '*no robust study summary was provided*' for the data referred to in the justification of the adaptation, and '*therefore, this information cannot be evaluated*'. Moreover, according to the Draft Decision, the Appellant did not provide and document '*a read-across justification assessing the structural similarity and a systematic comparison of toxicological properties and thus, the requirements in Annex XI, Section 1.5. have not been fulfilled*'.

8. On 20 November 2013, the Agency and the Appellant held a teleconference to clarify the points raised in the Draft Decision.

9. On 4 December 2013, the Appellant submitted its comments on the Draft Decision. As regards the sub-chronic toxicity and pre-natal developmental toxicity endpoints, the Appellant stated that it would '*update the IUCLID file to include robust study summaries from analogue substances for the end-point together with a formal justification document for the use of read-across*'.

10. On 7 February 2014, the Registrant submitted an updated registration dossier, which included robust study summaries for repeated dose toxicity, reproductive and developmental toxicity. The updated dossier also contained a justification for using a read-across adaptation for the sub-chronic toxicity, pre-natal developmental toxicity and two-generation reproductive toxicity endpoints (hereinafter the 'read-across adaptation').

11. The Appellant's read-across adaptation relies on a grouping approach whereby data derived from studies on a number of other cyclic anhydrides (hereinafter the 'source substances') are applied to the Substance. These source substances are maleic anhydride (hereinafter 'MA'), hexahydrophthalic anhydride (hereinafter 'HHPA'), tetrahydrophthalic anhydride (hereinafter 'THPA'), tetrahydromethylphthalic anhydride (hereinafter 'MTHPA'), phthalic anhydride (hereinafter 'PA'), trimellitic anhydride (hereinafter 'TMA'; the source substances and the Substance are hereinafter collectively referred to as the 'grouped substances' or the 'cyclic anhydrides').

12. The read-across justification document submitted in the Appellant's updated registration dossier states that '*[t]he defined group [i.e. the cyclic anhydrides] is made up of substances consisting of a (bi)cyclic ring structure with the carboxylic acid*

*anhydride group as the single reactive and toxic functional moiety'. A*ccording to the same document '*[i]n all substances, the reactive anhydride moiety, which is deemed mainly responsible for the (eco)toxicological properties of the cyclic anhydrides, rapidly hydrolyses to form the di-acid once in contact with an aqueous medium*'. As regards the assessment of structural analogues, the document further states that '*the defined group is made up of substances consisting of a a (bi)cyclic ring structure with the carboxylic acid anhydride group as the single reactive and toxic functional moiety responsible for both the irritant and sensitising properties of the group*'. It furthermore adds that '*[s]tructural differences such as the level of saturation in the ring structure, presence or different location of substituted functional group are expected to have no or only negligible influence with regard to eco- and systemic toxicity*'. Under the title 'studies in support of human health effects', the Appellant explained that '*[a]ll of the substances are expected to be skin and respiratory sensitisers with sensitising effects experimentally confirmed for HHPA, THPA, PA, TMA and MA. For these effects the intact anhydride moiety is essential, as the respective di-acids are not classified as skin/inhalation sensitisers*'. Moreover, '*[t]he available mammalian studies may be considered sufficiently rigorous to serve in demonstrating similarities with the registered substance. The [No Observed (Adverse) Effect Levels] derived from sub-acute studies are generally similar, any differences being more a reflection of the dose-levels examined than differing toxicity. […] Also, based on available experimental data, there is no indication that these types of anhydrides might pose a risk with regard to reproductive and developmental toxicity*.'

13. Following submission of the Appellant's comments and its registration dossier update the Agency revised the Draft Decision (hereinafter the 'revised Draft Decision'). In the revised Draft Decision, the Agency re-assessed and rejected the read-across adaptation proposed by the Appellant with regard to both the sub-chronic toxicity and the pre-natal developmental toxicity endpoints.

14. As regards the request for the sub-chronic toxicity study, the Agency noted in the revised Draft Decision that '*[b]ased on the information provided, [the Agency] understands that the [read-across] hypothesis is based on i) the (bi)cyclic structures with a common 5-member ring carboxylic acid anhydride group as the only reactive functional group, ii) the carboxylic acid anhydride group is responsible for the (eco)toxicological effects in the group of substances, and iii) structural differences have no or only negligible influence with regard to systemic toxicity*'. The Agency acknowledged that 4-MHHPA and the other cyclic anhydrides to which the Appellant referred in the read-across proposal '*share a common functional group (i.e. 5-member ring carboxylic acid anhydride)'*. However, it considered that '*the Registrant has failed to prove that the common functional group is the responsible for the (eco)toxicological effects and why the structural differences have only negligible influence with regard to systemic toxicity*'. The Agency added that, '*based on the data provided, different structures seem to result in different effects in the repeated dose toxicity which indicates that the structural differences have an influence with regard to systemic toxicity. In particular, in two sub-chronic toxicity studies (90-day) and a two-generation reproductive toxicity study it was observed that maleic anhydride (MA) causes renal effects which were not observed in studies with other substances*. *In addition, it can be seen* a *high variability in the [No Observed Adverse Effect Levels] provided by the [Appellant] for the different substances with data for sub-acute repeated dose toxicity (i.e. 100 to 1250 mg/kg) and this variability did not follow an evident trend*'. The Agency therefore considered that the Appellant's read-across

adaptation for the sub-chronic toxicity endpoint did not fulfil the requirements of Section 1.5 of Annex XI.

15. With regard to the pre-natal developmental toxicity endpoint, the Agency stated in the revised Draft Decision that the Appellant *'has provided mainly reproductive and developmental toxicity screening studies that do not cover the key parameters of the pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations or the studies have not been conducted according to any accepted guideline and cannot be assessed due to the lack of data in the reporting'*. In addition, the revised Draft Decision stated that a pre-natal developmental toxicity study with MA was not sufficient to justify a read-across in accordance with Section 1.5 of Annex XI, as *'the toxicological effects for MA are differentiated from the other substances and the [Appellant] has failed to prove that the structural differences have only negligible influence with regard to systemic toxicity'*.

16. The Agency therefore concluded in the revised Draft Decision that the read-across adaptation proposed by the Appellant had not been adequately justified and had to be rejected. The Agency consequently maintained in the revised Draft Decision the request for a sub-chronic toxicity study, a pre-natal developmental toxicity study as well as additional information on reproductive toxicity.

17. On 12 June 2014, the Agency notified the revised Draft Decision to the Competent Authorities of the Member States (hereinafter the 'MSCAs') and invited them to submit proposals for amendment pursuant to Article 51(1).

18. Four MSCAs submitted proposals for amendment relating to the part of the revised Draft Decision requiring a two-generation reproductive toxicity study or, alternatively, an EOGRTS. No proposals for amendment on the parts of the revised Draft Decision on sub-chronic toxicity and pre-natal developmental toxicity were submitted.

19. On 18 July 2014, the Agency notified the proposals for amendment to the Appellant and invited it to provide comments on them pursuant to Article 51(5).

20. The Agency reviewed the proposals for amendment received and amended the revised Draft Decision accordingly (hereinafter the 'amended Draft Decision'), in particular by removing the request for a two-generation reproductive toxicity study or, alternatively, an EOGRTS. On 28 July 2014, the Agency referred the amended Draft Decision to the Member State Committee (hereinafter the 'MSC').

21. On 18 August 2014, the Appellant submitted its comments on the MSCAs' proposals for amendment. Since the proposals for amendment focused exclusively on the reproductive toxicity endpoint, the Appellant commented exclusively on that endpoint. The Appellant's comments were forwarded to the MSC for its consideration.

22. On 1 September 2014, the MSC reached unanimous agreement on the amended Draft Decision. On 28 November 2014, the Agency adopted the Contested Decision in accordance with Article 51(6). The Contested Decision, whilst not requiring a two-generation reproductive toxicity study or, alternatively, an EOGRTS, requires the Appellant to submit inter alia a sub-chronic toxicity study and a pre-natal developmental toxicity study by 5 December 2016.

Procedure before the Board of Appeal

23. The Appellant filed the present appeal on 27 February 2015.

24. On 4 May 2015, the Agency lodged its Defence requesting the Board of Appeal to dismiss the appeal as unfounded.

25. Following consultation with the Parties, the appeal proceedings were stayed between 23 June 2015 and 1 September 2015 in accordance with Article 25 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; hereinafter the 'Rules of Procedure').

26. The Appellant filed its observations on the Defence on 10 November 2015.

27. On 11 November 2015, following a change in the composition of the Board of Appeal, a new legally qualified member was appointed for this case.

28. On 26 January 2016, the Agency submitted its observations on the Appellant's observations on the Defence and responded to questions posed by the Board of Appeal.

29. On 5 February 2016, the Parties were notified of the Board of Appeal's decision to close the written procedure. On 16 February, the Appellant requested a hearing to be held. As a result, in accordance with Article 13 of the Rules of Procedure, the Parties were summoned to a hearing which was held on 19 April 2016. At the hearing, the Parties made oral presentations and responded to questions from the Board of Appeal.

Reasons

30. The Appellant puts forward five pleas in law in support of its appeal, alleging (i) a violation of essential procedural requirements, (ii) an infringement of substantive requirements under the REACH Regulation, (iii) a violation of animal welfare requirements, (iv) an infringement of the principle of proportionality and (v) an infringement of the principle of the protection of legitimate expectations.

The first plea, alleging a violation of essential procedural requirements under Articles 50 and 51

Arguments of the Parties

31. The Appellant claims, first, that the Agency acted in violation of Articles 50 and 51. It argues that '*its comments were not duly taken into account, as they are not reflected in the Contested Decision*'. In particular, the Contested Decision '*[does] not reflect the Appellant's formal comment, submitted to [the Agency] on 4 December 2013, such that the required 90-day sub-chronic toxicity study conducted by the oral route of exposure would not add any more information towards the hazard assessment than the existing 28-day sub-chronic toxicity study because a [derived no-effect level] cannot be derived from either study for the property of concern, respiratory sensitisation, this being the basis on which [4-MHHPA] has been identified [by the Agency as a substance of very high concern] in a parallel evaluation'*.

32. Second, the Appellant claims that, in violation of its right to be heard, it was given the opportunity to comment only on the amendments proposed by the MSCAs to the revised Draft Decision and not on the revised Draft Decision itself. This was despite the fact that the revised Draft Decision '*included significant and key new elements and*

raised new concerns' that formed the basis for rejecting the read-across adaptation. In particular, the Appellant was not given the opportunity to comment on the Agency's finding in the revised Draft Decision that toxicological effects for MA differ from those of the other cyclic anhydrides, on which the Agency based its conclusion that the Appellant had failed to show that structural differences among cyclic anhydrides only have a negligible influence on systemic toxicity. The Appellant notes that Articles 51(5) and 50(1) provide for the communication of '*any proposal for amendment*' and '*any draft decision*' prepared pursuant to Article 41(3) to the registrants concerned for their comments.

33. The Appellant adds that, if given the opportunity, it would have commented further on the Agency's refusal to accept the read-across adaptation and would have substantiated its view that the differences on toxicological effects seen between the cyclic anhydrides are likely to be a result of differences in dose levels investigated and experimental variability rather than due to structural differences.

34. The Appellant also questions whether the MSCAs received all of its comments on the Draft Decision since none of the MSCAs' proposals for amendment refer to the Appellant's arguments (see paragraph 31 above) relating to the derived no-effect level (hereinafter 'DNEL') as regards the sub-chronic toxicity study.

35. In response to the claim of the Appellant that the Agency ignored a comment relating to the sub-chronic toxicity endpoint, the Agency observes that the comment in question was not included in the Appellant's comments on the Draft Decision submitted on 4 December 2013. The Agency notes that the Appellant's comments to the Draft Decision in relation to the request for the sub-chronic toxicity study merely indicate that it '*will update the IUCLID file to include robust study summaries from analogue substances for the end-point together with a formal justification document for the use of read-across*'.

36. The Agency adds that it considered all of the Appellant's comments on the Draft Decision and all the additional information provided by the Appellant in its updated registration dossier.

37. The Agency further argues that the Contested Decision clearly explains why, for the purposes of sub-chronic toxicity, the 28-day study is not sufficient to meet the standard information requirement for a 90-day study. In a 28-day study the exposure duration is considerably shorter than 90 days and the number of animals per dose group is significantly lower, resulting in lower sensitivity. The Agency suggests that it may be for these reasons that the MSCAs did not submit proposals for amendment concerning the request for a sub-chronic toxicity study.

38. As regards the Appellant's claim that the Agency violated its right to be heard by not giving it an opportunity to comment on the revised Draft Decision, the Agency submits that, contrary to the Appellant's argument, the legal provisions clearly allow the Agency to limit the opportunity for a registrant to comment to the initial Draft Decision and any proposals for amendment made by MSCAs.

39. According to the Agency, the Appellant had all the opportunities foreseen by Articles 50 and 51 to make its views known. In addition, the Agency also provided the Appellant with the opportunity to clarify any unclear points in the Draft Decision by means of a teleconference. During the course of this teleconference the Agency granted the Appellant an additional two months to update its registration dossier in order to address the concerns identified in the Draft Decision. The Appellant duly

submitted an updated registration dossier. The Agency therefore effectively provided the Appellant with two opportunities to submit comments on the Draft Decision. All the information provided by the Appellant was taken into account in the decision-making process that lead to the Contested Decision.

40. The Agency adds that the revised Draft Decision reflects the information provided by the Appellant in its comments to the Draft Decision and in its updated registration dossier.

Findings of the Board of Appeal

(i) The first part of the first plea, concerning the alleged failure by the Agency to take the Appellant's comments into account

41. In support of the first part of the first plea the Appellant claims, first, that its comments on the Draft Decision were not taken into account by the Agency as they are not reflected in the Contested Decision. Second, the Appellant argues that the Agency did not notify its comments on the Draft Decision to the MSCAs because no MSCA made proposals for amendment as regards the requests of the contested studies.

42. In support of its first argument under the first part of the first plea, namely that its comments were not taken into account because they were not reflected in the Contested Decision, the Appellant explicitly identifies only one comment to which no response was given by the Agency (see paragraph 31 above). However, it must be observed that, as the Agency points out (see paragraph 35 above), this comment does not feature among the Appellant's comments under the heading concerning the sub-chronic toxicity study. Under this heading of the Appellant's comments of 4 December 2013, the Appellant merely states '*[it] will update the IUCLID file to include robust study summaries from analogue substances for the end-point together with a formal justification document for the use of read-across*.'

43. The Board of Appeal therefore finds that the Appellant's first argument in support of the first part of the first plea is factually incorrect because the Appellant did not make the comment in question. As a consequence, the argument cannot prosper.

44. For the sake of completeness, the Board of Appeal observes that the Appellant did submit a comment concerning the identification of the Substance as a Substance of Very High Concern (hereinafter 'SVHC') and the consequence of this for the information requests in the Draft Decision. That comment, which however related to the part of the Draft Decision concerning the PNDT endpoint and not the sub-chronic toxicity endpoint, was as follows: '*The registrant considers that, if [the proposal for identification of the Substance as an SVHC for respiratory sensitising properties] is accepted, the additional study/studies requested to identify a concern (or otherwise) for reproductive toxicity would not subsequently affect risk management or any restrictions that may be placed on use of the substance. The use of the significant number of animals that the requested study/studies would entail is therefore regarded as not being justifiable and higher tier animal tests should not be considered prior to clarification of the issues of equivalent concern to [carcinogenic, mutagenic or reproductive toxicant] status*.'

45. Even if the Appellant's first argument in support of the first part of the first plea (see paragraph 31 above) were to be understood as meaning that the Agency failed to take into account the comment concerning the PNDT endpoint (cited in the previous paragraph), the argument in question would be unfounded for the following reasons.

46. The Contested Decision actually answers the Appellant's comment in the following terms: '*A "pre-natal developmental toxicity study" for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.*' The Board of Appeal finds that this statement sufficiently explains the Agency's reason for the rejection of the Appellant's comment and that this demonstrates that the comment was addressed.

47. The succinct nature of the reasoning in the Contested Decision on the Appellant's comment (see paragraph 44 above) is, moreover, justified by the fact that the arguments upon which the Appellant relied consisted substantially in mere generic assertions and were not supported by concrete evidence of the link between the risk management measures implemented with regard to the sensitising properties of the Substance and the need to investigate its reproductive toxicity potential (see, by analogy, Case T-190/06, *Total and Elf Aquitaine* v *Commission*, EU:T:2011:378, paragraph 154).

48. The Board of Appeal observes furthermore that an appellant cannot merely assert that the Agency did not take its comments into account without providing evidence to demonstrate the veracity of that assertion. The fact that the Agency did not accept the claim that the 90-day sub-chronic toxicity study would not add '*any more information towards the hazard assessment than the existing 28-day sub-chronic toxicity study*' is in any event insufficient to demonstrate that the Agency did not carefully examine the comments made. The Appellant cannot confuse failure to observe the rights of the defence with failure to obtain the desired result by the exercise of those rights (see Case T-483/11, *Sepro Europe* v *Commission*, EU:T:2013:407, paragraph 78, and the case-law cited).

49. For all the reasons stated in paragraphs 42 to 48 above, the Board of Appeal rejects the Appellant's first argument in support of the first part of the first plea.

50. The Appellant further claims in support of the first part of the first plea that '*it is doubtful*' whether its comments during the compliance check procedure were forwarded to the MSCAs. The Appellant bases this claim on the fact that the MSCAs made no proposals for amendment regarding the requirement for sub-chronic toxicity and pre-natal developmental toxicity studies.

51. The Board of Appeal observes however that the fact that the MSCAs did not propose any amendments relating to sub-chronic toxicity and pre-natal developmental toxicity demonstrates, if anything, that the MSCAs agreed with the content of the revised Draft Decision as far as these two endpoints are concerned.

52. The Board of Appeal finds therefore that the Appellant's second argument in support of the first part of the first plea must also be rejected.

53. As a subsidiary point, the Board of Appeal observes that the Contested Decision is confusingly drafted insofar as its statement of reasons is not worded as a single and coherent analysis. The statement of reasons in the Contested Decision repeats first

the text of the initial Draft Decision and then adds text relating to the Appellant's comments and the Agency's assessment of those comments. It is possible that this way of drafting the Contested Decision may have given the Appellant the impression that some of its comments were not taken into account. For the reasons set out above, however, this does not call into question the legality of the Contested Decision.

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

(ii) The second part of the first plea, concerning the alleged infringement of the Appellant's right to comment on the revised Draft Decision

55. By the second part of its first plea the Appellant claims that the Agency failed to provide the Appellant with an opportunity to comment on the revised Draft Decision, thereby breaching Articles 50 and 51 as well as the Appellant's right to be heard.

56. It is necessary, in this regard, for the Board of Appeal to examine first whether the REACH Regulation provides registrants with a right to comment on the different drafts of a decision during a compliance check procedure.

57. The Appellant bases its claim on the wording of Articles 50(1) and 51(5).

58. First, as regards the Appellant's claim that it should have been allowed to comment on the revised Draft Decision under Article 50(1), the Board of Appeal recalls that this provision, which concerns registrants' and downstream users' rights, states that '*[t]he Agency shall notify any draft decision under Articles 40, 41 or 46 to the registrant(s) or downstream user(s) concerned, informing them of their right to comment within 30 days of receipt. If the concerned registrant(s) or downstream user(s) wish to comment, they shall provide their comments to the Agency. The Agency in turn shall inform the competent authority of the submission of the comments without delay. The competent authority (for decisions taken under Article 46) and the Agency (for decisions taken under Articles 40 and 41) shall take any comments received into account and may amend the draft decision accordingly*.'

59. Contrary to the Appellant's claim (see paragraph 32 above), Article 50(1) does not oblige the Agency to request comments from the concerned registrants on all amended drafts following the first draft of a compliance check decision. When read in context, it is evident that the words '*any draft decision*' in Article 50(1) refer to draft decisions adopted under Articles 40, 41 or 46, which is to say draft decisions concerning the examination of testing proposals, the compliance check of registrations and requests for further information during the course of substance evaluation. Article 41(3) in particular provides that, on the basis of an examination of the information provided upon registration, the Agency may '*prepare a draft decision requiring the registrant(s) to submit any information needed to bring the registration(s) into compliance with the relevant information requirements and specifying adequate time limits for the submission of further information. Such a decision shall be taken in accordance with the procedure laid down in Articles 50 and 51*.' There is nothing in Articles 41 and 50(1) to suggest that the Agency is required, under those procedural provisions, to invite registrants to comment on subsequent revised versions of an initial draft decision.

60. Second, as regards the Appellant's argument that it was not allowed to comment on the revised Draft Decision at the time it commented on the proposals for amendment submitted by the Member States, the Board of Appeal notes that Article 51(1)

provides that '*[t]he Agency shall notify its draft decision in accordance with Articles 40 or 41, together with the comments of the registrant, to the competent authorities of the Member States*'. This provision must be read in conjunction with Articles 41(3) and 50(1) (see paragraphs 58 and 59 above), to the effect that the Agency shall notify its draft decision, revised if necessary in light of the comments submitted by the registrant, to the MSCAs.

61. In accordance with Article 51(2), '*[w]ithin 30 days of circulation, the Member States may propose amendments to the draft decision to the Agency*'. In accordance with Article 51(5), '*[t]he Agency shall forthwith communicate any proposal for amendment to any registrants or downstream users concerned and allow them to comment within 30 days. The Member State Committee shall take any comments received into account*.' Contrary to the Appellant's claim, these provisions must be understood as giving an appellant the opportunity to comment on any proposals for amendment to the draft decision and not once more on the draft decision itself (see Case A-009-2014, *Albemarle Europe and Others*, Decision of the Board of Appeal of 12 July 2016, paragraph 222 and the previous decision cited therein).

62. The Board of Appeal finds therefore that it is not the objective of Articles 50(1) and 51(5) to allow a registrant to comment repeatedly on the Agency's assessment, as reflected in successive drafts of the decision. Indeed, if the Appellant's argument was accepted and comments were to be requested after every revision of a draft decision, in light of the registrant's previous comments, the evaluation procedure could potentially develop into an endless commenting exercise.

63. In the present case, the Appellant was given a possibility to comment on the Draft Decision pursuant to Article 50(1), as well as on the proposals for amendment submitted by the MSCAs pursuant to Article 51(5). The Board of Appeal therefore finds that the Agency did not depart from the procedure set in place by the legislator in the evaluation title of the REACH Regulation. In these circumstances the right to be heard must normally be deemed to have been respected (see, to that effect and by analogy, Joined Cases C-121/91 and C-122/91, *CT Control (Rotterdam) and JCT Benelux* v *Commission*, EU:C:1993:285, paragraph 49, Case C-177/00, *Italy* v *Commission*, EU:C:2003:6, paragraphs 23 to 25, and Case T-84/09, *Italy* v *Commission*, EU:T:2012:471, paragraphs 24 to 30).

64. The Board of Appeal observes, however, that Articles 50 and 51 do not make provision for a situation such as the one which the Appellant claims to be at issue in the present case, namely if the Agency revises a draft decision and includes new elements and concerns which were not contained in the initial draft decision.

65. The Board of Appeal considers that in certain circumstances it is possible that the addressees of a decision should be given the opportunity to comment beyond the opportunities foreseen in Articles 50 and 51 (see, to that effect, the decision in *Albemarle Europe and Others*, cited at paragraph 61 above, paragraph 225).

66. In order to identify whether the circumstances of the present case required that the Appellant be given further opportunities to comment, the Board of Appeal notes that, according to the Appellant, the revised Draft Decision contained '*significant and key new elements and raised new concerns*' on which it should have been given the opportunity to comment. In particular, the Appellant identifies one issue raised by the Agency in the revised Draft Decision which the Appellant considers was new.

67. The new issue, according to the Appellant, is the Agency's statement that toxicological effects for MA differ from those of other cyclic anhydrides. According to the Appellant, '*[it] was never given an opportunity to comment on what formed the basis of the final decision rejecting the read-across approach and requiring the contested data*'. In this regard, the Appellant notes that, if it had been given the opportunity to comment, it could have shown that '*renal effects were noted in sub-acute toxicity studies on [HHPA] and [THPA] although the incidence/severity of such effects was such that they could not be definitively linked to treatment*'. Furthermore, the Appellant would have shown that '*the renal effects observed in the sub-chronic 90-day study with MA were not observed with the same incidence/severity in a chronic study with the same substance*'.

68. As regards the differences in toxicological properties that may arise from structural differences among cyclic anhydrides, the Board of Appeal observes that the Agency had already stated in the initial Draft Decision that it considered that the Appellant had '*not provided and documented a read-across justification assessing the structural similarity and a systematic comparison of toxicological properties [upon registration] and thus, the requirements in Annex XI, Section 1.5 have not been fulfilled*'. The Agency gave the Appellant an opportunity to substantiate its read-across proposal and offered further assistance by organising a teleconference to discuss the Draft Decision. In the teleconference, the Agency clearly identified that it considered that there are structural differences between the source substances themselves and the target substance and that these differences had not been adequately addressed by the Appellant. The minutes of the teleconference of 20 November 2013 demonstrate this as the Agency pointed out that a '*hypothesis for the read-across and the justifications have to, inter alia: […] consider the structural dissimilarities between the substances and how those affect the read-across*'.

69. In its comments to the Draft Decision, the Appellant merely indicated that it would '*update the IUCLID file to include robust study summaries from analogue substances for the end-point together with a formal justification document for the use of read-across*' (see paragraph 9 above), which it subsequently did. The updated dossier contained a justification for using read-across as an adaptation. As regards the issue of the structural dissimilarities, the Appellant indicated that *'[s]tructural differences such as the level of saturation in the ring structure, presence or different location of substituted functional group are expected to have no or only negligible influence with regard to eco- and systemic toxicity*'.

70. The Board of Appeal observes that the Agency carried out an assessment of the updated registration dossier (see paragraph 13 above). As a result of that assessment, the Agency could either abandon the request for sub-chronic toxicity and PNDT studies if the Appellant had shown that such requests were unfounded, as a result for example of an adequately justified read-across, or revise its arguments in support of those study requests.

71. In consequence of its assessment the Agency found that the request for sub-chronic toxicity and PNDT studies in the Draft Decision were still valid as the proposed read-across was not sufficiently justified. The Agency did not modify its initial opinion that the provided information was insufficient.

72. As regards the renal effects observed in studies on MA, the Board of Appeal notes that the information which the Agency took into account in concluding that the toxicological effects for MA differ from those of other cyclic anhydrides was supplied by the

Appellant itself. Thus, what the Appellant seems to be arguing is that the Agency should have warned it of its intention to rely on the information which the Appellant had itself provided by its dossier update and to give the Appellant an opportunity to comment on the assessment made on the basis of that information. However, a party which itself submitted the facts in question was by definition in a position to state their possible relevance to the resolution of the case at the time when it submitted them (see, by analogy, Case T-392/09, *1. garantovaná* v *Commission*, EU:T:2012:674, paragraph 79 and the case-law cited).

73. In addition, nothing prevented the Appellant from providing more detailed or additional information concerning the justification for its read-across, such as the information which it supplied during the course of this appeal (see paragraph 133 below), at the same time as it provided its dossier update.

74. In light of the above, the Board of Appeal finds that, whilst the Agency revised its arguments in support of the request for sub-chronic toxicity and PNDT studies in response to the comments of the Appellant and the update of the registration dossier, the Agency did not take into account any information which the Appellant had not itself submitted or on which it did not have the possibility to comment before or during the compliance check procedure.

75. In addition, the Board of Appeal observes that the information relating to the read-across in the updated dossier should already have been included in the registration dossier when it was first submitted. In that case, the Agency would have had the possibility to assess this information and include its conclusions on it in the Draft Decision, on which the Appellant would then have been able to comment in accordance with Articles 50 and 51. However, the Appellant did not submit this information at the time of its initial registration of the Substance and thereby reduced of its own volition the possibility to respond to the assessment of the Agency.

76. The Board of Appeal therefore finds that the Appellant had sufficient opportunity to make known its views effectively on all the matters of fact and law which formed the basis for the Contested Decision. The Agency did not violate essential procedural requirements under Articles 50 and 51 or the Appellant's right to be heard.

77. The Appellant's first plea is therefore rejected in its entirety.

The second plea, alleging the infringement of substantive requirements under the REACH Regulation

Arguments of the Parties

78. By its second plea, the Appellant claims that the Contested Decision breaches Section 8.7 of Annex IX in so far as it requires it to perform a PNDT study. In the Appellant's view, such a study does not need to be performed on substances which are deemed to raise an equivalent level of concern to a substance which is carcinogenic, mutagenic or a reproductive toxicant (hereinafter 'CMR').

79. The Appellant points out that, by a parallel procedure, the Agency has already identified the Substance as a SVHC in accordance Article 57(f) due to its properties as a respiratory sensitiser raising an equivalent level of concern to a substance which has CMR properties. As the Substance has already been identified as a SVHC with regard

to its respiratory sensitising properties, the Appellant argues that there is no benefit to be derived from further hazard assessment as the most stringent risk management measures are already in place to protect users from the sensitisation hazard. The Agency cannot require a PNDT study to be performed without being inconsistent with its earlier finding that the adverse effects of the Substance are equivalent to it having CMR properties.

80. The Agency takes the view that the identification of the Substance as a SVHC due to its respiratory sensitising properties has no relevance to assessing the compliance of the registration dossier with the standard information requirements generally and the requirement for a pre-natal developmental toxicity study in particular.

81. First, the Agency argues that the identification of the Substance as a SVHC cannot render the registration dossier compliant with the standard information requirement for a PNDT study. A PNDT study provides information concerning the effects of prenatal exposure on pregnant test animals and on developing organisms. Neither the classification of the Substance as a respiratory sensitiser category 1 in accordance with Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (OJ L 353, 31.12.2008, p. 1) nor its identification as a SVHC due to its respiratory sensitising properties provide information on the reproductive toxicity of the substance.

82. Second, the second column of Section 8.7 of Annex IX does not provide that the requirement to submit a PNDT study can be waived if a substance has been identified as a SVHC because its respiratory sensitising properties raise an equivalent level of concern to a substance which has CMR properties.

83. The Agency also notes that the Appellant has not provided any evidence that the risk management measures it has put in place in order to address the respiratory sensitising properties of the substance would also be sufficient to address any potential reproductive toxicity.

Findings of the Board of Appeal

84. The present plea is directed against the Contested Decision in so far as it requires the Appellant to perform a PNDT study. As a preliminary remark, the Board of Appeal observes that such a study constitutes a standard information requirement for registration of the Substance for the Appellant's tonnage band in accordance with Section 8.7.2 of Annex IX.

85. The specific rules for adaptation contained in the second column of Section 8.7 of Annex IX (hereinafter the 'Column 2 adaptation') allow registrants to waive the requirement to submit studies on reproductive toxicity, including the PNDT study required by Section 8.7.2 of Annex IX, 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.'

86. The Board of Appeal notes that the Agency has found that, due to its respiratory sensitising properties, the Substance raises an equivalent level of concern to a substance with CMR properties and accordingly identified the Substance as a SVHC in accordance with Articles 57(f) and 59.

87. The Board of Appeal also observes that, contrary to the Appellant's assertion, the Column 2 adaptation contains a closed list of conditions which, if fulfilled, relieve registrants of the obligation to conduct studies on reproductive toxicity. The Column 2 adaptation allows the PNDT study to be waived *inter alia* for substances which are already known to be a genotoxic carcinogen or a germ cell mutagen, to have adverse effects on fertility or to cause developmental toxicity. In essence, pursuant to the Column 2 adaptation no further testing is required on reproductive toxicity if a Substance is already known to cause adverse effects to reproduction.

88. It is therefore apparent that the Column 2 adaptation does not make provision for waiving the requirement to conduct studies on reproductive toxicity on the basis that a substance has been identified as a SVHC due to its respiratory sensitising properties.

89. Indeed, the fact that the Substance has respiratory sensitising properties gives no indication as to its reproductive toxicity and therefore cannot justify the waiving of a requirement to provide standard information on the Substance's potential to cause reproductive toxicity.

90. As a consequence, the requirement to perform the study at issue cannot be waived under the Column 2 adaptation simply on the basis that the substance is a respiratory sensitiser. The Appellant's argument to that effect must be rejected.

91. 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, so that there is no benefit to be gained by further testing.

92. First, it must be pointed out that the Appellant's argument that there is no benefit to be derived from further hazard assessment and that it is therefore not obliged to perform the requested PNDT study is unfounded both in law and in fact.

93. 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 the Column 2 adaptation (quoted at paragraph 85 above), 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.

94. The Board of Appeal also notes that 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 a PNDT study may, in principle, lead to or affect authorisation and restriction decisions regarding the Substance or may lead to different risk management measures being required.

95. 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 pre-natal developmental toxicity.

96. Second, the Board of Appeal recalls that the compliance check procedure ensures that the standard information required by the REACH Regulation is provided by registrants.

97. In this case, the Agency performed a compliance check and found that this dossier did not comply with the standard information requirements regarding inter alia reproductive toxicity.

98. As a consequence, and because it is standard information that is missing, the Agency did not have any discretion as to whether to request this information or not. It has to be provided according to the REACH Regulation. Therefore, the Appellant's argument that stringent risk management measures are already in place to protect users from the sensitisation hazard, and that there is no benefit to be gained by further testing, is irrelevant.

99. The Appellant's second plea is therefore rejected.

The third and fourth pleas, alleging the violation of animal welfare requirements and the infringement of the principle of proportionality

100. The Board of Appeal observes that the claims and arguments put forward by the Appellant and the Agency in relation to the third and the fourth pleas overlap to a large extent. By raising these two pleas, the Appellant contests in essence whether the Agency's decision to reject the proposed read-across adaptation is well-founded. It is therefore appropriate to examine the third and fourth pleas together.

Arguments of the Parties

101. The Appellant argues that the Contested Decision requires it to perform a sub-chronic toxicity study '*despite the fact that such a study would not address the property of concern, which is respiratory sensitisation*'. As the study would not provide new information to support the hazard and risk assessment of the Substance, and as the oral route of administration is not appropriate for testing a respiratory sensitiser, the request breaches the principle of proportionality as well as Articles 13(1) and 25.

102. The Appellant submits that in the present case the use of a read-across adaptation would have provided a valid alternative to vertebrate animal testing. Had the Appellant been given sufficient opportunities to comment, in particular on the difference in toxicological effects between MA and the other cyclic anhydrides, and had the Agency fully assessed whether additional vertebrate animal testing was needed, the Agency would have accepted the Appellant's read-across approach in accordance with the legal requirement to minimise animal testing.

103. The Appellant further claims that the request in the Contested Decision for additional testing on vertebrate animals, regarding both the PNDT study and the sub-chronic toxicity study, is disproportionate. In particular, the Appellant argues that the request to perform the two studies at issue is not necessary as the Agency did not demonstrate that there was a potential risk, that this risk needed to be clarified and that the requested information had a realistic possibility of leading to improved risk management measures. Moreover, in the Appellant's view, the read-across adaptation provided in its dossier constitutes a less onerous alternative to performing the requested studies.

104. As regards the rejection by the Agency of the Appellant's proposed read-across adaptation, the Appellant argues that the differences in toxicological effects, seen between the cyclic anhydrides, on which the Agency based its decision, are likely to be a result of differences in the dose levels investigated and experimental variability rather than due to structural differences.

105. First, the Appellant contests the Agency's conclusion that the read-across adaptation could not be accepted because renal effects are only seen in studies on MA, but not with the other cyclic anhydrides. The Appellant argues that renal effects were also noted in sub-acute toxicity studies on HHPA and THPA although the incidence and severity of such effects was such that they could not be definitively linked to '*treatment*'. Moreover, according to the Appellant, renal effects observed in a sub-chronic toxicity study (90-day) with MA were not observed with the same incidence and severity in a 2-year chronic toxicity study with the same substance. The Appellant therefore concludes that there is evidence of a common effect and that the differences in the effects seen on the various cyclic anhydrides are likely to be a result of differences in dose levels investigated and experimental variability rather than due to structural differences. The Appellant further notes that the renal effects observed in the sub-chronic toxicity study (90-day) with MA occurred at high exposure levels and it is very likely that such effects in the kidney may also become apparent at higher exposure levels with other cyclic anhydrides, as the findings in a study with HHPA suggest.

106. Second, the Appellant observes that, for studies of the same duration, the No Observed Effects Level (hereinafter 'NOEL') for the cyclic anhydrides is within a relatively narrow range of 0.18 - 0.66 mmol/kg bw/day (approximately 30 - 100 mg/kg bw/day), suggesting that exposure levels at which toxicological effects occur are similar and that those effects are therefore triggered by the reactive moiety (the anhydride group) and not by the side chain.

107. With regard to the alleged breach of animal welfare requirements, the Agency acknowledges that Article 13(1) allows information on intrinsic properties of a substance to be generated by means other than animal tests, provided that the conditions for a column 2 adaptation or the rules set out in Annex XI are met. However, the REACH Regulation requires information to be generated through

experimental studies where these conditions are not met. This is the outcome of the compliance check leading to the Contested Decision. In the Agency's view, the Appellant did not fulfil the information requirements, in particular because it did not provide valid adaptations pursuant to Annex XI. As a consequence, the Agency was obliged to request the studies in the Contested Decision and did not breach Articles 13 or 25.

108. As regards the alleged breach of the principle of proportionality, the Agency notes that the conditions for adapting the standard information requirements in question were not met in the registration dossier, including its update. Therefore, the Agency could only request the Appellant to provide information to fulfil these standard information requirements.

109. As regards the reasons for rejecting the Appellant's read-across adaptation, the Agency claims that certain pieces of evidence submitted by the Appellant during the course of the appeal proceedings, namely summaries of repeated-dose studies investigating systemic toxicity in several of the source substances, are inadmissible as they are not intended to support facts already alleged during the decision-making procedure.

110. In any event, according to the Agency, this information is insufficient to justify the read-across. The renal effects observed in the 2-year chronic toxicity study conducted with MA are more severe than those observed in the 90-day sub-chronic toxicity study on the same substance. However, it is typical of chronic toxicity studies that the longer the exposure period the more severe the effects. Moreover, the study results on HHPA and THPA, on sub-acute toxicity, were not considered by the Agency during the original assessment of the read-across approach as those studies were not provided in the registration dossier for the Substance, and no information other than the NOEL and/or No Observed Adverse Effect Level (hereinafter 'NOAEL') values obtained from these studies was mentioned in the read-across justification document.

111. The Agency further notes that, '*in the read-across approach in general, the identification of just one common effect would not be sufficient to predict the toxicity of the target substance from the toxicity observed in a study with a source substance. Other effects – additional to such common effect – may occur. Without clearly explaining why the differences in the chemical structures of the substances under consideration would not lead to such other effects, the prediction cannot be accepted*.'

112. Moreover, the Agency notes that the grouped substances are structurally different from one another. The Appellant has not shown that the structural differences do not impact systemic toxicity.

113. The Agency therefore argues that, based on the available data, the toxicological profiles of the grouped substances are not similar and that there seems to be no evident pattern in the toxicity of the grouped substances, suggesting that the structural differences may affect toxicity. It is consequently not possible to predict the properties of the Substance on the basis of the data obtained from the source substance, MA.

114. Finally, the Agency points out that the Contested Decision still allows the Appellant to adapt the information requirements in lieu of performing the requested studies. The Contested Decision states, *'[t]he Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure*

compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.' The Contested Decision does not prevent the Appellant from exploring ways other than testing on vertebrate animals to address the data gaps identified in the Contested Decision.

Findings of the Board of Appeal

115. By its third and fourth plea the Appellant claims, in essence, that the Agency was not justified in rejecting its proposed read-across. As a consequence, according to the Appellant, the Contested Decision breaches Articles 13(1) and 25 in so far as it requests a sub-chronic toxicity study, and the principle of proportionality in so far as it requests a sub-chronic toxicity study and a PNDT study.

116. The Board of Appeal observes at the outset that, contrary to the Appellant's argument (see paragraph 101 above), the request for a sub-chronic toxicity study in the Contested Decision is not aimed at providing information relating to respiratory sensitisation. Instead, it is apparent from the Contested Decision that the request for a sub-chronic toxicity study is intended to address the absence of adequate information in the Appellant's dossier on the sub-chronic toxicity endpoint.

117. The Board of Appeal further notes that the requirement to submit certain information for registration purposes stems directly from the REACH Regulation.

118. Moreover, the dossier evaluation provisions allow the Agency to check whether registrations are in compliance with the information requirements set out in the REACH Regulation. The discretionary powers of the Agency are therefore limited to examining whether a read-across adaptation submitted in a registration dossier complies with the rules governing adaptations set out in Annex XI. If the Agency finds that a read-across adaptation does not comply with these rules, it must require the performance of the relevant test or tests in order to satisfy the information requirements established in the REACH Regulation.

119. However, the wrongful rejection of a read-across on the part of the Agency would require a registrant to perform unnecessary testing on vertebrate animals, thereby leading to a breach of the principle of proportionality as well as the rules concerning animal welfare set out in Articles 13(1) and 25 (see, to that effect, Case A-006-2012, *Momentive Specialty Chemicals*, Decision of the Board of Appeal of 13 February 2014, paragraphs 96 to 99 and 118).

120. In order to decide on the Appellant's claim that the Contested Decision breaches Articles 13(1) and 25 in so far as it requires the Appellant to perform a sub-chronic toxicity study, and that the Contested Decision breaches the principle of proportionality in so far as it requires the Appellant to perform a sub-chronic toxicity study and a pre-natal developmental toxicity study, the Board of Appeal therefore needs to examine whether the Agency was justified in rejecting the read-across proposed by the Appellant on the basis that the conditions of Annex XI were not met.

121. In the present case, the Appellant proposes to read-across the information on sub-chronic toxicity and pre-natal developmental toxicity relating to the Substance from other cyclic acid anhydrides in the same group, namely the source substances MTHPA, HHPA, THPA, PA, TMA and MA (see paragraph 11 above).

122. The Board of Appeal notes, in this regard, that Annex XI sets out the general rules for adaptation of the standard testing requirements. Section 1.5 of Annex XI provides as follows:

'*Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). This avoids the need to test every substance for every endpoint. […]*

The similarities may be based on:

(1) a common functional group;

(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or

(3) a constant pattern in the changing of the potency of the properties across the category. […]'

123. The Board of Appeal considers that, when relying on a read-across adaptation to satisfy a standard information requirement, registrants bear the burden of establishing that the proposed read-across adaptation complies with the conditions set out in Section 1.5 of Annex XI. Whilst registrants can expect a certain level of expertise within the Agency, it is not the task of the Agency to develop, or improve, read-across adaptations on their behalf. Registrants should in particular explain the premise for the read-across adaptation proposed, for example by creating an implicit or explicit hypothesis, and then show that the evidence supports that premise within the legal requirements of the REACH Regulation. It is then the Agency's task to examine whether registrants have in fact satisfactorily achieved this (see *Momentive Specialty Chemicals*, cited in paragraph 119 above, paragraph 60).

124. In the present case, the Appellant's read-across proposal is based, first, on the premise that the substances in the read-across group, namely the source substances and the Substance, are structurally similar in that despite some structural differences they have a common functional group (a 5-member ring carboxylic acid anhydride). Neither party disputes the fact that the substances in the read-across group share a common functional group.

125. The second premise of the Appellant's read-across adaptation is that the common functional group is responsible for the toxicity of the substances in the read-across group. According to the Appellant, the structural differences which exist between these substances have no, or only a negligible, influence on toxicity.

126. Contrary to the Appellant's argument, the Agency takes the view that the Appellant has not established the validity of the second premise. In particular, the Agency points out that there are structural differences among the grouped substances which could have an influence on toxicity. First, according to the Agency, the test results relating to MA indicate renal effects while the results for the other source substances do not. Second, the NOAELs for the source substances have a high variability. In the absence of an explanation on those two points by the Appellant, the Agency argues that it was entitled to reject the read-across adaptation.

127. The Board of Appeal recalls in this regard that, during the course of the compliance check procedure, and in particular during the teleconference with the Appellant before the latter submitted its comments and updated its registration dossier, the Agency pointed out that there is a need to address concerns regarding the possible impact of structural differences on the properties of the cyclic anhydrides. The minutes of that teleconference state that the Agency pointed out that the read-across justification to be submitted by the Appellant '*has to fulfil the requirements set in Annex XI, Section 1.5. Thus, a hypothesis for the read-across and the justifications have to, inter alia: […] consider the structural dissimilarities and how those affect the read-across, consider toxicokinetics/metabolism of the substances [and] substantiate all claims with data […]*.' The minutes of the teleconference further state that the Agency reminded the Appellant that it should '*provide a data matrix comparing the relevant physicochemical, toxicological and ecotoxicological data between the registered substance and the analogues [sic] substances and thus supporting the argument that the toxicological properties for the endpoints in question can be predicted from data existing on the analogue substance(s)*'.

128. The Board of Appeal therefore considers that, without prejudice to its assessment, the Agency made the Appellant fully aware of the information which it needed to provide in order to justify the proposed read-across.

129. However, it is apparent from the Contested Decision and from the information submitted by the Parties during these proceedings that the Appellant has neither explained the variability between the NOAELs for the cyclic anhydrides, nor established that the structural differences between the members of the grouped substances do not lead to different toxicological effects. In particular, the Appellant has not explained why studies on MA show renal effects which are absent from studies on the other cyclic anhydrides.

130. First, as regards the difference in NOAELs which, according to the values presented in the read-across justification for sub-acute repeated dose toxicity studies, range from 100 to 1250 mg/kg, the Appellant confined itself to stating that the lowest value, namely 100 mg/kg for MTHPA, '*was based on local effects (irritation of the stomach mucosa) probably arising from pH effects of the di-acid degradation product. When systemic toxicity is considered the [NOAEL] can be regarded as being markedly higher*.' The Board of Appeal notes, however, that the second lowest NOAEL reported in the read-across justification is 300 mg/kg, which still leaves an unexplained range in NOAELs of 300 to 1250 mg/kg. During the course of these appeal proceedings the Appellant has failed to explain the reason behind this difference.

131. The Board of Appeal therefore finds that the Appellant has not explained the difference between the NOAELs for the grouped substances.

132. Second, the Board of Appeal observes that the Appellant has not explained, during the course of the compliance check procedure or these appeal proceedings, why studies on MA show renal effects which are absent in studies on the other source substances.

133. In this context, the Appellant submitted certain study summaries, including summaries of studies on HHPA and THPA, with the Notice of Appeal. As a preliminary point, the Board of Appeal notes that the Agency objects to the admissibility of these study summaries. This evidence is however intended to demonstrate that HHPA and THPA also cause kidney effects and that the source substances and the Substance are therefore likely to have similar toxicological effects. This new evidence is consequently

intended to support facts previously alleged during the decision-making procedure and is therefore admissible (see *Momentive Specialty Chemicals*, cited in paragraph 119 above, paragraph 36; Case A-007-2012, *Italcementi Fabbriche Riunite Cemento*, Decision of the Board of Appeal of 25 September 2013, paragraph 51; Case A-001-2012, *Dow Benelux*, Decision of the Board of Appeal of 19 June 2013, paragraph 46).

134. Regardless of whether this new evidence is admissible, according to the Agency, those studies do not demonstrate that HHPA and THPA also cause kidney effects. In this regard, the Board of Appeal notes that the Appellant concedes that '*the incidence/severity of [the observed renal effects in HHPA and THPA] was such that they could not be definitely linked to treatment*'.

135. The Board of Appeal further observes that renal effects were observed in the control group in the studies on HHPA and THPA and that the findings of those studies therefore cannot be considered as reliable evidence that renal effects are caused by HHPA and THPA. The Appellant did not rebut this finding when this point was put to it by the Board of Appeal at the oral hearing.

136. In addition, the Board of Appeal notes that the Appellant has not demonstrated that kidney effects were observed in the studies conducted with the other source substances, even though some of those studies were conducted at higher doses than those used in the MA studies. In light of these observations, the Board of Appeal finds that the Appellant has not established that the observed differences in the toxicity profile of the cyclic anhydrides with regard to renal effects should be attributed to study designs and experimental variability rather than to the structural differences between the different substances. The Appellant has therefore not established that the grouped substances are likely to have similar toxicological properties as a result of a structural similarity within the meaning of Section 1.5 of Annex XI.

137. For the reasons stated in paragraphs 121 to 136 above, the Board of Appeal finds that the Agency did not commit an error in rejecting the read-across adaptation proposed by the Appellant on the basis that the conditions of Section 1.5 of Annex XI were not met. In particular, given the unexplained differences between the NOAELs for the grouped substances, and the unexplained differences in renal effects between those substances, the Appellant has not adequately justified the premise that the structural differences between the grouped substances do not cause different toxicological effects.

138. As a consequence, the Agency had no discretion as to whether to request the Appellant to perform the sub-chronic toxicity test, which is a standard information requirement under Section 8.6.2 of Annex IX. Consequently, contrary to the Appellant's claims under its third plea, the Agency did not breach the animal welfare requirements in Articles 13(1) and 25 by requesting a sub-chronic toxicity study.

139. Moreover, as regards the Appellant's argument that the oral route of administration is not appropriate for testing a respiratory sensitiser and that the request to perform a sub-chronic toxicity study is therefore unjustified, the Board of Appeal reiterates that the request for the study is not predicated on a concern regarding respiratory sensitisation, but on the legal obligation to produce information regarding the sub-chronic toxicity of the substance (see paragraph 116 above). As the Agency correctly points out, whilst the Substance is already classified as a respiratory sensitiser it is still necessary to evaluate the systemic toxicity of the Substance. The arguments raised by the Appellant concerning the most appropriate route of administration are

therefore irrelevant to the assessment of the legality of the request for a sub-chronic toxicity study.

140. Finally, as regards the Appellant's fourth plea, alleging a breach of the principle of proportionality by the Agency in requesting a sub-chronic toxicity study and a PNDT study as these studies are not necessary and less onerous measures are available, the Board of Appeal recalls that the studies at issue constitute standard information which must be provided under Sections 8.6.2 and 8.7.2 of Annex IX. The Board of Appeal further recalls its finding, at paragraph 137 above, that the Agency did not commit an error in rejecting the read-across adaptation proposed by the Appellant. Once the Agency had rejected the proposed read-across, it enjoyed no margin of discretion as to whether to request a pre-natal developmental toxicity study and a sub-chronic toxicity study. Consequently, it did not breach the principle of proportionality by requesting the studies to be performed (see, by analogy, Case T–637/11, *Euris Consult* v *Parliament*, EU:T:2014:237, paragraph 101).

141. The Appellant's third and fourth pleas are therefore rejected.

The fifth plea, alleging the infringement of the principle of the protection of legitimate expectations

Arguments of the Parties

142. By its fifth plea, the Appellant argues that it had a legitimate expectation that its read-across adaptation from the source substances to the Substance would be accepted because, in a parallel decision, the Agency has accepted, and relied on, data relating to closely related cyclic acid anhydrides, such as HHPA, for the purposes of identifying the Substance as a SVHC under Articles 57(f).

143. That expectation was reinforced by the fact that the Appellant has simply applied the Agency's own Guidance on Grouping of Substances and Read-Across Approach: Part 1: Introductory Note, 2013 (hereinafter the 'Grouping Guidance'). Section 3.2 of the Grouping Guidance states that the hypothesis for the read-across should describe *'the characteristics defining the structural similarities between the source and target substances and any other similarities identified: similarity in breakdown products, or similarities in modes of action'*.

144. Based on the Grouping Guidance, the Appellant concluded that as the grouped substances all have the same classification, a similar structure and the same modes of action, information relating to one substance can be transposed to another substance within that group. That argument was also used by the Agency in the context of the SVHC identification procedure. However, according to the Appellant, the Agency concluded in the present case that structural differences between the members of the grouped substances prevent the use of read-across in this instance, thereby contradicting its own reasoning behind the inclusion in the candidate list of 4-MHHPA as a SVHC.

145. With regard to the Appellant's argument that the Agency has accepted and relied on data on some of the source substances in order to identify the Substance as a SVHC, the Agency states that the Appellant is wrong in claiming that the Agency used a read-across approach to identify the Substance as a SVHC using data for HHPA. The Agency argues that the Appellant appears to be confusing the concept of read-across, which

involves using data on one or more substances to predict the properties of another, with the concept of cross-reactivity between sensitising substances.

146. The Agency is of the opinion that it is evident from the supporting documents to the decision identifying 4-MHHPA as a SVHC that a read-across approach was not used to determine the sensitising properties of 4-MHHPA. Instead, real case data was used which reported the effects observed in individuals who were exposed to HHPA or 4-MHHPA, or both. One issue that increased the concern in relation to these substances is cross-reactivity. In this context cross-reactivity means that if an individual becomes sensitised to, for example, 4-MHHPA and is later exposed to HHPA, the individual could develop clinical symptoms up to and including occupational asthma. It is therefore cross-reactivity between the substances that has been important in the SVHC identification process and not the use of a read-across approach.

147. With respect to the Appellant's argument that it applied the Agency's own guidance, the Agency acknowledges that section 3.2 of the Grouping Guidance mentions that the hypothesis for the read-across should describe the characteristics defining the structural similarities between the source and target substances and any other similarities identified.

148. However, according to the Agency, it is very clear from the Grouping Guidance that the structural similarity of the target and source substances cannot be simply assumed but that the similarity needs to be assessed and justified in detail. For example, section 3.4 of the Grouping Guidance clearly provides that the impact of the structural differences between the target and source substances on the endpoint under consideration also needs to be assessed and that *'[t]he analysis of structural similarity should consider all appropriate elements, notably: Presence and number of common functional groups; Presence and relevance of non-common functional groups; Similarity of the "core structure" apart from the (non-)common functional groups; Potential differences due to reactivity; Potential differences due to steric hindrance; Presence of structural alerts; Position of the double bonds; Presence of stereoisomers'.*

149. The Agency also notes that it clearly explained during the teleconference with the Appellant what information would need to be submitted to potentially justify the read-across adaptation. The Appellant cannot claim that it correctly followed the Grouping Guidance in establishing its read-across argument. The deficiencies in its read-across adaptation have been clearly highlighted in the Contested Decision and during the decision-making process.

Findings of the Board of Appeal

150. At the outset, the Board of Appeal observes that the right to rely on the principle of the protection of legitimate expectations presupposes that precise, unconditional and consistent assurances originating from authorised, reliable sources have been given to the person concerned by the competent authorities of the European Union. In accordance with the Court of Justice's settled case-law, that right applies to any individual in a situation in which an EU institution, body or agency, by giving that person precise assurances, has led him to entertain well-founded expectations. Precise, unconditional and consistent information, in whatever form it is given, constitutes such an assurance (see Joined Cases C-630/11 P to C-633/11 P, *HGA and Others* v *Commission*, EU:C:2013:387, paragraph 132 and the case-law cited).

151. When examining the Appellant's fifth plea, the Board of Appeal must therefore determine whether the Agency gave the Appellant precise, unconditional and consistent assurance that it would accept its read-across adaptation.

152. First, with regard to the Appellant's argument that the Agency has accepted and relied on data relating to some of the source substances in order to identify the Substance as a SVHC, the Board of Appeal finds that the identification of the Substance as a SVHC was not taken on the basis of a read-across between the Substance and HHPA but was rather based on the cross-reactivity between HHPA and the Substance, both respiratory sensitisers, and the intrinsic properties of the Substance.

153. This is confirmed by the judgment of the General Court in Case T-135/13, *Hitachi Chemical Europe and Others* v *ECHA*, EU:T:2015:253, currently under appeal before the Court of Justice (Case C-324/15 P), which concerns the identification of the Substance as a SVHC. In paragraph 94 of that judgment, the General Court found that '*[the Substance] was not identified as a substance of very high concern because of a read-across to it of data relating to HHPA. As ECHA confirmed at the hearing, [the Substance] was inter alia classified […] on the basis of its intrinsic properties and not on the basis of a read-across from data relating to HHPA.*' Despite a specific question by the Board of Appeal during the hearing, the Appellant has not claimed that this finding of fact by the General Court has been appealed to the Court of Justice. Therefore, in the context of this appeal, this finding has to be considered as final.

154. The Appellant's argument that the Agency based the identification of the Substance as a respiratory sensitiser on a read-across from HHPA but refused to accept such a read-across when examining the completeness of the Appellant's registration dossier is therefore factually incorrect and must be rejected.

155. Second, in any event, the Board of Appeal notes that the read-across adaptation at issue in the present case regards the toxicity of the substance and not its properties as a respiratory sensitiser. As a consequence, even if the Agency had used a read-across with regard to respiratory sensitisation, which is not the case, this could not be deemed to constitute a precise and unconditional assurance that a read-across adaptation would be accepted for other endpoints. Therefore, the Appellant could not nurture legitimate expectations that its read-across adaptation would be accepted.

156. Finally, as regards the Appellant's arguments that it applied the Agency's Grouping Guidance when preparing the read-across adaptation, the Board of Appeal notes that that guidance is couched in general terms and explains in a generic manner, inter alia, the Agency's view on the information which must be provided by registrants who intend to rely on a read-across adaptation to meet the information requirements for registration purposes (see, for instance, the extracts quoted in paragraphs 143 and 148 above). The guidance indicates the information that is needed to justify a read-across adaptation but does not, and cannot, prejudge the Agency's assessment of whether the information provided fulfils those information requirements. Consequently, the Grouping Guidance cannot constitute a precise and unconditional assurance that the Appellant's read-across adaptation would be accepted in practice and is therefore not capable of giving rise to legitimate expectations in the present case.

157. The Appellant's fifth plea must therefore be rejected.

158. As all of the Appellant's pleas have been dismissed, the present appeal must be rejected in its entirety.

Claim for the reimbursement of costs

159. In its Notice of Appeal the Appellant sought the reimbursement of its costs arising from these proceedings.

160. The Board of Appeal observes that there is no legal basis in the Rules of Procedure for the reimbursement of costs that are not, as provided in Articles 17 and 21(1)(h) thereof, related to the taking of evidence. This has been further clarified by the Commission Implementing Regulation of 25 May 2016 amending the Rules of Procedure. Article 17a now provides that the parties shall bear their own costs.

161. 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

162. 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 Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (OJ L 107, 17.4.2008, p. 6), the appeal fee shall be refunded if the decision is rectified in accordance with Article 93(1) of the REACH Regulation or the appeal is decided in favour of an appellant.

163. As the appeal has been dismissed, the appeal fee shall not be refunded.

Effects of the Contested Decision

164. According to Article 91(2), an appeal before the Board of Appeal shall have suspensive effect.

165. The Contested Decision, upheld in the present appeal proceedings, required the registrant, now the Appellant, to submit inter alia information on sub-chronic toxicity and pre-natal developmental toxicity by 5 December 2016, which is two years and eight days from the adoption of the Contested Decision. The Board of Appeal considers however that, because of the duration of the present appeal proceedings, the deadline set in the Contested Decision should be interpreted, in the light of the principle of suspensive effect laid down in Article 91(2), as if it referred to two years and eight days from the date of notification of the final decision of the Board of Appeal.

166. Consequently, the information on sub-chronic toxicity and pre-natal developmental toxicity required by the Contested Decision shall be submitted within two years and eight days from the date of notification of the Board of Appeal's Decision in present case.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Dismisses the appeal;**
2. **Decides that the information on sub-chronic toxicity and pre-natal developmental toxicity required by the Contested Decision shall be submitted by 28 October 2018;**
3. **Rejects the claim for the reimbursement of costs incurred in these proceedings;**
4. **Decides that the appeal fee shall not be refunded.**

Mercedes ORTUÑO
Chairman of the Board of Appeal

Alen MOČILNIKAR
Registrar of the Board of Appeal