EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

13 December 2017

(Substance evaluation – Article 42 – Section 8.7.2. of Annex IX – Grounds for concern – Pre-natal developmental toxicity – Mutagenicity – Manifest error of assessment – Duty to state reasons – Article 25 – Right to be heard)

Case number	A-023-2015
Language of the case	English
Appellants	S.A. Akzo Nobel Chemicals NV, Belgium Arkema GmbH, Germany Pergan GmbH, Germany REACH Compliance Services Limited (trading under the name REACH24H Consulting Group), Ireland United Initiators GmbH & Co. KG, Germany
Representatives	Ruxandra Cana and Indiana de Seze Steptoe & Johnson LLP, Belgium
Intervener	PETA International Science Consortium Ltd (PISC), United Kingdom
Contested Decision	Decision of 14 August 2015 on the substance evaluation of tert-butyl perbenzoate adopted by the European Chemicals Agency pursuant to Article 46(1) 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) (the 'REACH Regulation')

THE BOARD OF APPEAL

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

Registrar: Alen Močilnikar

gives the following

Decision

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Background to the dispute

1. On 20 December 2012, the Agency adopted a testing proposal decision pursuant to Article 40(3) of the REACH Regulation (all references to Articles, Recitals and Annexes hereinafter concern the REACH Regulation unless stated otherwise). The testing proposal decision concerned tert-butyl perbenzoate (CAS No 614-45-9, EC No 210-382-2) (the 'Substance'). The testing proposal decision required the lead registrant for the Substance, who is also one of the Appellants, to provide information on a pre-natal developmental toxicity ('PNDT') study (OECD Test Guideline ('TG') 414) pursuant to Section 8.7.2. of Annex IX by 20 June 2014.

2. The Substance was included in the Community rolling action plan ('CoRAP') for substance evaluation in 2013. This was on the basis of an opinion of the Member State Committee (the 'MSC') due to initial grounds for concern relating to '*sensitization and Exposure/Wide dispersive use; Consumer use*'. The CoRAP was published on the website of the European Chemicals Agency (the 'Agency') on 20 March 2013. The Competent Authority of Italy was appointed as the evaluating Member State Competent Authority (the 'eMSCA').

3. According to the Appellants, at the time the Substance was included on the CoRAP the following consumer uses were disseminated on the Agency's website:

   '*PC 1: Adhesives, sealants*

   PC 3: Air care products

   PC 8: Biocidal products (e.g. disinfectants, pest control)

   PC 9a: Coatings and paints, thinners, paint removes

   PC 9b: Fillers, putties, plasters, modelling clay

   PC 9c: Finger paints

   PC 18: Ink and toners

   PC 31: Polishes and wax blends

   PC 35: Washing and cleaning products (including solvent based products)

   PC 39: Cosmetics, personal care products

   ERC 8b/8e: Wide dispersive indoor/outdoor use of reactive substances in open systems'.

4. According to the Contested Decision, '*[i]n the course of the evaluation, the [eMSCA] noted additional concern regarding genotoxicity, pre-natal developmental toxicity and Human exposure assessment and risk characterisation with potential human risk via the environment*'.

5. Following an evaluation of the Substance pursuant to Article 45(4), the eMSCA concluded that further information was required in order to assess the concerns identified (see paragraphs 2 and 4 above). The eMSCA prepared a draft decision pursuant to Article 46(1) which was submitted to the Agency on 20 March 2014. The draft decision contained the following information requirements:

   '*1. Perform a human exposure assessment and a quantitative risk characterisation for all relevant exposure scenarios taking into account the selected DNELs for long-term systemic effects.*

   2. Provide sufficient and consistent information on the specification of personal protective equipment and the duration of use for all scenarios where the use of personal protective equipment is advised (CSR).'

6. The draft decision stated that the *'eMSCA considered that no further information was required to clarify the concern for sensitisation and carcinogenicity'.*

7. On 29 April 2014, the Agency sent the draft decision to the Appellants and invited them pursuant to Article 50(1) to provide comments within 30 days of the receipt of the draft decision. The draft decision stated that '*[t]his decision is based on the registration dossier(s) on [date], i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1)*'.

8. On 21 May 2014, the Appellants provided comments to the Agency on the draft decision. The draft decision was subsequently modified by the eMSCA (the 'revised draft decision').

9. On 3 June 2014, the Appellants provided the robust study summary for the PNDT study which had been required in the testing proposal decision of 20 December 2012 (see paragraph 1 above). On 24 June 2014, the Appellants updated their registration dossier with the detailed experimental figures from that study.

10. On 10 September 2014, the Agency sent a communication pursuant to Article 42(2) to the Member States and the Commission closing the dossier evaluation related to the testing proposal decision of 20 December 2012. This communication included a recommendation for follow-up action to be taken in a dossier or substance evaluation.

11. On 5 March 2015, the eMSCA notified the revised draft decision to the Competent Authorities of the other Member States ('MSCAs') and the Agency in accordance with Article 52(1). The eMSCA invited them to submit proposals for amendment within 30 days, pursuant to Articles 52(2) and 51(2). The revised draft decision stated that '*this decision is based on the registration dossier(s) on 28 February 2014*'. Proposals for amendment were subsequently received from, amongst others, the Danish MSCA and the Agency.

12. The Agency's proposals for amendment included a proposal that the reference to the version of the registration dossier on which the Contested Decision was based should be amended to allow the dossier update of 24 June 2014 to be taken into consideration.

13. The Agency also proposed adding to the Contested Decision a requirement for a PNDT study in a second species. The Agency stated that this addition was necessary following the results of the PNDT study performed on the first species (see paragraph 9 above).

14. The Danish MSCA proposed adding to the Contested Decision a requirement to provide information on an *in vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay, OECD TG 489) in rats, oral route, with examination of liver and either glandular stomach or duodenum/jejunum.

15. On 10 April 2015, the Agency notified the addressees of the Contested Decision of the proposals for amendment, including the proposals for a PNDT study and a Comet assay, and invited them, pursuant to Articles 52(2) and 51(5), to provide comments within 30 days.

16. The eMSCA examined the proposals for amendment and amended the revised draft decision accordingly (the 'amended draft decision'). In particular, a PNDT study in a second species and a Comet assay, as proposed by the Agency and the Danish MSCA respectively, were added to the Contested Decision. In addition, the amended draft decision changed the date up to which dossier updates could be considered in the decision-making process to 24 June 2014, as proposed by the Agency.

17. On 20 April 2015, the Agency referred the amended draft decision to the MSC.

18. By 11 May 2015, the addressees of the Contested Decision provided comments on the proposals for amendment.

19. On 18 May 2015, an MSC written procedure was launched.

20. On 28 May 2015, the MSC reached unanimous agreement on the Contested Decision.

21. During the MSC meeting of 8 to 11 June 2015, a presentation of the conclusions of the written procedure was made.

22. On 14 August 2015, the Agency adopted the Contested Decision requiring the Appellants to provide the following information by 21 November 2016:

    '*1. Pre-natal developmental toxicity study (test method: EU B.31./OECD [TG] 414) in rabbits, oral route;*

    2. In vivo alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay, OECD [TG] 489) in rats, oral route, with examination of liver and either glandular stomach or duodenum/jejunum;

    3. Perform a human exposure assessment and a quantitative risk characterisation for all relevant exposure scenarios […]; and

    4. Provide sufficient and consistent information on the specification of personal protective equipment and the duration of use for all scenarios where the use of personal protective equipment is advised (CSR).'

Procedure before the Board of Appeal

23. On 13 November 2015, the Appellants filed this appeal.

24. On 24 February 2016, the Agency filed its Defence.

25. On 28 April 2016, the Appellants filed their observations on the Defence.

26. On 17 May 2016, PISC was granted leave to intervene in this case in support of the Appellant.

27. On 20 June 2016, the Agency filed observations on the Appellants' observations on the Defence and replied to questions from the Board of Appeal.

28. On 20 June 2016, the Appellants replied to questions from the Board of Appeal.

29. On 25 July 2016, the Intervener filed its statement in intervention.

30. On 22 and 26 September 2016 respectively, the Appellants and the Agency filed their observations on the statement in intervention.

31. On 26 January 2017, pursuant to a request from the Board of Appeal, the Agency submitted the draft substance evaluation report prepared by the eMSCA and various communications between the Agency and the MSCAs related to the written procedure leading to the adoption of the Contested Decision.

32. On 26 January 2017, the Appellants informed the Board of Appeal that they had not received a copy of the substance evaluation report prior to the present appeal proceedings.

33. On 28 March 2017, a hearing was held at the Appellants' request. At the hearing, the Parties and the Intervener made oral submissions and responded to questions from the Board of Appeal.

Form of order sought

34. The Appellants, supported by the Intervener, request the Board of Appeal to:

    - Partially annul the Contested Decision insofar as it requests the Appellants to conduct:

1. a PNDT study (test method: EU B.31./OECD TG 414) in rabbits, oral route (the 'second species PNDT study'), and
2. an *in vivo* alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay, OECD TG 489) in rats, oral route, with examination of liver and either glandular stomach or duodenum/jejunum (the 'Comet assay');

- If the Board of Appeal upholds the abovementioned testing requirements, amend the Contested Decision to allow 24 months, instead of 15 months, for the requested information to be submitted to the Agency;
- Order the refund of the appeal fee; and
- Take such other or further measures as justice may require.

35. If the appeal is found to be inadmissible or is dismissed the Appellants request the Board of Appeal to amend the deadline set in the Contested Decision to take account of the suspensive effect of the appeal.

36. The Agency requests the Board of Appeal to dismiss the appeal in its entirety as unfounded.

Reasons

37. The Board of Appeal will examine the Appellants' numerous pleas as follows:

I. Pleas concerning the request to conduct a second species PNDT study;

II. Pleas concerning the request to conduct a Comet assay;

III. Pleas concerning both the request to conduct a second species PNDT study and a Comet assay.

I. Pleas concerning the request to conduct a second species PNDT study

38. The Board of Appeal will examine the Appellants' pleas concerning the request to conduct a second species PNDT study in the following order:

A. Manifest error of assessment in interpreting the information contained in the registration dossier to conclude that there is a concern that needs to be addressed;

B. Breach of the REACH Regulation, in particular Articles 42 and 46, through the unlawful use of the substance evaluation procedure instead of the compliance check procedure;

C. The Agency's breach of its own guidance by changing the date up to which dossier updates will be considered – legitimate expectations;

D. Misuse of powers by the Agency;

E. Breach of the duty to state reasons; and

F. The Agency exceeding its competence by submitting proposals for amendment to itself.

A - Manifest error of assessment in interpreting the information contained in the registration dossier to conclude that there is a concern that needs to be addressed

39. The Appellants allege, in essence, that the Agency cannot require the Appellants to submit information on a second species PNDT study because it has not demonstrated a concern with regard to the Substance related to developmental toxicity. In this respect, the Appellants allege three errors of assessment on the part of the Agency which they

consider led the Agency to mistakenly conclude that there is a concern for developmental toxicity. In examining the Appellants' plea the Board of Appeal will:

1. Set out the criteria to establish a concern under substance evaluation;
2. Set out the concern identified by the Agency in the present case to justify requesting the second species PNDT study; and
3. Examine the three errors claimed by the Appellants which led to the Agency mistakenly concluding that there is a concern for developmental toxicity.

1. Criteria to establish a concern under substance evaluation

40. In order to request further information under substance evaluation, the Agency must be able to indicate the grounds for considering that a substance constitutes a potential risk to human health or the environment. The Agency must also be able to demonstrate that the potential risk needs to be clarified, and that the requested measure, to clarify the concern, has a realistic possibility of leading to improved risk management measures (Case A-006-2014, *International Flavors & Fragrances*, Decision of the Board of Appeal of 27 October 2015, paragraph 76).

41. The identification of a potential risk is based on a combination of exposure information and hazard information (see, for example, Case A-005-2014, *Akzo Nobel Industrial Chemicals and Others*, Decision of the Board of Appeal of 23 September 2015, paragraph 61).

2. Concern underlying the request for a second species PNDT study

42. According to the Contested Decision there is a concern for '*developmental toxicity and a PNDT study on a second species should be requested to obtain comprehensive information on developmental toxicity of [the Substance] and conclude on the classification*'.

43. The developmental toxicity concern identified in the Contested Decision is based on the results of the OECD TG 414 study in rats (the 'first species PNDT study') submitted in the registration dossier updates of 3 and 24 June 2014. In that study, the Substance was tested at doses of 100, 300 and 1 000 mg/kg bw/day. The lead registrant concluded in its registration dossier that:

'*Treatment at 1 000 mg/kg bw/day was associated with lower maternal body weight gain during gestation and an initial effect on food consumption. No similar effects were apparent at 300 mg/kg bw/day and this dosage is considered to represent the No Observed Effect Level (NOEL) for the pregnant female.*

In-utero survival of the developing conceptus was unaffected by maternal treatment at 1 000 mg/kg bw/day although reduced fetal weight and external, visceral and skeletal findings indicated an adverse effect on fetal growth. The absence of any structural defects indicated that development per se was unaffected at this dosage. Only an equivocal increase in the incidence of fetuses/litter showing kinked/dilated ureter(s) prevented 300 mg/kg bw/day being classified as a fetal No Observed Effect Level and a dosage of 100 mg/kg bw/day is therefore considered to be a clear No Observed Effect Level (NOEL) for the developing conceptus.

Kinked/dilated ureters are considered reversible variations (Solecki, R, et al. Reproductive Toxicity 17 (2003) 635 – 637) and therefore not considered adverse. The NOAEL was therefore 300 mg/kg bw/day.'

44. In the Contested Decision, the Agency disputed the lead registrant's interpretation of the results of the first species PNDT study. The Contested Decision states:

'*[T]he slight maternal toxicity observed (5.3 % reduction of adjusted maternal body weight) does not usually lead to such a significant reduction in fetal body weight like here, 21%. In addition, [the Agency] noted that there were findings in ureter at 300 mg/kg bw/day where there was no maternal toxicity and no reduction in fetal body weight and thus, increased incidence of kinked and/or dilated ureters cannot be considered secondary to the maternal toxicity or reduced fetal body weight and delayed development at 300 mg/kg bw/day.*

The results from the first PNDT study suggest that [the Substance] may merit a classification for reproductive toxicity according to the CLP Regulation and could be a possible candidate for a proposal for harmonised classification and labelling according to Article 37 of [the CLP Regulation].'

3. The three errors claimed by the Appellants which led to the Agency mistakenly concluding that there is a concern for developmental toxicity

45. When an appellant claims that the Agency has made a manifest error of assessment, the Board of Appeal must examine whether the Agency has examined carefully and impartially all the relevant facts of the individual case which support the conclusions reached (see, by analogy, judgment of 19 January 2012, *Xeda International and Pace International* v *Commission*, T-71/10, EU:T:2012:18, paragraph 71; Case A-004-2014, *MCCP registrants*, Decision of the Board of Appeal of 9 September 2014, paragraph 42).

46. The Appellants argue that the Agency made three errors in its assessment of the results of the first species PNDT study. The Appellants argue that in the absence of these errors there would be no potential concern for developmental toxicity and therefore no additional information would be required.

47. As stated above in paragraph 40, the Agency must be able to indicate the grounds for considering that a substance constitutes a potential risk to human health or the environment in order to request additional information under substance evaluation. Risk is a combination of exposure and hazard.

48. The fact that there is evidence of potential exposure to the Substance has not been disputed by the Parties. Evidence of potential exposure includes:

- there are numerous consumer uses identified for the Substance (see paragraph 3 above),
- the Substance has been registered by several registrants at the 100 to 1 000 tonnes per year tonnage band, and
- the Contested Decision requests '*a human exposure assessment and a quantitative risk characterisation for all relevant exposure scenarios*' and '*sufficient and consistent information on the specification of personal protective equipment and the duration of use for all scenarios where the use of personal protective equipment is advised*'. These information requirements are relevant to exposure and have not been contested by the Appellants in these proceedings.

49. The Appellants argue that the Agency has not demonstrated a potential hazard in relation to the Substance due to three errors of assessment regarding the results of the first species PNDT study. In essence, the Appellants argue that the Agency:

(a) applied the wrong calculation method in evaluating the extent of the maternal toxicity seen in the first species PNDT study,

(b) reached an incorrect conclusion regarding the relevance of the increased incidence of fetuses with kinked/dilated ureters seen in the first species PNDT study as these incidences failed to attain statistical significance, and

(c) ignored the fact that the observed effects on the fetuses are reversible and therefore do not lead to classification as a reproductive toxicant 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, 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').

50. The Board of Appeal will consider these three alleged errors of assessment in turn.

(a) Maternal toxicity calculation

Arguments of the Parties

51. The Appellants argue that when considering the effects of maternal toxicity in the first species PNDT study the Agency miscalculated in concluding in the Contested Decision that there was a '*5.3 % reduction of adjusted maternal body weight*'. The Appellants further argue that the Agency was incorrect in interpreting this figure as showing the effects of maternal toxicity to be '*slight'* and consequently that the effects observed were not due to maternal toxicity but could be an indication of developmental toxicity.

52. The Appellants argue that if the Agency had applied the correct calculation method it would have been clear that the results of the first species PNDT study indicate that the effects observed indicate the presence of maternal toxicity and that the effects seen were therefore not indicative of developmental toxicity. The Appellants claim that the results of the first species PNDT study '*clearly show that at the dose of 1,000 [mg/kg bw/day] the substance is toxic to both fetuses and mothers and the observed effect is a general systemic effect, as opposed to a specific reprotoxic effect*'.

53. The Appellants argue that the level of maternal toxicity observed in the first species PNDT study exceeds the recommended level to assess developmental toxicity established by the International Life Sciences Institute/Health and Environmental Sciences Institute Workshop (Birth Defects Res. (Part B) Feb;92, 36-51, 2010; the 'conclusions of the ILSI/HESI workshop'). According to the Appellants, '*it was agreed by the ILSI/HESI that dose levels which resulted in decreased body weight gains of greater than 20 % should be avoided [when assessing developmental toxicity]*. *Reduced weight gains exceeding 20 % are considered indicative of marked maternal toxicity*.'

54. The Agency argues that the developmental toxicity observed in the first species PNDT study cannot be considered as secondary to maternal toxicity and that the Appellants' method of calculating maternal toxicity is not in accordance with the CLP Regulation. The Agency argues that the figure of 5.3 % (see paragraph 51 above) is '*below 10 %*' and that the maternal toxicity demonstrated in the first species PNDT study is '*slight'*. The effects seen in the first species PNDT study may therefore be indicative of developmental toxicity.

Findings of the Board of Appeal

55. The central issue in relation to the requirement to provide information on a second species PNDT study is whether the results of the first species PNDT study demonstrate that the Substance is potentially a developmental toxicant.

56. In examining whether a substance has the potential to be a developmental toxicant, the possible influence of maternal toxicity must be considered as *'[d]evelopment of the offspring throughout gestation and during the early postnatal stages can be influenced*

by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms' (Section 3.7.2.4.1. of Annex I to the CLP Regulation).

57. The Parties disagree on the extent of maternal toxicity observed in the first species PNDT study as they use different methods of calculation to arrive at their conclusions.

58. During the present proceedings, both Parties defended their calculations of maternal toxicity with reference to Section 3.7.2.4.4. of Annex I to the CLP Regulation. However, neither Party clearly explained how its calculation method was consistent with this provision. According to that provision:

'*Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight shall be included in the evaluation of maternal toxicity whenever such data are available. The calculation of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine.*'

59. The detailed experimental findings of the first species PNDT study were attached to the lead registrant's registration dossier update of 24 June 2014 and were submitted by the Appellants during the present proceedings. According to those results:

- the mean body weight on 3 days gestation was 243.7 g for the control group and 244.3 g for the group exposed to the Substance at 1 000 mg/kg bw/day, and
- the mean adjusted body weight (body weight minus gravid uterine weight) after 20 days was 299.3 g for the control group and 283.4 g for the group exposed to the Substance at 1 000 mg/kg bw/day.

60. The Agency and the Appellants use these results in different ways.

61. The Agency, using the figures in paragraph 59 above, calculate the difference in the adjusted body weight gain between the control group and the high dose group as 299.3 g - 283.4 g = 15.9 g.

62. The Appellants, using the figures in paragraph 59 above, calculate the mean adjusted body weight gain as 55.6 g (299.3 g – 243.7 g) for the control group and 39.1 g (283.4 g – 244.3 g) for the group exposed to the Substance at 1 000 mg/kg bw/day. The difference in the adjusted body weight gain between the high dose group and control group is therefore 16.5 g (55.6 g - 39.1 g).

63. The Appellants' calculation in this respect is correct as it takes account of the difference in weight of the control group and the exposed group at the start of the study. The Agency's calculation method reflects the actual difference in adjusted body weight after 20 days and does not take into account the small difference in mean body weights at the start of the test between the animals used in the control group and those in the exposed group (243.7 g and 244.3 g; see paragraph 59 above). The difference in mean body weights reflects the fact that the animals used in the two test groups were not of exactly the same size. This small difference in mean body weights at the start of the test, 0.6 g, does not however invalidate the Agency's assessment of maternal toxicity.

64. The crucial issue in this case is that there is a major difference between the Parties as to how to use the above figures (15.9 g or 16.5 g) to calculate the severity of maternal toxicity, which is the second step of their respective calculation methods.

65. The Appellants calculate the percentage change that the difference of 16.5 g represents as follows:
    - how much lower the maternal body weight gain in the exposed group is compared to the maternal body weight gain in the control animals (16.5 / 55.6 x 100 = 29.7 %),
    - how much higher the maternal body weight gain in the exposed groups should have been to reach the control value (16.5 / 39.1 x 100 = 42.2 %), and
    - the mean value of these two percentages ((29.7 % + 42.2 %)/2) is 35.9 %.
66. The Agency calculates the percentage change that the 15.9 g represents by comparing the difference in the adjusted body weight gain between the control group and the high dose group (15.9 g) with the mean adjusted maternal body weight of the control animals (299.3 g) after 20 days. On this basis, the Agency concludes that the exposed animals had 15.9 / 299.3 g x 100 = 5.3 % lower mean adjusted maternal body weight than the control animals.
67. Neither the REACH Regulation nor the CLP Regulation include a method for calculating the percentage change in adjusted body weight following exposure to a substance. It is also not clear to the Board of Appeal how either Party arrived at their respective calculation method. Neither Party clearly explained how its calculation method is consistent with Section 3.7.2.4.4. of Annex I to the CLP Regulation (see paragraph 58 above). However the key issue is how much larger the animals subject to the testing would have been had they not been exposed to the Substance.
68. According to the Appellants, in the first species PNDT study the rats would have been 16.5 g heavier had they not been exposed to the Substance. In order to calculate what the 16.5 g difference means as a percentage it is necessary to calculate the difference in adjusted body weights of the control group compared to the exposed group after 20 days as a percentage of the mean adjusted body weight of the control group after 20 days. This amounts to an adjusted body weight gain of 16.5 / 299.3 g x 100 = 5.5 % in the control group, compared to the exposed group, after 20 days. Performing the same calculation with a figure of 15.9 g, as derived by the Agency, results in an adjusted body weight gain of 15.9 / 299.3 g x 100 = 5.3 % in the control group, compared to the exposed group, after 20 days. The difference between a 5.5 % change and a 5.3 % change does not impact this assessment of maternal toxicity.
69. Next, it is necessary to examine whether the Agency made an error in concluding that the approximately 5.5 % reduction in adjusted maternal body weight observed in the first species PNDT study equated to '*slight maternal toxicity*'. In essence, the Appellants contest the statement in the Contested Decision that '*[the Agency] considers that the slight maternal toxicity observed (5.3 % reduction of adjusted maternal body weight) does not usually lead to such a significant reduction in fetal body weight like here, 21 %*'.
70. In the OECD Test Guideline for PNDT (OECD TG 414) the highest dose level '*should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but no death or severe suffering.*' Consequently, it could be expected that some maternal toxicity would be observed in a PNDT study.
71. As stated in paragraph 53 above, the Appellants, basing themselves on the conclusions of the ILSI/HESI workshop, argue that '*dose levels which resulted in decreased body weight gains of greater that 20 % should be avoided […]. Reduced weight gains exceeding 20 % are considered indicative of marked maternal toxicity*.' The Appellants did not provide this document during the appeal proceedings. However, in a footnote to the Notice of Appeal the Appellants list '*recommendations/options*' based on the outcome of the discussions at the workshop. These '*recommendations/options*' included the following '*a comprehensive evaluation of all available data from general toxicity studies, range-finding Developmental and Reproductive Toxicology (DART) studies, class effects, structure-activity relationships, exposure studies, etc. is essential for*

appropriate dose selection for definitive DART studies. *The intent is to avoid marked maternal toxicity leading to mortality or decreased body weight gains of greater than 20 % for prolonged periods*'.

72. The Agency argues that the adjusted body weight change of approximately 5.5 % is '*below 10 %*' which indicates that the effects seen in the first species PNDT study cannot be assumed to be a result of maternal toxicity and may be the result of developmental toxicity. However, the Agency does not state on what grounds the 10 % threshold is based.

73. The method for calculating the adjusted maternal body weight change as a percentage for the purposes of assessing maternal toxicity, and how to further categorise this as, for example, '*slight'* or '*severe*', is not found in either the REACH Regulation or the CLP Regulation.

74. Neither of the Parties presented any evidence regarding how to categorise the level of maternal toxicity observed (for example, what percentage reduction in maternal body weight corresponds to '*slight*', '*moderate*' or '*severe*'). However, the reduction of adjusted maternal body weight of approximately 5.5 %, as calculated by the Agency, is well below the 20 % figure indicated in the conclusions of the ILSI/HESI workshop as being problematic for '*Developmental and Reproductive Toxicology (DART) studies*' (see paragraph 71 above) and on which the Appellants base much of their argument. Consequently, the categorisation of the approximately 5.5 % reduction of adjusted maternal body weight as '*slight'* cannot be considered to be misleading or unreasonable.

75. In view of all of the above, the Agency did not commit an error of assessment in concluding that an approximately 5.5 % reduction of adjusted maternal body weight is indicative of '*slight maternal toxicity'.* It cannot therefore be concluded that the effects seen in the first species PNDT study were wholly due to maternal toxicity. The effects seen may therefore have been due to some extent to the developmental toxicity of the Substance. On this basis, the Agency did not commit an error in concluding that there is a concern for developmental toxicity on the basis of the results seen in the first species PNDT study.

76. Moreover, Sections 3.7.2.4.1. and 3.7.2.4.2. of Annex I to the CLP Regulation acknowledge that the assessment of whether the development of offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental toxicity.

77. Section 3.7.2.4.2. of Annex I to the CLP Regulation provides:

'*[…] [T]he limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity.'*

78. Section 3.7.2.4.3. of Annex I to the CLP Regulation provides:

'*Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1 […].'*

79. As a consequence, even if the Appellants' arguments regarding the calculation method for determining the level of maternal toxicity had been correct, the Appellants would not have demonstrated *'that the developmental effects are secondary to maternal toxicity'.*

(b) Incidences of fetuses with kinked/dilated ureters failed to attain statistical significance

Arguments of the Parties

80. The Appellants dispute the statement in the Contested Decision that '*there were findings in ureter at 300 mg/kg bw/day where there was no maternal toxicity and no reduction in fetal body weight and thus, increased incidence of kinked and/or dilated ureters cannot be considered secondary to the maternal toxicity or reduced fetal body weight and delayed development at 300 mg/kg bw/day.'*

81. The Appellants argue that although it was observed in the first species PNDT study that the fetuses from the 300 mg/kg bw/day dose group showed an increased incidence of kinked/dilated ureters compared with the control group, this failed to attain statistical significance. '*Kinked and dilated ureters occur often in nature […] and should not be considered a significant toxic effect*'. The Appellants argue that this position is supported by the Solecki *et al.* publication (*Harmonization of rat fetal external and visceral terminology and classification Report of the Fourth Workshop on the Terminology in Developmental Toxicology*, Berlin, 18–20 April 2002, Reproductive Toxicology 17 (2003) 625–637).

82. The Appellants also argue that historical control data for developmental and reproductive toxicity studies using one strain of rat compiled by the Middle Atlantic Reproduction and Teratology Association ('MARTA') in 1993 showed incidences of convoluted (or kinked) and distended (or dilated) ureters. This shows that such effects are seen independently of exposure to a chemical.

83. The Agency argues that the historical data presented by the Appellants is not valid in the present case in particular because it is old, not from the same laboratory as that which performed the first species PNDT study, nor from the same strain of animal. The Agency also argues that the findings in the MARTA study can be interpreted in a different way to that presented by the Appellants.

84. The Agency argues that '*in assessment of the findings in the first PNDT study of kinked and dilated ureters [the Agency] took into account that they occur in conjunction with renal papilla absence and renal pelves dilatation, which may indicate hydronephrosis*'.

Findings of the Board of Appeal

85. The results of the first species PNDT study showed that between days 3 and 20 of gestation there was only a 0.8 g difference in the adjusted body weight change between the control group (55.6 g) and the group exposed to 300 mg/kg bw/day of the Substance (56.4 g). The Agency was therefore correct to conclude that there was no indication of maternal toxicity at that dose level. The increased incidence of kinked and/or dilated ureters seen in the group exposed to 300 mg/kg bw/day of the Substance may therefore have been due to developmental toxicity.

86. The Appellants firstly argue that the Agency failed to take into account its comments in relation to the statistical significance of the findings of kinked and dilated ureters.

87. In their observations on the proposals for amendment, the Appellants made similar comments related to the MARTA study and the Solecki *et al*. publication as those raised in the present proceedings (see paragraphs 81 and 82 above). Those observations were addressed in Section III(1) of the Contested Decision. This shows that the Agency did take into account the findings of the MARTA study and the Solecki *et al*. publication. However, it is clear that the Agency did not agree with the inferences drawn from those reports by the Appellants.

88. The Appellants' plea that the Agency committed an error of assessment by failing to take into account their comments on the proposals for amendment must therefore be rejected.

89. The Appellants presented the MARTA study to support their arguments that the increased incidence of kinked/dilated ureters observed in the 300 mg/kg bw/day dose group should not be considered a significant toxic effect. The MARTA study was part of a project to collect and summarise historical control data from developmental and reproductive toxicology studies, using one strain of rat (Sprague-Dawley Crl:CD® BR), conducted at various laboratories. The Appellants attached to their appeal the introduction to that study and tables related to '*visceral anomalies summary of all studies*', '*visceral anomalies gestation day 20*', and '*visceral anomalies gestation day 21*'. The Appellants also argue that the Solecki *et al* publication shows that kinked or dilated ureters are temporary delays in embryonic development and, as such, should be considered as variations.

90. However, the evidence produced by the Appellants does not support a finding that the effects observed at 300 mg/kg bw/day, specifically an increased incidence of kinked and/or dilated ureters, cannot have been caused by the developmental toxicity of the Substance. This finding is based on the following:

- the MARTA study does not examine effects caused by the Substance itself or even the unexposed control group,

- the first species PNDT study conducted on the Substance used the Sprague-Dawley Crl:CD® (SD) IGS BR rat strain. The MARTA study does not therefore concern the same strain of rat,

- the MARTA study may indicate that variations in the ureter occur in rats regardless of exposure to a substance but it cannot be concluded that the results in the first species PNDT study are not caused by the Substance,

- the Solecki *et al.* publication describes the result of an analysis on the classification of findings as malformations, variations and '*grey zone findings*'. It did not however analyse results from testing on the Substance; it cannot therefore be regarded as conclusive evidence as regards the developmental toxicity of the Substance,

- the findings in the first species PNDT study of kinked and dilated ureters occur in conjunction with the absence of renal papilla and renal pelves dilatation; together this raises a concern of congenital malformations (a possible cause of the hydronephrosis observed) caused by exposure to the Substance,

- in the first species PNDT study, the incidence of kinked and dilated ureters showed a clear dose response at the 300 and 1000 mg/kg bw/day dose levels; that is, the higher the exposure to the Substance the greater the incidence of kinked and dilated ureters, and

- the incidence of kinked and dilated ureters occurs at the 300 mg/kg bw/day dose level in the absence of any reduction in fetal body weight indicating that they cannot be assumed to have been caused by maternal toxicity.

91. In conclusion, the findings from the first species PNDT study regarding the increased incidence of kinked and/or dilated ureters in the group exposed to 300 mg/kg bw/day of the Substance cannot be assumed to be naturally-occurring or to have been caused by maternal toxicity. The effects seen may therefore be indicative of developmental toxicity. The Appellants' arguments do not resolve whether there is a developmental toxicity hazard, rather that they disagree with the Agency's interpretation of the data.

92. In view of the above, the Agency did not commit an error of assessment in concluding that '*there were findings in ureter at 300 mg/kg bw/day where there was no maternal toxicity and no reduction in fetal body weight and thus, increased incidence of kinked and/or dilated ureters cannot be considered secondary to the maternal toxicity or reduced fetal body weight and delayed development at 300 mg/kg bw/day.'*

(c) The incidence of kinked/dilated ureters observed in the first species PNDT study should be considered 'transient variations'

Arguments of the Parties

93. The Appellants argue that the findings of the first species PNDT study are indicative of developmental delays which do not meet the criteria set out in the CLP Regulation for classification as a reproductive toxicant. The results do not satisfy the guidance definition of significant toxic effects, i.e. irreversible effects such as structural malformations, embryo/fetal lethality or significant post-natal functional. This conclusion is supported by the Solecki *et al*. publication.

94. The Agency argues that there is a potential concern even if the kidney and ureter findings are considered as variations or malformations.

Findings of the Board of Appeal

95. Whether certain effects observed in the first species PNDT study are reversible is not decisive in deciding whether there is a potential concern that requires clarification. The aim of substance evaluation is to clarify uncertainty. In this case, whether the effects are reversible or not does not resolve the questions regarding the potential developmental toxicity of the Substance. One of the purposes of the requested study is to clarify whether effects on the ureter are caused by the Substance, are statistically relevant, and are reversible. Even if the ureter effects were reversible, such effects may still require clarification as part of the assessment of the developmental toxicity potential of the Substance. No conclusion has been reached to date in regard of the reversibility of effects.

96. The Appellants' arguments do not resolve whether there is a potential hazard with regard to developmental toxicity, just that they disagree with the Agency's interpretation of the data. Even if the Appellants' interpretation of the data were correct, this would not mean that there is not a potential concern for developmental toxicity based on all the results of the first species PNDT study.

97. The Appellants' plea that the Agency committed an error of assessment in concluding that a second species PNDT study is required despite the fact that the effects on the ureter observed are transient must therefore be rejected.

4. Conclusion on plea A

98. As stated in the Contested Decision, the first species PNDT study provides insufficient evidence to classify the Substance as a reproductive toxicant, but is sufficient to trigger a second species PNDT study to clarify the potential concern for developmental toxicity.

99. The Agency has demonstrated that the Substance poses a potential risk for developmental toxicity. The Agency has demonstrated that developmental toxicity needs to be further examined by conducting a second species PNDT study in order to clarify whether the potential risk is an actual risk. In this respect it should be recalled that the Agency has not yet concluded that the Substance is a developmental toxicant. The purpose of the PNDT study in the second species is to clarify the potential concern for developmental toxicity. The request for a second species PNDT study is consistent with the aims of substance evaluation.

100. The approach taken by the Agency in the Contested Decision is also consistent with 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* v *Council*, T-13/99, EU:T:2002:209, paragraph 144).

101. The Agency examined carefully and impartially all the relevant facts of the present case which support the conclusions reached. The Appellants' argument that the Agency committed an error of assessment in concluding that there is a potential concern for developmental toxicity that should be examined through a second species PNDT study is therefore rejected.

B - Breach of the REACH Regulation through the use of the substance evaluation procedure instead of the compliance check procedure

Arguments of the Parties

102. The Appellants argue that the Agency was under an obligation to review the lead registrant's dossier update of 24 June 2014 under the dossier evaluation procedure pursuant to Article 42. In support of their plea the Appellants argue that:

- '*the follow up on the Appellants' dossier update further to the Contested Decision will be the responsibility of the eMSCA while, had Article 42 been correctly followed, the dossier update on the PNDT endpoint would have been the responsibility of [the Agency]. […] [Only the Agency] has reviewed the results of the first PNDT. The eMSCA has not carried out such review. The Appellants have serious concern that the follow up of the Contested Decision on that particular endpoint may not provide the assurances that their earlier comments and reservations on the necessity of a second PNDT study may have been duly considered and heard*',
- if the Agency had requested the second species PNDT study under Article 42 '*…Member States would have had an opportunity to submit Proposals for Amendment on the Agency's draft decision adopted in that context (on the basis of Article 51(2)). The Appellants would also have had two opportunities to comment (once on the draft compliance check draft decision, and secondly on such proposals for amendment)*',
- based on the Board of Appeal's previous decisions, '*it is advisable that, in general, and more in particular where the test requirements correspond to standard requirements in the Annexes to the REACH Regulation, a compliance check procedure should precede a substance evaluation procedure*', and
- the cost of performing the test must now be shared by all registrants regardless of the tonnage band at which they registered the Substance. If the test was requested under dossier evaluation the cost of performing the test would only need to be shared by those who registered the Substance according to the Annexes IX and X tonnage bands.

103. The Agency contests the Appellants' arguments for the following reasons:

- the second species PNDT study set out in Column 2 of Section 8.7.2. of Annex IX is an adaptation and not a standard information requirement. It can be requested under either dossier evaluation or substance evaluation,
- the particular nature of the information request in the present case, as well as the need for procedural economy, justify the choice to request the second species PNDT study under the substance evaluation process, and

- the addressee of the decision requesting a first species PNDT study (i.e. the lead registrant) had met its obligations under that decision by updating its registration dossier with the requested information. As a result, the Agency rightfully sent an Article 42(2) notification to the Commission and the MSCAs closing the dossier evaluation (see paragraph 10 above). The Agency therefore did not breach Article 42.

Findings of the Board of Appeal

104. In order to assess whether the second species PNDT study should have been requested under dossier evaluation it is necessary to examine, first, whether a second species PNDT study is required for registration purposes under Annex IX. The Board of Appeal will then consider, second, whether the Agency breached Article 42 and, third, whether the Agency breached Article 46.

1. The second species PNDT study as a registration requirement under Annex IX

105. The information that must be provided for registration purposes includes the 'standard information' set out in Annexes VII to X (the 'testing Annexes'). Annex XI, and Column 2 of each testing Annex, detail how the information required by the testing Annexes can be adapted for registration purposes.

106. An information requirement for PNDT is included for the first time in Annex IX which sets out the information required for all substances manufactured or imported in quantities of 100 to 1 000 tonnes year.

107. Column 1 of Section 8.7.2. of Annex IX requires a '*[p]re-natal developmental toxicity study, one species, most appropriate route of administration, having regard to the likely route of human exposure (B.31 of the Commission Regulation on test methods as specified in Article 13(3) or OECD 414)*.'

108. Column 2 of Section 8.7.2. of Annex IX, entitled '*specific rules for adaptation from Column 1*' (emphasis added), provides that '*[t]he Study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data*'.

109. Where a registrant has performed a first species PNDT study, the application of Column 2 of Section 8.7.2 of Annex IX is a direct consequence of the Column 1 requirement. It is not optional. This is because it requires the registrant to consider the outcome of the first species test as well as all other relevant available data. The registrant must consequently either conduct a second species PNDT study or satisfy the information requirement through an adaptation. An adaptation can be provided pursuant to Annex XI or Column 2 of Section 8.7.2 of Annex IX.

110. If a registrant considers that a second species PNDT study is not required under Annex IX, pursuant to the adaptation possibility at Column 2 of Section 8.7.2. of Annex IX it must include a justification to that effect in its registration dossier (see Case A-004-2012, *Lanxess Deutschland*, Decision of the Board of Appeal of 10 October 2013, paragraph 79).

111. The requirement to provide a justification for not performing the second species PNDT study is made clear in the second paragraph of the introduction to Annex IX, which provides that '*[i]f the conditions are met under which column 2 of this Annex allows an adaptation to be proposed, the registrant shall clearly state this fact and the reasons for proposing each adaptation under the appropriate headings in the registration dossier*' (emphasis added).

112. Consequently, to meet their registration obligations, where a first species PNDT study has been conducted, registrants registering a substance at 100 to 1 000 tonnes per year must:

- conduct a second species PNDT study pursuant to Column 2 of Section 8.7.2 of Annex IX, or
- provide a justification as to why a second species PNDT study is not required at the Anne IX level pursuant to Column 2 of Section 8.7.2 of Annex IX, or
- satisfy the information requirement through the application of Annex XI.

113. To meet their registration obligations, registrants must provide this information in their registration dossiers. The information provided may then be verified by the Agency as part of a compliance check pursuant to Article 41(1).

2. Breach of Article 42

114. The Appellants argue that, by requesting the second species PNDT study under substance evaluation, the Agency breached Article 42 which sets out the procedure for the follow-up to dossier evaluation decisions.

115. Article 42 provides:

'*1. The Agency shall examine any information submitted in consequence of a decision taken under Articles 40 or 41, and draft any appropriate decisions in accordance with these Articles, if necessary.*

2. Once the dossier evaluation is completed, the Agency shall notify the Commission and the competent authorities of the Member States of the information obtained and any conclusions made. […]'.

116. The results of the first species PNDT study were provided by the lead registrant in dossier updates on 3 and 24 June 2014. This followed an Agency testing proposal decision of 20 December 2012. The lead registrant concluded that the results of the first species PNDT study, and other available information, showed that no further testing was required. In its opinion, there was no evidence that the Substance has an adverse effect on reproductive functions in the absence of maternal toxicity. In other words, the effects observed were either naturally occurring or caused by maternal toxicity and not developmental toxicity.

117. The Agency examined the information provided by the Appellants as a follow-up action consequent to the request for a first species PNDT study. On 10 September 2014, pursuant to Article 42(2), the Agency sent a communication to the Member States and the Commission closing the dossier evaluation related to the testing proposal decision of 20 December 2012. The communication confirmed that the lead registrant had complied with the testing proposal decision and included a recommendation for follow-up action in either a further dossier evaluation or a substance evaluation.

118. The Agency did not therefore breach Article 42 as it evaluated the information '*submitted in consequence*' of the testing proposal decision of 20 December 2012 and concluded that the lead registrant had complied with that decision and that the '*dossier evaluation was therefore complete*'. This course of action is consistent with Article 42(2).

119. In the circumstances of this case, the Agency was not required to follow the procedure set out in Article 42(1). As the testing proposal process was considered to be complete it was not necessary for the Agency to draft a decision in accordance with Article 40 and in turn go through the decision-making procedure foreseen in Articles 50 and 51. If the Agency had concluded that the information provided by the Appellants did not satisfy the information requested in the testing proposal decision of 20 December 2012, the Agency may, depending on the information provided, have been required to draft a new

decision in accordance with Article 42(1), following the procedure set out in Articles 50 and 51 (see Case A-019-2013, *Solutia Europe*, Decision of the Board of Appeal of 29 July 2015, paragraphs 73 to 91). This was however not the situation in the present case.

120. The Appellants' plea that the Agency breached Article 42 is therefore rejected.

3. Breach of Article 46

121. The Appellants argue that, by requesting the second species PNDT study under substance evaluation, the Agency breached Article 46.

122. Registrants at the 100 to 1 000 tonnes per year tonnage band must provide either the results of a second species PNDT study or an adaptation for registration purposes (see paragraphs 105 to 113 above). It is therefore clear that the Agency could have requested a second species PNDT study under dossier evaluation.

123. In the present case, however, the Agency requested the information under substance evaluation. Although dossier evaluation should normally precede substance evaluation, the standard information requirements set out in Annexes VII to X may, in certain circumstances, also be requested under substance evaluation (see *Akzo Nobel Industrial Chemicals and Others*, cited in paragraph 41 above, paragraphs 77 to 90). In order to be able to use the substance evaluation procedure rather than the dossier evaluation procedure, amongst other things:

(a) the Agency must be able to demonstrate that the substance concerned presents a potential risk to human health or the environment (see paragraph 40 above); and

(b) the rights of all current registrants of the substance concerned must not be prejudiced by the Agency's decision to follow the substance evaluation rather than the dossier evaluation procedure.

(a) Demonstration of a potential risk

124. As stated in paragraph 40 above, a potential risk must be demonstrated in order to request information under substance evaluation. A conclusion that the Appellants failed to provide certain standard information in their registration dossier cannot, on its own, constitute a potential risk (see *Akzo Nobel Industrial Chemicals and Others*, cited in paragraph 41 above, paragraph 75).

125. In the present case, the request to provide the second species PNDT study is not justified by a lack of standard information alone as it has been demonstrated that a potential risk to human health exists (see paragraphs 98 to 101 above).

(b) The Appellants' rights and the Agency's decision to request the information under substance evaluation

126. The Appellants' arguments that their rights were prejudiced by the Agency's choice of following the substance evaluation procedure rather than the dossier evaluation procedure are rejected for the following reasons.

127. First, all the addressees of the Contested Decision have registered the Substance at the 100 to 1 000 tonnes per year tonnage band. As a result, Section 8.7.2. of Annex IX is applicable to all addressees of the Contested Decision. None of the addressees of the Contested Decision are therefore required to provide information that they were not required to provide for registration purposes.

128. Second, as regards the Appellants' arguments on cost sharing (see paragraph 102 above), in the present case all the addressees of the Contested Decision have registered the Substance at the 100 to 1 000 tonnes per year tonnage band. Consequently, in the absence of any separate adaptations from individual registrants, they are required to

share the costs incurred in generating the information irrespective of whether the information was requested under dossier evaluation or substance evaluation.

129. With regard to the Appellants' arguments related to the potentially negative effects on future registrants, the Board of Appeal notes that the registration of the Substance by other manufacturers or importers is at present hypothetical. Furthermore, the Appellants have not shown that they have an interest in seeking to protect the rights of other (hypothetical) registrants.

130. Third, the Appellants did not conduct a second species PNDT study on the grounds that, in their opinion, the results of the first species PNDT study, and other available information, showed no concern. In the Contested Decision, the Agency addressed the adaptation – a justification for not performing a second species PNDT study – and rejected it. The Agency's reasoning for rejecting the adaptation was also found in its proposal for amendment. In the Contested Decision, the Agency also demonstrated that there was a potential risk that needs to be clarified. The Board of Appeal has found above that the Agency did not make an error of assessment in this respect (see paragraphs 98 to 101 above). In the present case, having regard to the content of Column 2 of Section 8.7.2. of Annex IX, the Agency's evaluation of the adaptation would have been the same under both dossier evaluation and substance evaluation. The Appellants' adaptation pursuant to Column 2 of Section 8.7.2. of Annex IX has therefore been taken into consideration and addressed by the Agency in the Contested Decision.

131. Fourth, the Appellants' arguments that, in the follow-up to the Contested Decision pursuant to Article 48, the eMSCA may not take into consideration the Appellants' earlier comments that a second species PNDT study is not necessary (see paragraph 102 above) are speculative. The eMSCA must take into account all available information when considering what additional action to take, if any, following the expiry of the time-limit set out in the Contested Decision. In addition, the Appellants' comments on the necessity for a second species PNDT study, made in the comments on the proposals for amendment, have been considered by the eMSCA prior to the adoption of the Contested Decision.

132. The eMSCA was aware of the dossier update including the results of the first species PNDT study. For example, in their comments of 26 May 2014 on the draft decision the Appellants informed the eMSCA that they would update their registration dossier by 20 June 2014 pursuant to the testing proposal decision. The Article 42(2) communication from the Agency also informed the Member States that the Appellants had provided the first species PNDT study. Therefore there is no evidence to suggest that the eMSCA does not have access to the updated registration dossier and will not take the registration update (the second species PNDT study) and the Appellants' earlier comments, arguing that a second species PNDT study is not necessary, into account in its follow up actions.

133. For the reasons set out in paragraphs 126 to 132 above, in the specific circumstances of the present case, the Appellants' rights were not prejudiced by the Agency's use of the substance evaluation procedure rather than the dossier evaluation procedure. The Appellants' plea that the Agency breached Article 46 is therefore rejected.

134. In general the Agency must provide sufficient reasoning to justify, in light of the objectives of the REACH Regulation and the substance evaluation process, and in particular the protection of human health and the environment, requesting information that should have ordinarily been requested following a dossier evaluation procedure under substance evaluation (*Akzo Nobel Industrial Chemicals and Others*, cited above in paragraph 41, paragraph 90). However, in the present case, the Agency considered that a second species PNDT study was not a standard information requirement and, as a result, it did not provide such a justification in the Contested Decision. Nevertheless, the Board of Appeal has found that the Agency was, in the present case, justified in requesting the second species PNDT study under substance evaluation. In the

circumstances of the present case, therefore, the absence from the Contested Decision of a justification for requesting a second species PNDT study under substance evaluation does not lead to the annulment of the contested information requirement. If the evaluation had been conducted under dossier evaluation the result would have been the same.

C - The Agency's breach of its own guidance by changing the date by which dossier updates will be considered – legitimate expectations

Arguments of the Parties

135. The Appellants argue that by amending the date after which no dossier updates would be taken into consideration and therefore enlarging the scope of the substance evaluation process to include the first species PNDT study, the Agency failed to follow its own guidance (*Evaluation under REACH: progress report 2015 – recommendations to registrants*, version February 2016; the '2015 evaluation report').

136. The Agency argues that it made a proposal to change the date of the dossier update in a proposal for amendment. This proposal was accepted by the eMSCA and agreed in the MSC. The Agency did not therefore unilaterally amend the draft decision with regard to the cut-off point for updates.

Findings of the Board of Appeal

137. The Appellants' plea that the Agency breached its own guidance by changing the cut-off point for updates in effect amounts to an allegation that their legitimate expectations were breached.

138. 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 judgment of 13 June 2013, *HGA and Others* v *Commission*, C-630/11 P to C-633/11 P, EU:C:2013:387, paragraph 132 and the case-law cited).

139. The Appellants' claim that their expectations were based on the 2015 evaluation report, which states:

'*[I]f the substance is listed within the first year of the CoRAP, where the eMSCA will begin their evaluation once the CoRAP is published, registrants should avoid submitting new dossier updates for that substance. Instead, any planned dossier update should be communicated and agreed with the eMSCA beforehand, to prevent delays in the evaluation process.*

Observation: By default, dossier updates received after the day on which the draft decision was notified to the registrants will only be considered if agreed in advance with the eMSCA. Dossier updates received after the deadline agreed with the eMSCA will not be taken into account'.

140. A similar statement is found in the letter accompanying the draft decision of 29 April 2014, which states:

'*[U]pdates of the registrations received after the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation will normally not be taken into consideration.*

However, such an update may be taken into consideration if agreed in advance with the [eMSCA]. The registration update should support the Registrant comments submitted during the 30 day commenting period. The update must be received within 60 days after notification of the draft decision to the registrant (i.e. 60 days after receipt of the present communication […].'

141. The Appellants updated their dossier with the results of the first species PNDT study on 3 and 24 June 2014. This was after the draft decision was sent to them for comments but before the expiry of the 60-day deadline for a dossier update referred to in the previous paragraph.

142. The revised draft decision of 5 March 2015, which the eMSCA notified to the MSCAs and the Agency requesting proposals for amendment, stated:

'*This decision is based on the registration dossier(s) on 28 February 2014, i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) […]*'.

143. However, the date of 28 February 2014 in the revised draft decision was clearly incorrect as the draft decision was actually notified to the Appellants on 29 April 2014.

144. The Agency stated in its proposals for amendment that:

'*[The Agency] considers that the update of 24 June 2014 should be considered in this decision making phase since it has been submitted within 60 days after the notification of the [draft decision] to the Registrant(s) and this update was anticipated by the Registrant in its comment of 21 May 2014 ("we agree with the proposed time frame of 12 months. In fact, we anticipate this being ready for our Annex IX lead dossier update that is due June 20, 2014.").*

Therefore [the Agency] suggests to change the sentence "This decision is based on the registration dossier(s) on 28 February 2014, i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation." with the following one: "This decision is based on the registration dossier(s) on 24 June 2014".'

145. The Appellants stated in their observations on the Agency's proposal for amendment that they '*agreed*' with this proposed amendment.

146. The Agency's proposal for amendment was accepted by the eMSCA and then the MSC. The Contested Decision states that it '*is based on the registration dossier(s) on 24 June 2014*.' In other words, the dossier updates of 3 and 24 June 2014, including the results of the first species PNDT study, are taken into account in the Contested Decision.

147. It is clear from the above that the date up to which dossier updates would be taken into account was changed in order to allow the results of the first species PNDT study to be taken into account.

148. The letter of 29 April 2014 (see paragraph 140 above) states that updates after the cut-off point '…*will <u>normally</u> not be taken into consideration'* [emphasis added]. It does not state that the updates will in no circumstances be taken into consideration. However, it is also clear that the circumstances of the change of date did not fall within the circumstances foreseen in that letter or the 2015 substance evaluation report (see paragraph 139 above). In particular, the update did not '*support the Registrant comments submitted during the 30 day commenting period*', and, although the eMSCA was aware of the lead registrant's intention to update its dossier it was not '*agreed in advance with the eMSCA*'.

149. However, the Appellants were made aware that the cut-off point for updates was proposed to be amended when they were notified of the Agency's proposals for amendment. In acknowledgment of this proposal the Appellants indicated that they agreed to the proposed change (see paragraph 145 above).

150. The Agency and the eMSCA were aware that the first species PNDT study would be included in a dossier update. On 18 October 2013, for example, the Appellants informed the eMSCA by email that the update would be made by the deadline set in the testing proposal decision (i.e. 20 June 2014). All parties concerned were therefore aware that the results of the first species PNDT study would be available and may have an impact on the on-going substance evaluation. In practice the dossier was updated on 3 June 2014 with the robust study summary and on 24 June 2014 with the full experimental results.

151. The Agency has introduced a cut-off point in the substance evaluation decision-making process after which it will not take into account new dossier updates. The cut-off point introduced by the Agency is an administrative practice which is necessary to ensure the efficient functioning of the decision-making process. The Board of Appeal has held previously that practices such as the setting of a cut-off point in a decision-making process may fall within the Agency's margin of discretion (see by analogy A-001-2014, *CINIC Chemicals Europe*, Decision of the Board of Appeal of 10 June 2015, paragraph 78).

152. In exercising its discretion the Agency is required to take into consideration all the relevant factors and circumstances of the situation the act was intended to regulate (see, by analogy, judgment of 7 March 2013, *Rütgers Germany and Others v ECHA*, T-96/10, EU:T:2013:109, paragraph 100). Likewise, Article 47(1) requires that, '*an evaluation of a substance shall be based on all relevant information submitted on that particular substance and on any previous evaluation under [Title VI – Evaluation]*.' The Board of Appeal has also previously held that the Agency may be required to take into account substantial new information that comes to light before the adoption of the decision in question. In particular, the early assessment of information coming to light after the cut-off point and before the adoption of a decision can serve the objectives of the protection of human health and the environment (see *CINIC Chemicals Europe*, cited in the previous paragraph, paragraphs 68 to 105). Administrative practices designed to facilitate the decision-making process must not operate to frustrate the Agency's obligation to take into account all information.

153. In this respect, the first species PNDT study showed a potential concern for developmental toxicity (see paragraphs 42 to 101 above). The results of the first species PNDT study are therefore highly relevant for the substance evaluation of the Substance. That information must therefore be taken into account in the decision-making process.

154. The general rule stated in the 2015 evaluation report (see paragraph 139 above) and the letter accompanying the draft decision of 29 April 2014 (see paragraph 140 above) is that there will be no changes in the date before which updates must be made in order for them to be considered. However, in the present case, the Agency was justified in taking the registration dossier update into account for the following reasons:

- The Appellants were informed of, and agreed with, this course of action;
- The Appellants were fully aware of the updated information which was generated by themselves;
- The information was clearly relevant for the decision-making process; and
- The early assessment of this information, before the adoption of the Contested Decision, served the objectives of the protection of human health and the environment by ensuring that information relevant for the evaluation of the Substance would be requested as quickly as possible.

155. The Board of Appeal finds therefore that, whilst the Agency departed from its position in the 2015 evaluation report and its letter of 29 April 2014, in the present case the Agency did not breach the Appellants' legitimate expectations. The Appellants' plea is therefore rejected.

D - Misuse of powers

Arguments of the Parties

156. The Appellants argue that by using the substance evaluation procedure to assess the information submitted under Article 40, instead of using the procedure under Article 42, the Agency misused its powers. In particular, it:

- avoided the need to assess the dossier update of 24 June 2014 against the requirements of Annex IX, and
- took a procedural short-cut that did not allow the Member States to submit formal proposals for amendment pursuant to Article 51(2) on the added requirement to perform a second species PNDT study. Had the Agency used the Article 42 procedure the Members States would have had the possibility to make such proposals for amendment.

157. The Agency disputes the Appellants' arguments.

Findings of the Board of Appeal

158. In assessing whether the Agency misused its powers, the Board of Appeal must examine whether the Agency adopted a measure with the exclusive or main purpose of achieving an end other than that stated or evading a procedure specifically prescribed by the REACH Regulation for dealing with the circumstances of the case (judgment of 12 November 1996, *United Kingdom* v *Council*, C-84/94, EU:C:1996:431, paragraph 69). It is for the Appellants to provide objective evidence that the Agency acted unlawfully by misusing its power (Case A-004-2014, *MCCP registrants*, Decision of the Board of Appeal of 9 September 2014, paragraph 43).

159. The Board of Appeal has found, in paragraphs 39 to 134 above, that the Agency could legitimately require the second species PNDT study under substance evaluation.

160. It is correct that the competent authorities of the Member States could not provide proposals for amendment within the meaning of Article 51(2) related to the proposal for a second species PNDT study. Nonetheless, the MSC members, having before them the proposal for amendment regarding the second species PNDT study and the Appellants' comments on that proposal, adopted the Contested Decision without using the possibility under the written procedure to either stop the procedure or disagree with the draft decision.

161. The Appellants' argument that the Agency chose to follow the substance evaluation procedure to avoid the need to assess the new information against the requirements of Annex IX is also rejected. The Appellants' justification regarding the adaptation possibility in Column 2 of Section 8.7.2. of Annex IX was addressed in the Contested Decision as part of the Agency's demonstration of the potential risk (see paragraphs 42 to 101 above).

162. The Agency did not adopt the Contested Decision with the exclusive or main purpose of achieving an end other than that stated or evading a procedure specifically prescribed by the REACH Regulation for dealing with the circumstances of the case. As a result, the Appellants' plea that the Agency misused its powers must be rejected.

E - Breach of the duty to state reasons

Arguments of the Parties

163. The Appellants argue that the Agency failed to state reasons in the Contested Decision regarding the Appellants' comments and arguments on:

- the findings in the Solecki *et al*. publication,
- the Agency's evaluation of maternal toxicity,
- the statistical significance of the effects observed on fetuses at lower dose levels, and
- the reversibility of effects observed in the first species PNDT study.

164. The Appellants argue that, as the Contested Decision was not discussed at an MSC meeting, they were denied an opportunity to understand whether, and if so how, their comments were taken into consideration.

165. The Agency contests the Appellants' arguments for the following reasons:

- for the purposes of the duty to state reasons, the Contested Decision does not need to address all comments made by the Appellants during the decision-making process,
- the Agency set out the reasons for the information requests; the Appellants seem rather to disagree with the scientific assessment set out in the Contested Decision, and
- the Contested Decision was agreed by the MSC in a written procedure and the MSC's rules of procedure were correctly followed.

Findings of the Board of Appeal

166. Pursuant to the second paragraph of Article 296 of the Treaty on the Functioning of the European Union and Article 130 of the REACH Regulation, the Agency must state the reasons for any decision it takes.

167. A statement of reasons must be appropriate to the act at issue and must disclose in a clear and unequivocal fashion the reasoning followed by the institution which adopted the measure in question, in such a way as to enable the persons concerned to ascertain the reasons for the measure and to enable the European Union judicature to exercise its power of review (see judgment of 21 December 2016, C*lub Hotel Loutraki and Others* v *Commission*, C-131/15 P, EU:C:2016:989, paragraph 46). Whether a statement of reasons is adequate depends on all the circumstances of a case, in particular, the content of the measure in question, the nature of the reasons given and the interest which the addressees of the measure, or other parties to whom it is of direct and individual concern, may have in obtaining explanations (see judgment of 10 March 2016, *HeidelbergCement* v *Commission*, C-247/14 P, EU:C:2016:149, paragraph 16 and the case-law cited).

168. Having regard to the above, the Appellants' arguments regarding an alleged breach of the duty to state reasons must be rejected for the following reasons.

169. First, the Contested Decision states that '*the [MSC] took the comments of the Registrant on the proposals for amendment into account*'. According to case-law, such a statement may be sufficient to satisfy the requirements laid down in the case-law referred to in paragraph 167 above (see, to that effect, judgment of 16 March 2016, *Dextro Energy* v *Commission,* T-100/15, EU:T:2016:150, paragraph 124).

170. Second, the reasons for requesting the second species PNDT study are clearly set out in Section III(1) of the Contested Decision. The reasoning behind the request was also included in the Agency's proposals for amendment. This is sufficient for the Appellants to ascertain the reasons for the request for a second species PNDT and enables the Board of Appeal to exercise its power of review.

171. Third, Section III(1) of the Contested Decision contains a section addressing, albeit succinctly, some of the Appellants comments on the proposals for amendment. For example, in relation to the Appellants' arguments on reversibility the Contested Decision states that '*[t]he effects observed in rats (markedly reduced fetal weight and markedly [increased] incidence of dilated ureters at dose levels inducing slight or no maternal toxicity) are considered developmental delays per se insufficient to trigger classification as Repro 1B; conversely, such effects provide sufficient evidence to trigger a study in a second species, in order to assess whether in non-rodents the substance might induce severe and irreversible developmental toxicity*'.

172. The Appellants, however, seem to disagree with the conclusions reached by the Agency. In this respect, the duty to state reasons is different from the correctness of those reasons. The duty to state reasons is an essential procedural requirement which must be distinguished from the question whether the reasoning is well founded, which is concerned with the substantive legality of the measure at issue (judgment of 14 October 2010, *Deutsche Telekom* v *Commission,* C-280/08 P, EU:C:2010:603, paragraph 130, and Case A-006-2012, *Momentive Specialty Chemicals*, Decision of the Board of Appeal of 13 February 2014, paragraph 113). In addition, it is not necessary for the reasoning to go into all the relevant facts and points of law, since the question whether the statement of reasons for a measure satisfies the duty to state reasons must be assessed with regard not only to its wording but also to its context and to all the legal rules governing the matter in question. In particular, the Agency is not required to adopt a position on all the arguments relied on by the parties concerned, but it is sufficient if it sets out the facts and the legal considerations having decisive importance in the context of the decision (see judgment of 30 April 2014, *Hagenmeyer and Hahn* v *Commission*, C-17/12, EU:T:2014:234, paragraph 173 and the case-law cited).

173. Fourth, the Contested Decision was agreed in a written procedure. The draft decision was therefore not discussed at an MSC meeting prior to unanimous agreement being reached by the MSC on the Contested Decision. In addition, there is no requirement under the REACH Regulation for a draft decision to be discussed at a MSC meeting. Moreover, the participation of registrants in MSC meetings is not prescribed by the REACH Regulation. It is at the discretion of the MSC to decide whether such participation is appropriate (see Case A-006-2012, *Momentive Specialty Chemicals*, Decision of the Board of Appeal of 13 February 2014, paragraph 127). The Agency also did not therefore breach the Appellants' right to be heard, an implicit argument of the Appellants under their plea regarding the duty to state reasons, by the fact that the Appellants were not able to discuss the draft decision leading to the Contested Decision at a MSC meeting.

F - The Agency exceeded its competence by submitting proposals for amendment

Arguments of the Parties

174. The Appellants argue that, having regard to Article 51, the Agency has no power to submit proposals for amendment. The Appellants argue that the Agency '*only has the responsibility to either take a decision in the absence of any [proposals for amendment] received, or to modify the decision if [proposals for amendment] have been received*'.

175. The Agency argues that, according to Article 52, the procedure set out in Article 51 for dossier evaluation is applied '*mutatis mutandis'* to substance evaluation. Consequently, the procedure in Article 51 is not to be applied literally but needs to be adapted to the situation where the roles of the actors involved have changed.

176. The Agency argues that if it '*…would not be in a position to influence the decision-making and bring a case to the [MSC] meeting for discussion by all Member States, [the Agency] could face a substance evaluation decision that may have severe scientific or procedural shortcomings. In such situation [the Agency] would need to refuse adopting that decision and resources of the Member States would have been wasted*'.

Findings of the Board of Appeal

1. Relevant legislation

177. Article 46(1) provides:

'*If the competent authority considers that further information is required, including, if appropriate, information not required in Annexes VII to X, it shall prepare a draft decision, stating reasons, requiring the registrant(s) to submit the further information and setting a deadline for its submission. A draft decision shall be prepared within 12 months of the publication of the Community rolling action plan on the Agency's website for substances to be evaluated that year. The decision shall be taken in accordance with the procedure laid down in Articles 50 and 52*'.

178. Article 50(1) provides:

'*The 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*'.

179. Article 51(2) to (8) provide:

'*2. Within 30 days of circulation, the Member States may propose amendments to the draft decision to the Agency.*

3. If the Agency does not receive any proposals, it shall take the decision in the version notified under paragraph 1.

4. If the Agency receives a proposal for amendment, it may modify the draft decision. The Agency shall refer a draft decision, together with any amendments proposed, to the Member State Committee within 15 days of the end of the 30-day period referred to in paragraph 2.

5. The 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.

6. If, within 60 days of the referral, the Member State Committee reaches a unanimous agreement on the draft decision, the Agency shall take the decision accordingly.

7. If the Member State Committee fails to reach unanimous agreement, the Commission shall prepare a draft decision to be taken in accordance with the procedure referred to in Article 133(3).

8. An appeal may be brought, in accordance with Articles 91, 92 and 93, against Agency decisions under paragraphs 3 and 6 of this Article'.

180. Article 52(1) provides:

'*1. The competent authority shall circulate its draft decision in accordance with Article 46, together with any comments by the registrant or downstream user, to the Agency and to the competent authorities of the other Member States.*'

181. Article 52(2) provides that the decision-making procedure set out in Article 51(2) to (8) for dossier evaluation decision must be applied to the substance evaluation decision-making process '*mutatis mutandis'.*

2. Assessment

182. Article 51 sets out the procedure to be followed under dossier evaluation. With regards to substance evaluation, Article 52(2) provides that Article 51(2) to (8) applies '*mutatis mutandis'*. This must be taken to mean that the procedure in Article 51(2) to (8) applies with the necessary changes. For the purposes of the Appellants' plea the question of what those necessary changes are must be examined.

183. Article 47 provides that '*an evaluation of a substance shall be based on all relevant information submitted on that particular substance and on any previous evaluation*'. The Board of Appeal has also previously held that the Agency must take into account substantial new information which comes to light prior to the adoption of the decision in question (see paragraph 152 above). There must therefore be a possibility for the Agency, in some form or other, to bring relevant information to the attention of the evaluating Member State Competent Authority and the other Member States and their competent authorities.

184. In the present case, if the Agency had not had the possibility to contribute to the decision-making process prior to the adoption of the final decision, it could have led to the Contested Decision being adopted without *'all relevant information',* and substantial new information in this case, being taking into account.

185. Article 51(2) does not explicitly foresee the possibility for the Agency to make proposals for amendment in the same way as the Member States. However, that provision sets out first and foremost the procedure to be followed for dossier evaluation. Under dossier evaluation the Agency is responsible for preparing draft decisions. There was therefore no need for the legislature to foresee the possibility for the Agency to make proposals for amendment to its own draft. In contrast, under substance evaluation the draft decision is prepared by the evaluating Member State Competent Authority. As the initial drafter of the decision is another body (the evaluating member state competent authority), and in view of the Agency's obligation to ensure that all relevant information is taken into account (see paragraphs 152 and 183 above), it is necessary to interpret Article 51(2) to (8) as meaning that the Agency is given the possibility to make proposals for amendment. This allows the Agency to ensure, for example, that the correct legal procedures are followed and all relevant information is taken into account.

186. It should also be borne in mind that proposals for amendment made by the Agency are not automatically included in a final substance evaluation decision. The registrants are given the opportunity to comment on such proposals for amendment and, if included in the draft decision, they must be agreed unanimously by the MSC.

187. In view of the above, the Appellants' plea that the Agency exceeded its competence by submitting proposals for amendment to itself must be rejected.

II. Pleas in relation to the request to provide information on a Comet assay

188. Before examining the Appellants' substantive pleas the Board of Appeal will assess the Agency's plea that the Appellants' arguments regarding exposure to the Substance are inadmissible.

A - Admissibility of the Appellants' arguments on exposure

Arguments of the Parties

189. In their observations on the Defence the Appellants argue that it was clear from the Chemical Safety Report attached to the lead registrant's registration dossier that the only anticipated route of exposure is dermal. The Appellants' argue that exposure via the inhalation route can be excluded as a result of the Substance's extremely low vapour pressure and very low fugacity. According to the Appellants, '*[t]he likelihood of exposure by oral ingestion is not expected from the identified uses and the environmental instability*'. The Appellants argue that a study aimed at investigating the possible mutagenic effect on stomach tissue does not respond to a plausible risk and is therefore not necessary.

190. The Agency argues that the Appellants' arguments on exposure, as set out in the previous paragraph, are inadmissible because they were not raised in the Notice of Appeal.

Findings of the Board of Appeal

191. The rules on the admissibility of pleas in law are set out in Article 12(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; as amended by Commission Implementing Regulation (EU) 2016/823, OJ L 137, 26.5.2016, p. 4; the 'Rules of Procedure')

192. Article 12(2) provides that '*[n]o new plea in law may be introduced after the first exchange of written pleadings unless the Board of Appeal decides that it is based on new matters of law or of fact that come to light in the course of the proceedings*'.

193. The Appellants' arguments regarding exposure do not constitute a new plea in law within the meaning of Article 12(2) of the Rules of Procedure for the following reasons.

194. First, the arguments on exposure are presented in support of the plea raised in the Notice of Appeal that the Agency committed a manifest error of assessment in interpreting the information in the registration dossier as demonstrating that there is a concern that needs to be addressed.

195. Second, the arguments on exposure support the Appellants' argument, made in the Notice of Appeal, that the risk identified by the Agency is hypothetical as the Substance will not reach the stomach. For example, in the Notice of Appeal the Appellants state that '*clarifying the mutagenic potential of the Substance is only of academic interest since the toxicokinetic properties of the Substance show that it is not possible in realistic situations'* [emphasis added].

196. Third, it has not been disputed by the Agency that the Appellants' conclusions on exposure (see paragraph 189 above) can be reached from the information available in the Chemical Safety Report. Consequently, the arguments on exposure do not constitute a new fact.

197. The Agency's inadmissibility arguments are therefore rejected.

B - Pleas concerning the requirement to perform a Comet assay

198. The Appellants raise four pleas in law:

1. Manifest error of assessment in interpreting the information contained in the registration dossier as demonstrating that there is a concern.
2. Manifest error of assessment in concluding that there is a mutagenicity concern *in vivo* despite the available scientific information to the contrary.
3. The Comet assay is not appropriate to address the alleged concern.
4. Failure to state reasons for disregarding the eMSCA's initial conclusion that no information on carcinogenicity is needed.

1. Manifest error of assessment in interpreting the information contained in the registration dossier as demonstrating that there is a concern

Arguments of the Parties

199. The Appellants argue that the Agency committed a manifest error of assessment in interpreting the information in the lead registrant's registration dossier as meaning that there is a mutagenicity concern for the Substance.

200. The Appellants argue that the Agency committed a manifest error of assessment by failing either to consider completely, or inadequately interpreted, their comments on the proposals for amendment. If these comments had been addressed properly the Agency would have concluded that there was not a mutagenicity concern. These comments indicated that:

- whilst *in vitro* mutagenicity studies showed some positive results, available toxicokinetic information (NTP micronucleus study, Matthews, H.B. 1992; the 'NTP micronucleus study') shows that the Substance degrades rapidly in biological media, in particular in the stomach, to non-mutagenic metabolites,
- as degradation to non-mutagenic substances occurs rapidly, additional testing would only be potentially justified if it is plausible that the Substance will come in contact with parts of the body where a mutagenic potential could be expressed; the Contested Decision, however, fails to provide any justification that this is indeed plausible,
- a study by Hanausek *et al.* (Hanausek, M. *et al.* Carcinogenesis vol. 25 no. 3, p. 431, 2004, the 'Hanausek study') clearly establishes that the Substance '*did not produce detectable mutations in the c-Ha-ras protooncogene, indicating it does not possess tumor initiating or complete carcinogenic activity*', and
- '*the likelihood of exposure by oral ingestion is not expected from the identified uses and the environmental instability*'.

201. The Agency argues that:

- it took into account the Appellants' comments on the proposals for amendment,
- it took into account all available information, including the NTP micronucleus study and the Hanausek study,
- the Contested Decision explains that the Substance may reach '*the precise location of the body where a mutagenic potential could be expressed*',
- only dermal exposure was investigated in the Hanausek study and other first sites of contact were not addressed, and

- besides showing that the Substance caused oxidative DNA damage, the Hanausek study also showed that the Substance caused a significant increase in all three biomarkers associated with tumour promoting activity.

202. The Agency argued at the hearing that, based on the judgment of the Court of Justice of 21 July 2011 in Case C-15/10, *Etimine*, EU:C:2011:504, for classification purposes it is only necessary to look at hazard. It is not necessary to perform a risk assessment or exposure assessment for classification purposes.

Findings of the Board of Appeal

203. The Appellants argue in essence that the Agency committed a manifest error of assessment by (a) failing to take into account its comments on the proposals for amendment and (b) by failing to demonstrate a concern that would justify requesting additional information to investigate potential mutagenicity.

(a) Failure to take into account the Appellants' comments on the proposals for amendment

204. As stated in paragraph 45 above, when examining whether the Agency has made a manifest error of assessment, the Board of Appeal must examine whether the Agency has examined carefully and impartially all the relevant facts of the individual case which support the conclusions reached.

205. The Appellants' arguments that the Agency failed to take into account their comments on the proposals for amendment, and in particular the relevance of the NTP micronucleus study and the Hanausek study, are rejected for the following reasons.

206. The robust study summary for the NTP micronucleus study, included in the lead registrant's registration dossier and attached to the Notice of Appeal, also addresses the Hanausek study. The robust study summary was used by the Appellants to justify their argument that no further testing is needed to examine mutagenicity. These arguments were not therefore raised for the first time in the proposals for amendment. The lead registrant's registration dossier, including the robust study summary for the NTP micronucleus study, was the main basis for the substance evaluation and was reflected in the substance evaluation report.

207. The results of the NTP micronucleus study were also discussed in the proposals for amendment submitted by Danish MSCA. The Appellants' comments on the proposals for amendment included similar observations to those included in the robust study summary for the NTP micronucleus study as well as additional comments. The issues raised were therefore addressed in both the substance evaluation report and the proposals for amendment submitted by Denmark.

208. The Appellants' comments related to the Hanausek study and the NTP micronucleus study are further discussed in Section III(2) of the Contested Decision. The Contested Decision sets out why the Hanausek study cannot be used to rule out a local genotoxicity potential. The Contested Decision acknowledges that in toxicokinetic studies the Substance rapidly degrades in the stomach and therefore no systemic exposure is observed after oral administration. However, genotoxic effects at the site of contact could not be excluded. In relation to the NTP micronucleus study the Contested Decision states that '*[t]he negative in vivo micronucleus assay on peripheral lymphocytes (NTP, Matthews, H.B. 1992) submitted by the Registrant(s) cannot be considered an appropriate study, as no evidence of target cell exposure (local cytotoxicity, i.e. alteration of PCE/NCE ratio) was reported. Moreover, toxicokinetic studies (NTP, Matthews, H.B.; 1992) demonstrated that [the Substance] is rapidly degraded in the stomach and consequently no systemic exposure is observed after oral administration*'.

209. In light of the above, it is clear that the Appellants' comments on the proposals for amendment, and in particular the relevance of the NTP micronucleus study and the Hanausek study, were taken into consideration in the decision-making process. The Appellants' arguments that the Agency failed to take into account this information appears to relate more to the fact that they disagree with the Agency's interpretation of that information.

210. The Board of Appeal will next consider whether the Agency nonetheless made an error of assessment in concluding, based on the available information, that there was a concern for mutagenicity which required further investigation.

(b) Failure to establish a mutagenicity concern

(i) Criteria for establishing a concern

211. As stated in paragraph 40 above, under substance evaluation, in order to establish the necessity of a request for additional information there must, amongst other things, be grounds indicating that a substance constitutes a potential risk to human health or the environment, the potential risk needs to be clarified, and the requested measure, in clarifying the concern, has a realistic possibility of leading to improved risk management measures.

212. As stated in paragraph 41 above, the identification of a potential risk is based on a combination of exposure information and hazard information.

213. The Agency's argument (see paragraph 202 above) that it is not necessary to demonstrate potential exposure under substance evaluation is therefore rejected.

214. In its judgment of 21 July 2011, *Etimine*, C-15/10 (EU:C:2011:504, paragraph 75), the Court of Justice found that it is not necessary to take into consideration exposure in the assessment of a substance's intrinsic properties. However, that case concerned classification and labelling. Under substance evaluation, the generation of information must be tailored to addressing a potential risk and real information needs (see Recital 63 and Case A-005-2014, *Akzo Nobel Industrial Chemicals and Others*, Decision of the Board of Appeal of 23 September 2015, paragraph 60). A potential risk requires there to be both hazard and exposure elements.

(ii) Hazard concern identified by the Agency in the present case to justify requesting the Comet assay

215. According to the Contested Decision:

'*[The Substance] causes both chromosome aberrations and gene mutations in vitro. The [Substance] yielded a positive result in the in vitro mammalian chromosome aberration test (NTP, Matthews, H.B. 1992) with and without metabolic activation (Klimisch score 2, reliable with restrictions) according to the Registrant(s).*

The [Substance] also yielded positive results in the AMES test (NTP, Matthews, H.B. 1992) in Salmonella typhimurium strains TA100, TA1537, and TA98, with and without metabolic activation, as well as in the Mouse Lymphoma Forward Mutation Assay (Pence, D.H.;1984) with and without metabolic activation. Both studies are Klimisch score 2 (reliable with restrictions) according to the Registrant(s). This indicates that the substance causes gene mutations in vitro.'

(iii) The manifest errors which the Appellants claim lead the Agency to conclude mistakenly that there is a mutagenicity concern

216. When an appellant claims that the Agency has made a manifest error of assessment, the Board of Appeal must examine whether the Agency has examined carefully and impartially all the relevant facts of the individual case which support the conclusions reached (see paragraph 45 above).

217. The Appellants argue in essence that additional *in vivo* tests for mutagenicity are not necessary because the Substance rapidly degrades to non-mutagenic metabolites and therefore will not reach a location where mutagenic potential could be expressed, and the Hanausek study shows that the Substance does not have mutagenic potential.

- *The Substance will not reach a location where mutagenic potential could be expressed due to rapid degradation*

218. The Appellants arguments that it is not plausible for the Substance to reach the precise location of body where a mutagenic potential could be expressed are rejected for the following reasons.

219. First, the robust study summary for the NTP micronucleus study concludes, amongst other things, that the Substance, which is highly reactive, '*…degraded in a 20 % suspension of stomach contents in this buffer in a concentration-dependent fashion. [The Substance] concentrations of 1.1, 0.11, and 0.011 mg/ml degraded by 0, 31, and 74 %, respectively, in 1 hour at 37 °C in a suspension of stomach contents*'. From these findings, whilst the Substance may degrade rapidly, it is possible that a significant amount of the Substance will remain in the stomach after one hour.

220. Second, the robust study summary for the NTP micronucleus study also concludes that '*the stability of [the Substance] in a suspension of stomach contents was concentration dependent but was thought to be sufficient to permit some absorption of the parent molecule into stomach tissue*' (emphasis added). From this statement it is clear that some exposure of the stomach to the Substance is possible.

221. Third, whilst the fact that the Substance degrades rapidly means there is likely to be limited or no systemic exposure after oral administration, based on the results of the *in vitro* mutagenicity study, there may be genotoxic effects at the site of contact.

- *The Hanausek study shows that the Substance does not have mutagenic potential*

222. Neither the Hanausek study nor its robust study summary were submitted in the present appeal proceedings. The Appellants state that the robust study summary was included in their registration dossiers.

223. It is not disputed that the Hanausek study showed that the Substance did not induce mutations in the c-HA-ras protooncogene in mouse model skin. However, only dermal exposure was examined. The findings of the Hanausek study do not therefore exclude the potential for mutations in other genes related to carcinogenesis or in the c-Ha-ras protooncogene at other sites of contact.

224. The Parties agree that the Hanausek study showed increases in the three biomarkers associated with tumour promoting activity. Tumours can be the result of mutations in genes other than the c-Ha-ras protooncogene.

225. In light of the above, it cannot be concluded that the Hanausek study shows that the Substance does not have mutagenic potential. The Appellants' arguments in this regard are therefore rejected.

226. In view of paragraphs 203 to 225 above, the Appellants' arguments that the Agency made a manifest error of assessment in interpreting the information contained in the registration dossier as demonstrating that there is a concern must be rejected.

2. Manifest error of assessment in concluding that the Substance may be mutagenic *in vivo*

Arguments of the Parties

227. The Appellants contest the finding in the Contested Decision that the Hanausek study '*cannot be used to rule out a local genotoxic potential, because it does not directly address genotoxicity but tumour initiation/promotion activity and because it is not a guideline study, currently used for risk assessment*'.

228. The Appellants argue that the Agency has failed to interpret the Hanausek study correctly. In the study the Substance did not produce detectable mutations in the c-Ha-ras protooncogene. This indicates that it '*does not possess tumour initiating or complete carcinogenic activity*'.

229. The Appellants also contest the finding in the Contested Decision that in the Hanausek study '*induction of 8-OH-dG is reported, indicating oxidative DNA damage at the site of contact*'.

230. The Appellants argue that the Agency failed to take that into account the findings in the Cooke *et al.* publication (FASEB Journal Vol. 17, July 2003). In particular the Appellants argue that according to the Cooke *et al.* publication '*the mere presence of 8-OH-dG in DNA is unlikely to be necessary or sufficient to cause tumor formation; there are many pathological conditions in which levels of 8-OH-dG in DNA are elevated with no increased incidence of carcinogenesis'.*

231. The Agency argues that the Hanausek study and Cooke *et al.* publication were taken into account in the decision-making process.

232. The Agency stated in the Contested Decision that, based on the information available in the registration dossier, the Substance causes both chromosome aberrations and gene mutations *in vitro*. It is therefore appropriate to consider *in vivo* mutagenicity studies pursuant to Section 8.4.4. of Annex VIII.

Findings of the Board of Appeal

233. The Appellants argue in essence that the Agency incorrectly considered, or failed to consider, (a) the Hanausek study and (b) the Cooke *et al.* study.

(a) The Hanausek study

234. As mentioned in paragraph 222 above, neither the Hanausek study nor its robust study summary were submitted in the present appeal proceedings.

235. However, the Parties agree that the Hanausek study, which is referred to in the Contested Decision, concluded that the Substance did not induce mutations in the c-Ha-ras protooncogene in mouse model skin and that there were no mutations in codons (units of genetic code) 12, 13 and 61.

236. Nevertheless, it is not disputed that only dermal exposure was investigated in that study and that significant increases in all three biomarkers associated with tumour promoting activity were reported in the study. Tumours can be the result of mutations in genes other than the c-Ha-ras protooncogene.

237. From the information provided by the Parties in the present proceedings, the Hanausek study does not therefore rule out the potential for mutations in different genes related to carcinogenesis or in the ras family of genes in other first contact tissues such as the stomach.

238. The Appellants have not therefore shown that the Agency committed an error of assessment in its consideration of the Hanausek study.

(b) The Cooke *et al.* publication

239. The Cooke *et al.* publication is not referred to in the Contested Decision. The Agency argues that it nonetheless took this publication into account.

240. The Cooke *et al.* publication is not a study on the Substance but rather a publication which reviews the basis for the biological significance of oxidative DNA damage.

241. The Cooke *et al.* publication was not provided in these appeal proceedings. The Board of Appeal can only consider the quotation from the study included in the appeal proceedings and the Appellants' related comments on the proposals for amendment.

242. Statements in the Cooke *et al.* publication such as '*unlikely to be necessary or sufficient to cause tumor formation*' (emphasis added) do not resolve the issue of mutagenicity potential of the Substance. The publication rather appears to indicate the need for further studies due to the uncertainty surrounding the issue.

243. The Appellants state in their submissions that the Cooke *et al.* publication shows that '*8-OH-dG does not necessarily indicate tumor promotion*' (emphasis added). This statement also demonstrates the existing uncertainty in this regard.

244. Whilst the Cooke *et al.* publication may be relevant for the evaluation of the Substance, the section of that publication provided by the Appellants does not provide evidence capable of rebutting the finding that there is a potential concern for mutagenicity that should be investigated further.

245. The Agency did not therefore commit an error of assessment in its consideration of the Cooke *et al.* publication.

246. The Appellants' arguments that the Agency committed a manifest error of assessment in its consideration of the evidence regarding the Hanausek study and the Cooke *et al.* study must therefore be rejected.

Conclusion on the arguments related to the mutagenic toxicity of the Substance and the alleged errors of assessment (Sections 1 and 2 above)

247. The Agency did not conclude in the Contested Decision that the Substance is a mutagenic toxicant. The Contested Decision concludes only that there is a potential mutagenicity concern that requires investigation through further testing.

248. As indicated at paragraph 48 above, there is potential exposure to the Substance. As all of the Appellants' arguments with regard to a manifest error of assessment have been rejected (see paragraphs 198 to 246), there is a potential hazard concern for the mutagenic potential of the Substance. It must therefore be concluded that there is a potential risk for mutagenicity. The Appellants' plea that the Agency committed a manifest error of assessment in this regard is therefore rejected.

3. Appropriateness of the Comet assay to assess the mutagenic toxicity of the Substance

Arguments of the Parties

249. The Appellants argue that the requested study is not appropriate to address the mutagenic effects of the Substance as it rapidly degrades in the stomach.

250. The Agency argues that the requested test is a validated OECD test guideline. It is considered by the OECD and the Agency's Guidance (*Guidance on Information Requirements and Chemical Safety Assessment* - Chapter R.7a, August 2014, version 3.0) as an appropriate test to address mutagenicity.

Findings of the Board of Appeal

251. The Appellants' plea that the Comet assay is not appropriate to examine the concerns identified in the Contested Decision related to mutagenic effects is rejected for the following reasons.

252. First, in an *in vivo* study where the Substance is administered by way of oral gavage, the Substance will be placed in direct contact with stomach tissue. In the requested test the Substance can be administered at a volume which means that both the stomach and the fore-stomach are exposed to the Substance at more or less the same time. Consequently, even if the Substance degrades rapidly, the test should still be able to examine the concern for genotoxicity in the stomach.

253. Second, as stated in paragraph 219 above, even if the Substance degrades rapidly it is possible that a significant amount of the Substance will remain in the stomach after one hour.

254. Third, the Comet assay can detect the effects of both DNA-damaging gene mutagens and of chromosome-breaking substances. The Comet assay is also able to assess effects in several different tissues. It can analyse DNA damage at the initial site of contact (for example glandular stomach/jejenum), and in metabolising tissue (such as liver tissue). The Comet assay is therefore appropriate to examine a range of effects caused by developmental toxicity.

4. Failure to state reasons as to why the conclusion reached by the eMSCA, that there is no concern for carcinogenicity, has been disregarded

Arguments of the Parties

255. The Appellants argue that there is no justification in the Contested Decision as to why the Agency chose to disregard the earlier conclusions of the eMSCA, set out in the draft decision, regarding carcinogenicity.

256. The Agency argues that the eMSCA only reached a preliminary conclusion based on its initial assessment. This conclusion was subject to the peer-review of the other Member States and the Agency during the decision-making process.

257. The Agency argues that the circumstances leading to the request for the Comet assay changed during the substance evaluation as a result of the validation and publication of a new OECD test guideline in September 2014.

Findings of the Board of Appeal

258. The Appellants' plea regarding the failure to state reasons must be examined in the light of the criteria set out in paragraph 167 above.

259. The Substance was included in the CoRAP on the basis of an opinion of the MSC and due to initial grounds for concern relating to sensitisation and carcinogenicity.

260. The draft decision of 20 March 2014 and the revised draft decision of 5 March 2015 included a statement that the '*eMSCA considered that no further information was required to clarify the concern for sensitisation and carcinogenicity*'.

261. However, in the Contested Decision itself this statement is removed and the Appellants are requested to provide information on a Comet assay. The Contested Decision adds in Section III(2) that '*[t]his request was added to the decision as a result of a proposal for amendment by [the Danish MSCA] received during the consultation phase of the Draft Decision*'.

262. The Agency's argument regarding the new OECD test guideline is irrelevant. A new test guideline may be more appropriate to examine a potential concern. However, it has no bearing on the necessity for that examination. In other words, the fact that there is a new test guideline is irrelevant in examining whether there is a potential concern that could be subject to further examination pursuant to substance evaluation. The fact that there is a new test guideline is also irrelevant when examining this plea with regard to the duty to state reasons.

263. The conclusion initially reached by the eMSCA was based on its own assessment of the information available to it. The proposal for amendment from the Danish MSCA was based on that MSCA's own assessment of the available information. The eMSCA, the members of the MSC and the Appellants all had the opportunity to give their opinions on the conclusions reached by the Danish MSCA, in its proposal for amendment, regarding the need for a Comet assay.

264. The reasoning for requesting the Comet assay was contained in the Contested Decision. The Appellants, by their involvement in the decision-making process, were aware of the reasoning behind the information request even if they disagreed with that reasoning. As the Contested Decision sets out why the Agency considers that the Substance is potentially mutagenic, it is not necessary for the Contested Decision to explain why there was an apparent change from the initial conclusion reached by the eMSCA. In the decision-making process the eMSCA indicated its agreement with the change proposed by Denmark and supported the need for a Comet assay to examine the mutagenic potential of the Substance.

265. In light of the above, the Appellants' plea that the Agency failed to state reasons for disregarding the eMSCA's conclusion that '*no further information was required to clarify the concern for […] and carcinogenicity*' is rejected.

III. Pleas concerning both the request for a PNDT study and a Comet assay

266. The Board of Appeal will examine the Appellants' pleas in the following order:

A - Breach of Article 25;

B - Deadline imposed to provide the requested information;

C - Breach of the principle of proportionality; and

D - Breach of the right to be heard.

A - Breach of Article 25

Arguments of the Parties

267. The Appellants, supported by the Intervener, argue that the Agency breached Article 25 for the following reasons:

- the burden of proof lies with the Agency to show that it considered alternatives to animal testing,
- no further animal testing is required,
- in considering whether testing was required the Agency should have properly addressed and considered the Appellants' comments during the substance evaluation procedure, and
- with regard to the request for a Comet assay, as an alternative to animal testing, the Agency could have first requested an examination of degradation in the stomach.

268. The Agency contests the Appellants' arguments for the following reasons:

- the Appellants did not identify suitable animal-free tests to investigate the mutagenicity concern,
- the Appellants did not comment on the use of animal tests in their comments on the proposals for amendment,
- there are no alternatives to the two testing requirements contested in the present proceedings, and
- the OECD test guideline for the Comet assay reduces animal testing to the greatest extent possible.

Findings of the Board of Appeal

269. Article 13 of the Treaty on the Functioning of the European Union provides that '*in formulating and implementing the Union's agriculture, fisheries, transport, internal market […] policies, the Union and the Member States shall, since animals are sentient beings, pay full regard to the welfare requirements of animals […]*.'

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

271. The protection of animal welfare is therefore an important consideration in the framework of European Union legislation and the REACH Regulation in particular. Under the REACH Regulation the Agency has a legal obligation to consider animal welfare in its decision-making. Where the Agency requires additional testing pursuant to a substance evaluation it must ensure that vertebrate animals are used only as a last resort. The Agency's actions should not run counter to the principles of Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33; See Case A-004-2014, *Altair Chimica and Others*, Decision of the Board of Appeal of 9 September 2015, paragraphs 106 to 108).

272. The Board of Appeal will examine the Appellants' arguments, first in relation to the second species PNDT study, and second in relation to the Comet assay, in light of the above.

1. Second species PNDT study

273. The Appellants' arguments that the Agency breached Article 25(1) in requesting a second species PNDT study are rejected for the following reasons.

274. First, the Appellants' arguments that no information is required in relation to developmental toxicity have been rejected by the Board of Appeal (see paragraphs 39 to 101 above).

275. Second, the Contested Decision states that the Agency '*considers that there is no alternative to a study in vertebrate animals available to assess the possible developmental toxicity of the registered substance*'. Whilst such a statement does not in itself show that the Agency has taken sufficient action to consider alternatives to testing on vertebrate animals, it does show that consideration was given to this obligation. Furthermore, the Appellants have not contested this statement, other than by claiming that no testing is required at all.

276. Third, the Appellants have not demonstrated that the requested information on developmental toxicity could have been obtained by other means.

277. In this respect, the Agency, pursuant to a substance evaluation, examined and subsequently rejected the Appellants' use of the adaptation in Column 2 of Section 8.7.2. of Annex IX to justify not performing the second species PNDT study. The Board of Appeal has found that the Agency did not commit an error of assessment in this respect (see paragraph 130 above). If this examination was conducted under the compliance check procedure, the Agency would have had no other option but to request the second species PNDT study (see, to that effect, Case A-004-2015, *Polynt*, Decision of the Board of Appeal of 19 October 2016, paragraphs 118 and 119). Therefore, although requested under substance evaluation, the request was the same as it would have been pursuant to dossier evaluation and respects the obligations therein with regard to animal testing being a last resort.

2. Comet assay

278. The Contested Decision does not contain a similar statement to that included for the second species PNDT study regarding the lack of alternatives to testing on vertebrate animals (see paragraph 274 above). It is therefore not clear from the Contested Decision whether alternatives to animal testing were considered during the decision-making process. In addition, the Agency has not provided any evidence to show that it considered alternatives to animal testing prior to the adoption of the Contested Decision.

279. However, the fact that the Agency has failed to demonstrate, during the procedure leading to the adoption of the Contested Decision, that it considered alternatives to tests on vertebrate animals pursuant to Article 25(1) is not sufficient to lead to the annulment of the Contested Decision for the following reasons.

280. First, the Appellants' arguments that no information is required in relation to mutagenicity have been rejected (see paragraphs 203 to 226 above). The Agency was justified in requiring additional information.

281. Second, during the present proceedings the Agency stated that there are no alternatives to the Comet assay. The Board of Appeal has also rejected the Appellants' plea that the Comet assay is inappropriate to examine the concern identified (see paragraphs 251 to 254 above). The Appellants have not provided evidence to support their claim that there are non-animal testing alternatives to address the mutagenicity concern identified. The Appellants suggested at the oral hearing that the Agency could have first examined degradation in the stomach before requesting the Comet assay. However, this is not a suitable alternative to examine the potential mutagenicity of the Substance as the Board

of Appeal has already found that exposure to the Substance in the stomach is possible even taking into account the rate of degradation (see paragraph 217 to 220).

282. The Appellants' plea that the Agency breached Article 25 is therefore rejected.

B - Deadline imposed to provide the requested information

Arguments of the Parties

283. The Appellants request that, if the Board of Appeal upholds the requested tests, the Contested Decision should be amended to allow 24 months for the relevant dossier update.

284. The Appellants argue that the 15 months' deadline set in the Contested Decision to provide the requested information is not appropriate as:

- the requested tests would require more time to complete, analyse, and summarise in a registration dossier update,
- a laboratory contacted by the Appellants stated that the OECD TG 414 study would take 18 months to complete,
- the lead registrant was granted 18 months to perform the first species PNDT study in the testing proposal decision of 20 December 2012 (see paragraph 1 above), and
- the OECD test guideline for the Comet assay (OECD TG 489) was only validated in September 2014. Therefore laboratories do not yet have much experience in performing the test.

285. The Agency argues that the time provided in the Contested Decision to conduct the requested tests and provide the requested information is adequate for the following reasons:

- the Appellants have only contacted one laboratory to get an estimate of how long it would take to conduct the second species PNDT study; the Agency has contacted test houses which indicated that 12 months would be sufficient to conduct the tests,
- it is the Agency's consistent practice to give registrants 12 months (plus another three months following substance evaluation decisions to agree on who is to conduct the test) to submit the study results; this practice can be seen from some of the previous decisions available on the Agency's website, and
- the two tests can be conducted simultaneously.

Findings of the Board of Appeal

286. The Appellants' plea that the deadline to provide the requested information should be extended from 15 to 24 months is rejected. The Appellants have not demonstrated that the deadline to provide the information requested in the Contested Decision is insufficient for the following reasons.

287. First, the evidence from the test house contacted by the Appellants does not demonstrate that the information could not be provided within 15 months. For example, the test house contacted by the Appellants indicated that, at that time, there would be a delay of around 4 months before it could start the second species PNDT study. It is not clear that similar delays would apply now or would be faced in other test houses.

288. Second, the Agency stated at the hearing that it had also contacted test houses that indicated that around 12 months would be sufficient to perform the tests.

289. Third, the second species PNDT study and the Comet assay can be conducted in parallel.

290. The Board of Appeal notes that the Agency, in its proposal for amendment regarding the second species PNDT study, indicated that 24 months should be allowed to perform the test. This proposal was not, however, included in the Contested Decision and, as explained above, the request to extend the deadline has not been accepted. If the 15 month deadline cannot be met this should be thoroughly explained in the updated registration dossier.

C - Breach of the principle of proportionality

Arguments of the Parties

291. The Appellants argue that the Contested Decision does not meet the '*necessity*' and '*appropriateness*' tests established in the principle of proportionality. The second species PNDT study and the Comet assay are not necessary to clarify real concerns and the Comet assay is not appropriate to address the mutagenicity concern.

292. The Agency contests the Appellants' arguments.

Findings of the Board of Appeal

293. The principle of proportionality requires that European Union measures do 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 and the case-law cited; see also Case A-005-2011, *Honeywell Belgium*, Decision of the Board of Appeal of 29 April 2013, paragraphs 115 to 117).

294. In paragraphs 39 to 101 and 203 to 226 above, the Board of Appeal has found that the Agency has demonstrated potential concerns that need to be clarified in relation to developmental toxicity and mutagenicity respectively. The Appellants' claim that the required information is not necessary is therefore rejected.

295. In paragraphs 251 to 255 above the Board of Appeal has found that the Comet assay is appropriate to investigate the mutagenicity concern.

296. The Board of Appeal has found above (see paragraphs 105 to 113) that a registration at the 100 to 1 000 tonnes per year tonnage band must include information on a second species PNDT study or an adaptation pursuant to Section 8.7.2. of Annex IX or to Annex XI. The requirement to provide that information therefore stems directly from the REACH Regulation.

297. In the present case, the Contested Decision was adopted under the substance evaluation process. Under dossier evaluation the Agency can check whether registrations are in compliance with the information requirements set out in the REACH Regulation. The discretionary powers of the Agency in this respect are therefore limited to examining whether a study or an adaptation have been submitted and whether it is in compliance. If an adaptation has been submitted the Agency needs to check whether it complies with the rules governing adaptations set out in Annex XI and Column 2 of the testing Annexes. If the Agency finds that an 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.

298. However, the wrongful rejection of an adaptation on the part of the Agency would require a registrant to perform unnecessary testing. In this case, the required testing would be disproportionate.

299. In the present case however the Agency examined and rejected the Appellants' use of the adaptation in Column 2 of Section 8.7.2. of Annex IX to justify not performing the second species PNDT study. The Board of Appeal has found that the Agency did not commit an error of assessment in this respect (see paragraph 130 above). Under the compliance check procedure, the Agency would have had no other option but to request the second species PNDT study. Therefore, although requested under substance evaluation, the request was the same as it would have been pursuant to dossier evaluation.

300. The Appellants' plea that the Agency breached the principle of proportionality is therefore rejected.

D - Breach of the right to be heard

Arguments of the Parties

301. The Appellants argue that their right to be heard was breached for the following reasons:

- the Agency took into consideration the Appellants' dossier update regarding the first species PNDT study after the original cut-off point for new updates to be considered (see paragraphs 135 to 155 above),
- the Contested Decision was adopted under the substance evaluation procedure rather than the dossier evaluation procedure,
- in view of the short time between the submission of the proposals for amendment and the adoption of the revised draft decision by the MSC, it is doubtful that the Appellants' comments on the proposals for amendment were considered by the MSC even if they were sent to the MSC,
- the Appellants were not given an opportunity to comment on the version of the decision discussed at the MSC, or to participate in a MSC meeting, and
- the use of the written procedure deprived the Appellants of an opportunity to develop their comments on the proposals for amendment and to answer questions at an MSC meeting.

302. The Agency contests the Appellants' arguments for the following reasons:

- the procedure in Articles 50 to 52 was correctly followed. Registrants do not have the right to comment on the version of the decision sent to the MSC in a written procedure,
- the opportunity to attend the MSC meeting at which a draft decision is discussed has been introduced by the Agency and is not included in the REACH Regulation,
- the decision was agreed in a written procedure so the draft decision was not discussed at an MSC meeting,
- the statement of reasons to the Contested Decision includes a reference to the registrants' comments on the proposals for amendment. This explains adequately why these comments did not change the decision, and
- the fact that the decision was agreed by the MSC within a relatively short period of time cannot put in doubt the fact that the Appellants' comments were taken into account in the decision-making process.

Findings of the Board of Appeal

303. In accordance with Article 41(2) of the Charter of Fundamental Rights of the European Union every person has the right to be heard before any individual measure which would affect him or her adversely is taken.

1. The Appellants' right to heard and the Agency's consideration of the dossier update after the original cut-off point for new updates

304. Articles 50 to 52 foresee certain opportunities for registrants to provide observations during the dossier and substance evaluation processes. In the present case, the Appellants were 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 and the Agency pursuant to Article 51(5). 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, judgment of 6 July 1993, *CT Control (Rotterdam) and JCT Benelux* v *Commission*, C-121/91 and C-122/91, EU:C:1993:285, paragraph 49, judgment of 9 January 2003, *Italy* v *Commission*, C-177/00, EU:C:2003:6, paragraphs 23 to 25, and judgment of 26 September 2012, *Italy* v *Commission*, T-84/09, EU:T:2012:471, paragraphs 24 to 30).

305. However, in certain circumstances the addressees of an Agency decision must be given the opportunity to comment beyond the opportunities foreseen in the REACH Regulation. This may be the case, for example, if during the decision-making process there is a major change in a decision imposing additional obligations on the addressees (see Case A-004-2015, *Polynt*, Decision of the Board of Appeal of 19 October 2016, paragraphs 55 to 77).

306. Similarly, if relevant information comes to light during the decision-making process, the Agency may, depending for example on the relevance and importance of the new information, be required to re-start, or repeat certain steps of, the decision-making process laid down in Articles 50 to 52. This might be necessary in some cases to ensure that all the relevant actors are given the opportunity to comment on that information, especially if this information has not been generated by the registrant itself (A-001-2014, *CINIC Chemicals Europe*, Decision of the Board of Appeal of 10 June 2015, paragraph 90).

307. In the present case, the first species PNDT study came to light during the decision-making process and was clearly relevant and important information in the evaluation of the Substance. The results of the study led, in large part, to the inclusion in the Contested Decision of a requirement to perform a second species PNDT study. However, the Agency was not required to re-start the decision-making process. The Appellants' right to be heard was respected, in relation to the requirement to perform a second species PNDT study, for the following reasons.

308. First, the Appellants had the opportunity to comment on the proposals for amendment which introduced the requirement to provide information on the second species PNDT study (as well as the Comet assay). The Appellants provided observations on the proposals to require this information (see paragraph 18 above).

309. Second, the MSC had the same information available to it as would have been the case if the proposed second species PNDT study had been included in the initial draft decision. The MSC members had available to them the updated registration dossier, the revised draft decision with the additional information requirements, the proposals for amendment, and the Appellants' comments on the proposals for amendment.

310. Third, the MSC members, having before them the proposal for amendment regarding the second species PNDT study and the Appellants' comments on that proposal, adopted the Contested Decision without using the possibility under the written procedure to either stop the procedure or disagree with the draft decision. If they wished to disagree with the draft decision or stop the written procedure they could have done so. However, no requests to stop the written procedure or disagreements to the draft decision were submitted.

311. The Appellants' arguments are therefore rejected.

2. The Appellants' right to be heard and the Agency's use of the substance evaluation procedure instead of the dossier evaluation procedure

312. The Appellants' arguments that by following the incorrect procedure the Agency breached their right to be heard (see paragraph 301 above) are rejected for the following reasons.

313. Article 51(5) must be understood as giving the Appellants the opportunity to comment on any proposals for amendment to the draft decision and not, once more, on the draft decision itself (see A-009-2014, *Albemarle Europe and Others*, Decision of the Board of Appeal of 12 July 2016, paragraph 222).

314. Therefore, if the requirement for the second species PNDT study had been included in the initial draft decision the Appellants would have had one chance to comment on the proposal. Likewise, as the request for a second species PNDT study had been included in proposals for amendment they had one chance to comment on it.

315. In the present case the Appellants were given, and made use of, the opportunity to provide observations on the Agency's proposal for amendment introducing the requirement for a second species PNDT study. They therefore had the opportunity to provide observations on the request for the second species PNDT study.

316. The Appellants' comments on the proposal for amendment introducing the second species PNDT study were made available to the MSC. The members of the MSC were able to stop the written procedure or disagree with the amended draft decision if they disagreed with it but they did not do so.

317. The possibility to discuss a draft decision at an MSC meeting is not a right given to registrants in the REACH Regulation. The fact that this decision was agreed by written procedure therefore did not deprive the Appellants of their right to be heard.

318. In conclusion, all the relevant actors were given the opportunity to make their views known on the inclusion of the requirement for a second species PNDT study.

319. In view of the above, the Appellants' arguments are rejected.

3. Appellants' arguments in relation to the right to be heard by the MSC

320. The Appellants' arguments with regard to their right to be heard by the MSC (see paragraph 301 above) are rejected for the following reasons.

321. First, during these appeal proceedings, the Agency provided evidence that the Appellants' observations on the proposals for amendment were sent to the MSC. The lead registrant's comments on the proposals for amendment to the draft decision were communicated to the MSC on 18 May 2015 in the '*RCOM document*'. The RCOM document is a communication designed to facilitate collaboration between the Member States, the Agency and the MSC and was prepared by the eMSCA.

322. Second, although the time allowed to the MSC to consider the Appellants' comments on the proposals for amendment was short, the MSC was nonetheless given the opportunity to consider those comments. No Member State indicated during the written procedure that they did not have sufficient time to consider these comments.

323. Third, the REACH Regulation does not foresee the possibility for registrants to comment on the version of the decision discussed by the MSC.

324. Fourth, registrants do not have the right to attend the MSC meeting at which a draft decision is considered and potentially agreed. In any case, in the present case the decision was agreed in a written procedure and the case was not discussed at an MSC meeting prior to its agreement.

IV. Conclusion on the appeal

325. In view of all of the above, the Appellants' appeal is dismissed in its entirety.

Refund of the appeal fee

326. 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 appeal is decided in favour of an appellant.

327. As the appeal has not been decided in favour of the Appellants, the appeal fee shall not be refunded.

Effects of the Contested Decision

328. The Contested Decision, upheld in the present appeal proceedings, required the Appellants, to submit the required information by 21 November 2016 which is 15 months and 7 days from the date of that Decision.

329. However, in light of the application of the suspensive effect provided for in Article 91(2), the information required by the Contested Decision must be submitted within 15 months and 7 days from the date of notification of the Board of Appeal's decision in the present case.

On those grounds,

THE BOARD OF APPEAL

1. **Dismisses the appeal.**
2. **Decides that the information requested in the Contested Decision must be submitted to the Agency by 20 March 2019.**
3. **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