EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

17 December 2019

(Substance evaluation – Potential risk – Read-across – Risk management measures)

Case numbers	Joined Cases A-003-2018, A-004-2018, and A-005-2018
Language of the case	English
Appellants	BASF SE, Germany (A-003-2018) Kemira Oyj, Finland (A-004-2018) Kemira Oyj, Finland (A-005-2018)
Representatives	Jean-Philippe Montfort and Thomas Delille, Mayer Brown Europe-Brussels LLP, Belgium
Interveners	(I) The French Republic Represented by: Ministère de la transition écologique et solidaire (MTES), France (II) Grace GmbH, Germany, and Grace Silica GmbH, Germany Represented by: David Scannell Brick Court Chambers, United Kingdom Lydia Duff W.R. Grace and Co., United States of America
Contested Decisions	A-003-2018 against a decision of 21 December 2017 on the substance evaluation of aluminium chloride (notified to the Appellant through the annotation number SEV-D-2114385103-55-01/F); A-004-2018 against a decision of 21 December 2017 on the substance evaluation of aluminium chloride basic (notified to the Appellant through the annotation number SEV-D-2114385031-58-01/F); and A-005-2018 against a decision of 21 December 2017 on the substance evaluation of aluminium sulphate (notified to the Appellant through the annotation number SEV-D-2114385168-39-01/F); all adopted by the European Chemicals Agency (the 'Agency') pursuant to Article 46 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (OJ L 396, 30.12.2006, p. 1; corrected by OJ L 136, 29.5.2007, p. 3)

THE BOARD OF APPEAL

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

Acting as Registrar: Marc Goodacre

gives the following

Decision

Background to the dispute

1. In 2010, BASF SE, the Appellant in Case A-003-2018, registered aluminium chloride ('AC'; EC No 231-208-1, CAS No 7446-70-0) at the 1 000 tonnes or more per year tonnage band.

2. In 2013, aluminium sulphate ('AS'; EC No 233-135-0, CAS No 10043-01-3) was included in the Community rolling action plan ('CoRAP') for substance evaluation in 2015. This was due to initial grounds for concern relating to '*Human health/Suspected [carcinogenic, mutagenic or reprotoxic properties (CMR)]; Suspected sensitiser; Exposure/Wide dispersive use; Consumer use; High RCR [Risk Characterisation Ratio]; Aggregated tonnage'.*

3. Regarding AS, the '*Justification Documents for the Selection of a CoRAP Substance*', published on 20 March 2013, states that '*there are several uncertainties regarding [AS] that should be clarified: uncertainty regarding carcinogenicity and [genotoxicity], uncertainty regarding skin sensitisation (with spraying uses), uncertainty regarding the granulometry of the tested material*'.

4. In 2014, Kemira Oyj, the Appellant in Case A-005-2018, registered AS at the 1 000 tonnes or more per year tonnage band.

5. In 2014, AC was included in the CoRAP for substance evaluation in 2015. This was due to initial grounds for concern relating to '*Human health/Suspected CMR, Exposure/High RCR; exposure of workers, high (aggregated) tonnage'*.

6. In 2014, Kemira Oyj, the Appellant in Case A-004-2018, registered aluminium chloride basic ('ACH'; EC No 215-477-2, CAS No 1327-41-9) at the 1 000 tonnes or more per year tonnage band.

7. In 2014, ACH was added to the CoRAP for substance evaluation in 2015. This was due to initial grounds for concern relating to '*Human health/Suspected CMR, Exposure/high (aggregated) tonnage'.*

8. Regarding ACH and AC, the '*Justification Documents for the Selection of a CoRAP Substance*', published on 26 March 2014, refers to '*similar substances/grouping possibilities*'. That document also provides that ACH and AC are soluble aluminium compounds and '*[…] may be grouped with other registered soluble aluminium compounds. A preliminary analysis would be needed to define the scope of such a category'*.

9. The Competent Authority of France was appointed as the evaluating Member State Competent Authority (the 'eMSCA') for the substance evaluation of AS, AC and ACH (the 'three Substances').

10. On 11 March 2016, following the substance evaluations of the three Substances, the eMSCA submitted three draft decisions to the Agency pursuant to Article 46(1) of the REACH Regulation[1].

11. The three draft decisions contained a number of information requests including, in all three, a request for a:

    '*Combined* in vivo *mammalian erythrocyte micronucleus test in bone marrow and modified* in vivo *mammalian comet assay on the following tissues: liver, kidney, glandular stomach and duodenum; test methods EU 8.12./OECD [TG] 474 and OECD [TG] 489 in rats, oral route, using the analogue substance [AS]*'.

[1] All references to Articles hereinafter concern the REACH Regulation unless stated otherwise.

12. On 26 April 2016, the Agency sent the draft decisions to the relevant Appellants and invited them, pursuant to Article 50(1), to provide comments.

13. On 31 May 2016, the Appellants provided comments to the Agency on the draft decision, or decisions, relevant to them. With regards to the combined study referred to in paragraph 11 above, the Appellants contested the rejection of the proposed read-across between certain soluble and insoluble aluminium salts. The Appellants also argued that the *in vitro* and *in vivo* studies relied on by the eMSCA to demonstrate a potential concern for genotoxicity are not reliable whereas the reliable *in vitro* studies submitted by the Appellants give no indication of genotoxicity.

14. On 17 July 2017, the eMSCA notified three revised draft decisions to the competent authorities of the other Member States ('MSCAs') and the Agency in accordance with Article 52(1).

15. In accordance with Articles 51(5) and 52(2), proposals for amendment were submitted in relation to each of the draft decisions.

16. The Danish and Dutch MSCAs supported the request for information set out in paragraph 11 above in all three decisions. The Dutch MSCA asked for an additional study to be taken into account in all three decisions (Cunat *et al.* (2000)[2]).

17. The UK MSCA proposed that the combined study referred to in paragraph 11 above should be removed from all three decisions as the standard *in vitro* genotoxicity tests conducted on the three Substances all gave negative results and therefore do not indicate a concern for genotoxicity.

18. On 24 August 2017, the Agency notified the addressees of each of the draft decisions of the relevant proposals for amendment and invited them, pursuant to Articles 52(2) and 51(5), to provide comments.

19. On 22 September 2017, the Appellants submitted comments on the relevant proposals for amendment. With regard to AC, Case A-003-2018, the Appellant stated amongst other things that '*a concern for genotoxicity does not exist based on the available information*'. With regard to ACH and AS, Cases A-004-2018 and A-005-2018, the Appellant stated amongst other things that '*the mutagenicity concern has not been demonstrated and that the requested study should not be requested in the final [Agency] decision*'. The Appellants argued that the Agency failed to apply a proper weight-of-evidence approach by disregarding high quality studies demonstrating that there is no concern and giving excessive weight to studies and reports of acknowledged poor quality. In support of their claim that there is no concern for genotoxicity, the Appellants submitted a study on dialuminium chloride pentahydroxide (DCP). The Appellants argued that a read-across from DCP to the three Substance is possible.

20. The three draft decisions were discussed at the Member State Committee ('MSC') meeting of 24 to 26 October 2017.

21. Just prior to the MSC meeting, the Agency sent the Appellants slides to be presented by the eMSCA at that meeting. The slides referred to information on an *in vivo* micronucleus assay performed using AC (Paz *et al.* (2017)[3]) to support the concern for genotoxicity.

[2] '*Bioavailability and Intestinal Absorption of Aluminium in Rats. Effects of Aluminium Compounds and Some Dietary Constituents*'. Biological Trace Elements Research, Vol. 76, pp. 31 – 55.
[3] '*Evaluation of* in vivo *and* in vitro *toxicological and genotoxic potential of aluminium chloride*', Chemosphere 175, (2017), pp. 130 – 137.

22. At the MSC meeting, the Appellants sought to introduce the results of an *in vitro* comet assay on AC (Villarini *et al.* (2017)[4]) to support their arguments that there is no concern for genotoxicity. However, according to the minutes of the MSC meeting, that study was not taken into account on the grounds that it was introduced too late in the decision-making process.

23. At the MSC meeting, the MSC reached unanimous agreement on the three Contested Decisions.

24. On 21 December 2017, the Agency adopted the three Contested Decisions requesting the addressees of those Decisions to update their registration dossiers with information on, amongst other things, a:

    '*Combined* in vivo *mammalian erythrocyte micronucleus test and* in vivo *mammalian comet assay with additional specific investigation on oxidative DNA damage on the following tissues: liver, kidney, glandular stomach and duodenum; test methods EU B.12./OECD [TG] 474 and OECD [TG] 489 in rats, oral route'*.

25. All three Contested Decisions require that the information is generated using AS, which is the substance subject to appeal in Case A-005-2018.

26. Under '*Note for consideration*', all Contested Decisions state that:

    '*…further testing on mutagenicity will be considered in case of positive results obtained in the comet assay. You are therefore invited to consider integrating a Pig-a assay in the requested study, which would require additional animals. The results of the Pig-a assay would provide further information on mutagenicity and reduce the need for further testing*'.

27. The three Contested Decisions state that *'based on envisaged read-across (structural similarity validated but pending on substance composition clarification), genotoxicity of the three aluminium salts currently under substance evaluation [the 'three Substances'] has been evaluated jointly. […]*'.

28. According to the Contested Decision in Case A-003-2018, following the evaluation of AC, the eMSCA concluded that further information was required in order to clarify concerns relating to '*sub-chronic local effects for respiratory tract, mutagenicity, developmental neurotoxicity and physico-chemical properties'.* The Appellant was requested to update its registration dossier with the information requested in the Contested Decision by 3 January 2020.

29. According to the Contested Decision in Case A-004-2018, following the evaluation of ACH, the eMSCA concluded that further information was required in order to clarify concerns relating to '*mutagenicity and developmental neurotoxicity'.* The Appellant was required to update its registration dossier with the information requested in the Contested Decision by 28 June 2019.

30. According to the Contested Decision in Case A-005-2018, following the evaluation of AS, the eMSCA concluded that further information was required in order to clarify *'mutagenicity and neurodevelopmental concerns'.* The Appellant was required to update its registration dossier with the information requested in the Contested Decision by 28 June 2019.

Procedure before the Board of Appeal

31. On 16 March 2018, the Appellants filed their respective appeals in Cases A-003-2018, A-004-2018 and A-005-2018.

[4] '*No evidence of DNA damage by co-exposure to extremely low frequency magnetic fields and aluminum on neuroblastoma cell lines*', Mutat Res Gen Tox En 823 (2017), pp. 11 – 21.

32. On 30 April 2018, the Board of Appeal joined Cases A-003-2018, A-004-2018 and A-005-2018 following the Appellants' requests to that effect.

33. On 21 May 2018, the Agency filed its Defence for the joined Cases.

34. On 8 June 2018, the French Republic was granted leave to intervene in the joined Cases in support of the Agency.

35. On 21 June 2018, Grace and Grace Silica were jointly granted leave to intervene in the joined Cases in support of the Appellants.

36. On 20 July 2018, the Appellants filed their observations on the Defence and replied to questions from the Board of Appeal.

37. On 20 July 2018, the Agency submitted copies of the substance evaluation reports related to each of the three Substances following the Board of Appeal's request to that effect.

38. On 25 July 2018, the French Republic filed its statement in intervention.

39. On 20 August 2018, Grace and Grace Silica filed their statement in intervention.

40. On 14 September 2018, the Appellants and the Agency filed their respective observations on the French Republic's statement in intervention.

41. On 14 September 2018, the Appellants filed their observations on the substance evaluation reports submitted by the Agency on 20 July 2018.

42. On 14 September 2018, the Agency filed its observations on the Appellants' observations on the Defence.

43. On 28 September 2018, the Agency and the Appellants filed their respective observations on the statement in intervention filed by Grace and Grace Silica.

44. On 12 November 2018, the Agency filed its reply to questions from the Board of Appeal.

45. On 29 November 2018, the Chairman of the Board of Appeal at the time – Mercedes Ortuño - designated Ioannis Dimitrakopoulos to act in the present joined Cases as the Chairman of the Board of Appeal, pursuant to the fourth subparagraph of Article 3(2) of Commission Regulation (EC) No 771/2008 laying down the rules of organisation and procedure of the Board of Appeal of the European Chemicals Agency (OJ L 206, 2.8.2008, p. 5, as amended by Commission Implementing Regulation (EU) 2016/823, OJ L 137, 26.5.2016, p. 4).

46. On 14 May 2019, a hearing was held at the Appellants' request. At the hearing, the Parties and the Interveners made oral submissions and responded to questions from the Board of Appeal.

Form of order sought

47. In all three appeals the respective Appellant, supported by Grace and Grace Silica, requests the partial annulment of the relevant Contested Decision, with regard to all addressees, in so far as it requires information on a combined *in vivo* mammalian erythrocyte micronucleus test and an *in vivo* mammalian comet assay with additional specific investigation on oxidative DNA damage on the following tissues: liver, kidney, glandular stomach and duodenum (test methods EU B.12/OECD TG 474 and OECD TG 489 in rats, oral route) (the 'contested information requirement').

48. In all three appeals, the respective Appellant also requests the refund of the appeal fee.

49. The Agency, supported by the French Republic, requests the Board of Appeal to dismiss the three appeals as unfounded.

Reasons

50. In all three appeals, the Appellants raise the same pleas in law:

    1. Breach of Article 46 and the principle of proportionality since:
        (a) the contested information requirement is not necessary;
        (b) the Agency failed to demonstrate the adequacy of the contested information requirement to clarify the alleged concern on the mutagenic properties of the three Substances; and
        (c) the Agency did not adopt the least onerous measure to achieve the objectives pursued.
    2. Breach of Article 25;
    3. Breach of the right to be heard;
    4. Breach of the duty to state reasons;
    5. Breach of the principle of legal certainty; and
    6. Breach of the principle of equal treatment.

Breach of Article 46 and the principle of proportionality since the contested information requirement is not necessary

Arguments of the Appellants

51. The Appellants argue that the Agency failed to satisfy the criteria established by the Board of Appeal, for example in A-005-2014, *Akzo Nobel Industrial Chemicals and Others,* Decision of the Board of Appeal of 23 September 2015, for demonstrating the necessity for further information under substance evaluation. The Appellants argue that, according to those criteria, the Agency must be able to show that:

    - there are grounds for considering that a substance constitutes a potential risk (a combination of exposure and hazard) to human health or the environment,
    - the potential risk needs to be clarified, and
    - the requested measure, to clarify the concern, has a realistic possibility of leading to improved risk management measures ('RMMs').

Potential risk

52. The Appellants argue that the Agency failed to consider the real levels, and routes, of exposure to the three Substances. The Appellants argue that the registered uses of the three Substances are only a minor part of the overall human exposure to aluminium. Aluminium is ubiquitous in the environment with 95 % of the daily oral intake of aluminium coming from the diet. The Appellants argue that, although the three Substances are used for example in water treatment products, drinking water is only a minor source of exposure to aluminium.

53. The Appellants argue that the negative results from *in vitro* genotoxicity studies with the three Substances, included in the registration dossiers for those Substances, show that there is no genotoxicity concern.

54. The Appellants argue that the Agency should also have taken into account an *in vitro* comet assay on AC (Villarini *et al.* (2017)), introduced at the MSC meeting of 24 to 26 October 2017, to support their arguments that there is no genotoxicity concern (see paragraph 22 above).

55. The Appellants argue that there are negative results from *in vitro* studies. Those studies were all performed according to good laboratory practice (GLP) and OECD test guidelines and scored as Klimisch 1 for reliability. The Agency, however, gave unjustifiably high

importance to the results from positive *in vitro* and *in vivo* studies which were unreliable and contained serious deficiencies.

56. The Appellants argue that, according to the Agency's '*Guidance on information requirements and chemical safety assessment*'[5], when there is more than one study for an endpoint, the greatest weight should be assigned to the studies that are the most relevant and reliable. However, the Agency did not apply this methodology to the ranking and weighting of the available studies on genotoxicity for the three Substances.

57. The Appellants argue that the Agency did not follow its own Integrated Testing Strategy ('ITS')[6]. The Appellants argue that, had the Agency followed the ITS for mutagenicity, it would have concluded that the available information is sufficient to eliminate any concern for genotoxicity.

58. The Appellants argue that the Agency incorrectly dismissed the read-across proposals in their registration dossiers for genotoxicity from aluminium hydroxide (AH) and aluminium oxide (AO) to the three Substances. The available toxicokinetic studies indicate that the bioavailability of the three Substances, AH and AO are similar. The Appellants also argue that there is no evidence of different toxicological profiles between soluble salts, such as the three Substances, and insoluble salts, such as AH and AO.

59. The Appellants argue that the Agency incorrectly rejected their read-across proposals from the results of studies on DCP and aluminium acetate (AA).

Need to clarify the potential risk and improved risk management measures

60. The Appellants argue that the Agency failed to demonstrate that there is a real need for the contested information requirement as there is sufficient information on the three Substances to conclude that there is no concern for genotoxicity.

61. The Appellants argue that exposure to aluminium has been extensively studied by various regulatory bodies, covering exposure via diet and other sources, including from cosmetics and toys. All those regulatory bodies confirmed that there are no safety concerns associated with exposure to aluminium.

62. The Appellants argue that the Agency failed to demonstrate that the contested information requirement has a realistic possibility of leading to improved RMMs. In particular, no consideration was given in the Contested Decisions to the existing RMMs for the uses of the three Substances.

Arguments of the Agency

Potential risk

63. The Agency argues that it is evident from the registration dossiers and publicly available information that there are '*consumer and professional uses as well as worker exposure*' to the three Substances.

64. The Agency states that, according to a European Food Safety Authority (EFSA) opinion[7] (the '2008 EFSA Opinion'), although aluminium salts are potential genotoxicants there is no risk of genotoxicity from the low oral exposure to aluminium in the diet. However, unlike EFSA's opinion, which only addressed dietary intake, the Agency's assessment is not limited to oral exposure via the diet. The REACH Regulation assesses all exposures to all relevant human populations, including for example workers and consumers, by direct exposure and indirectly via the environment.

[5] Chapter R.4: Evaluation of available information, version 1.1, December 2011.
[6] Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance, Version 6.0, July 2017, Section R.7.7.
[7] Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). '*Safety of aluminium from dietary intake*'. The EFSA Journal, (2008), 6(7); 754: pp. 1 – 34.

65. The Agency argues that the potential for genotoxicity, in particular via an oxidative stress mode of action and suspected aneugenicity, is demonstrated by publicly available literature on *in vitro* studies conducted on the three Substances.

66. The Agency argues that '*in three* in vitro *alkaline comet assays […] with AC, DNA damage has been observed (DNA single strand breaks, delay in DNA repair). Three* in vitro *micronucleus assays with AC or AS gave positive results […]. In the first two […] of the three, AC or AS acted not only as clastogen, causing structural chromosome aberrations, but also as an aneuploidogen, causing numerical chromosome aberrations. Three* in vitro *mammalian chromosome aberration tests with AC or AS showed increased frequencies of chromosome aberrations […]*'.

67. The Agency argues that the findings in the *in vitro* studies are supported by a number of positive *in vivo* genotoxicity assays performed with AC and AS.

68. The Agency argues that '*two liver or bone marrow* in vivo *micronucleus assays […], one* in vivo *chromosome aberration assay […] and two* in vivo *sister chromatid exchange assays […] resulted in increased frequencies of hepatocytes or micronucleated polychromatic erythrocytes or chromosome aberrations or sister chromatid exchanges'*.

69. The Agency argues that its ITS for mutagenicity sets out the approach to be followed to meet the standard information requirements for registration purposes. Whether the standard information requirements for registration purposes have been met is the purpose of dossier evaluation. However, pursuant to Article 46, under substance evaluation the Agency may request information that goes beyond standard information requirements.

70. The Agency argues that the read-across proposals from AA and DCP to the three Substances cannot be accepted as the proposals lack '*confirmation of the bioavailability/specific toxicokinetic data*'. The Agency argues that the existing genotoxicity data on AH and AO also cannot be used to predict the genotoxic potential of the three Substances as the data could underestimate the hazard due to potential differences in absorption, bioavailability, reactivity and toxicity.

71. The Agency argues that the results of the studies performed on the three Substances and on the source read-across substances proposed by the Appellants are not sufficient to exclude the concern for genotoxicity raised by the positive *in vitro* and *in vivo* studies performed with the three Substances.

Need to clarify the potential risk and improved risk management measures

72. The Agency argues that existing information does not clarify the genotoxicity concern of the three Substances, in particular via aneugenicity and/or oxidative DNA damage. There is therefore a real need for the contested information requirement.

73. The Agency argues that, as stated in the Contested Decisions, the contested information requirement is necessary '*in order to determine the appropriate classification of aluminium salts for mutagenicity in somatic and germ cells*'.

74. The Agency argues that the contested information requirement could also impact risk assessment by identifying a threshold-based mode of action (e.g. for aneugenicity).

75. The Agency argues that classification of the three Substances as germ cell mutagens, together with the corresponding labelling, is a key element of safe use. As there are worker and consumer uses, a new classification as germ cell mutagen category 1B or 2 would result in important changes to RMMs. These include measures to ensure protection of workers from the risks related to exposure to mutagens at work, a potential ban for uses in cosmetic products, and a reassessment of the approval for pesticide use.

76. The Agency argues that the results of the contested information requirement, and a subsequent reclassification or identification of a threshold effect, could lead to a revision of the aluminium concentration levels allowed in drinking water.

77. The Agency argues that, if the three Substances are demonstrated to be mutagenic in somatic cells based on the contested information requirement, a further study may be requested to examine whether the three substances are also germ cell mutagens.

Arguments of France

Potential risk

78. France argues that there are numerous uses of the three Substances and the '*cumulative tonnage*' of the three Substances is above two million tonnes per year.

79. France argues that wide dispersive uses have been identified for the three Substances suggesting high worker exposure. Consumers are also exposed to the three Substances as they are used in drinking water treatment.

Need to clarify the potential risk and improved risk management measures

80. France argues that if the contested information requirement gives a positive result, a classification of the three Substances as germ cell mutagens, at least at category 2, would be warranted. For classification as category 1B it would be necessary to demonstrate that the three Substances have the potential to cause mutations in germ cells.

81. France argues that '*classification of a substance as genotoxic*' has severe implications for the use of that substance, for example on the classification and labelling of mixtures. Substances classified as category 1B germ cell mutagen must not be placed on the market for use by the general public. Such substances may also be included in the candidate list for substances of very high concern and may be prioritised for inclusion on the authorisation list.

82. France argues that classification as category 1B germ cell mutagen will also have implications for other legislation such as Directive 2004/37/EC of the European Parliament and of the Council on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (OJ L 158, 30.4.2004, p. 50), and Council Directive 98/83/EC on the quality of water intended for human consumption (OJ L 330, 5.12.1998, p. 32).

Arguments of Grace and Grace Silica

Read-across from studies on other substances

83. Grace and Grace Silica argue that the Agency erroneously rejected the proposed read-across from AH to the three Substances. In this respect, Grace and Grace Silica argue that:

- The three Substances transform into AH in the digestive system. Data on AH can therefore be expected to predict the genotoxic potential of the three Substances;
- The Agency misunderstands the chemistry of aluminium salts and has sought to rely on physico-chemical differences between the three Substances and AH that either do not exist or have '*no real-world application*';
- The bioavailability of aluminium ions from the three Substances and AH is comparable;
- The Agency's suggestion that differences in the systemic, developmental or sub-chronic toxicity of AH and other aluminium salts could prevent a read-across of genotoxicity data shows a fundamental misunderstanding of the endpoint-specific nature of read-across; and
- The Agency committed an error in suggesting that, even if a read-across from AH to the three Substances is possible in principle, the study relied on by the registrants

(Lillford (2010)[8]) is deficient because no proof of exposure to bone marrow was provided. In fact, proof of exposure of bone marrow is not required by OECD TG 474 where - as in the present case - existing toxicokinetic data (Schönholzer (1997)[9]) demonstrates bone marrow exposure. In any event, bone marrow exposure could not have been demonstrated in a genotoxicity study on AH as radioactive labelling would have generated false positive results.

Findings of the Board of Appeal

84. The Agency has to demonstrate the necessity for further information under substance evaluation. Therefore the Agency must establish that:

- there are grounds for considering that, based on a combination of exposure and hazard information, a substance constitutes a potential risk to human health or the environment,
- the potential risk needs to be clarified, and
- the requested measure, to clarify the concern, has a realistic possibility of leading to improved RMMs (see, for example, Case A-023-2015, *Akzo Nobel Chemicals and Others*, Decision of the Board of Appeal of 13 December 2017, paragraph 40; the criteria were confirmed in a judgment of 20 September 2019, *BASF Grenzach* v *ECHA*, T-125/17, EU:T:2019:638, paragraph 276).

85. From the outset, it should be highlighted that, with the objective in the REACH Regulation regarding protection of human health and the environment in mind, proof of a real risk is too high a threshold to meet in order to require further information, including testing, following a substance evaluation.

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

87. In this respect, pursuant to Article 46, it is not necessary for the Agency to demonstrate an '*actual risk*', only a '*potential risk*'. The aim of requesting additional information under substance evaluation is to clarify whether the '*potential risk*' is an '*actual risk*' (see, for example, Case A-023-2015, *Akzo Nobel Chemicals and Others*, Decision of the Board of Appeal of 13 December 2017, paragraph 99). This does not mean however that any evidence of a potential concern, no matter how weak, is sufficient to justify such a request.

88. The Agency must take into account all the available evidence before deciding, based on that evidence as a whole, that there is a potential risk which requires further investigation (see Case A-015-2015, *Evonik Degussa and Others*, Decision of the Board of Appeal of 30 June 2017, paragraph 123). The Agency must give due consideration to the quality and quantity of information both in support of the potential risk and against the existence of that potential risk.

89. However, in the present case, for the reasons set out below, it is unclear whether the Agency's conclusion that the contested information requirement is necessary, is based on all the available evidence. The Agency's failings in this respect relate to:

1. Identifying the concern in the three Contested Decisions;

[8] '*Induction of micronuclei in the bone marrow of treated rats*' (unpublished).
[9] *'Intestinal absorption of trace amounts of aluminium in rats studied with 26-aluminium and accelerator mass spectrometry*', Clinical Science 1997, 92, pp. 379 – 383.

2. Demonstrating the existence of a potential risk; and
3. Demonstrating that the contested information requirement has a realistic possibility of leading to improved RMMs.

1. Concern identified by the Agency

90. It is clear from the Contested Decisions that the Agency has identified genotoxicity as the concern to be clarified by the contested information requirement. However, there is a lack of clarity, and in some respects consistency, regarding the substance or substances of concern.

91. It is unclear from the Contested Decisions and the submissions in the present appeals whether the concern for genotoxicity relates to the three Substances specifically, or all soluble aluminium salts, or, more generally, the aluminium ion.

92. The Contested Decisions state that '*[the] available data are not sufficient to clarify the identified concern on potential genotoxicity of AC, ACH and AS* in vivo *that needs to be clarified with further information*' (emphasis added).

93. The Contested Decisions state that '*more information is required in order to determine the appropriate classification of aluminium salts for mutagenicity in somatic and germ cells…'* (emphasis added).

94. The Contested Decisions state that the results of *in vivo* micronucleus or chromosomal aberration assays '*raised concern on potential genotoxicity* in vivo *of aluminium soluble salts*' (emphasis added).

95. In the Defence, the Agency argues that the concern for genotoxicity is related to the positive findings in the genotoxicity studies on the three Substances rather than, more generally, the aluminium ion.

96. Other submissions in this case indicate that the genotoxicity concern may be related to soluble aluminium salts and/or the aluminium ion and its bioavailability. For example, at the hearing the Agency clearly stated that the concern was for the aluminium ion and its bioavailability.

97. The Agency stated in its observations on Grace and Grace Silica's statement in intervention that '*any toxicity observed is caused by the aluminium ion*'. In its statement in intervention, France states that there is a concern for the '*potential carcinogenicity of aluminium compounds*'.

98. In the substance evaluation reports, it is stated that '*[no] particular concern is expected from chloride, sulphate, nitrate and lactate ion*'.

99. The lack of clarity and consistency shown in paragraphs 90 to 98 above regarding the substance or substances for which there is a genotoxicity concern in turn creates a lack of clarity regarding how the contested information requirement can and will be used.

2. Potential risk

100. As stated in paragraph 84 above, potential risk is based on a combination of exposure and hazard information.

101. It is uncontested that there is exposure to the three Substances. With regards to hazard, the Agency examines in the Contested Decisions the available studies on the three Substances and the Appellants' read-across proposals.

102. The Contested Decisions contain a number of failings, in particular and not necessarily limited to, the assessment of the available studies on the three Substances (section 2.1. below), and the rejection of the read-across proposal between AH and the three Substances (section 2.2. below).

2.1. Available studies on the three Substances

103. For the following reasons, and irrespective of the substance or substances of concern (see paragraphs 90 to 98 above), the Agency has failed to demonstrate that its conclusion that the contested information requirement is necessary is based on all the available evidence.

104. The majority of the studies relied on by the Parties to demonstrate the presence or absence of a concern for genotoxicity have not been submitted in the present proceedings. The Board of Appeal is only able to assess the findings of those studies in so far as they are referred to in the Contested Decisions and the submissions in this case.

105. First, it is uncontested that the findings of the available *in vitro* genotoxicity studies on the three Substances relied on by the Parties are to some extent inconsistent regarding whether the three Substances are genotoxicants. However, based on the submissions in the present case, the studies on the three Substances relied on by the Appellants are more reliable than those relied on by the Agency. In this respect, based on the submissions in the present case, the *in vitro* studies on the three Substances included by the Appellants in their registration dossiers to demonstrate that there is no concern for genotoxicity are all considered to be reliable without restriction (Klimisch score 1) or reliable with restriction (Klimisch score 2).

106. It is uncontested that all the *in vivo* and *in vitro* studies relied on by the Agency to demonstrate a concern for genotoxicity in the section of the Contested Decisions entitled '*Reasons*' (see paragraphs 66 to 68 above) contain deficiencies in reporting and/or deviations from the requirements of the relevant OECD test guidelines. These deficiencies are acknowledged by the Agency in the Contested Decisions. For example, the Contested Decisions state:

'*the positive studies available with the three [Substances] have all deficiencies in reporting or deviations (e.g. single dose testing, no positive control data) that impaired to classify directly AC, ACH and AS for mutagenicity…*' (emphasis added).

107. The Contested Decisions also state that:

'*All the* in vivo *genotoxicity assays performed with AC, ACH or AS have reported positive effects. Nevertheless, these studies had deficiencies due to lack of reporting or deviations from OECD test guidelines…*' (emphasis added).

'*Chromosomal aberration and micronuclei have been observed* in vitro *with AC or other soluble aluminium salts in studies with some shortcomings […]' (*emphasis added).

'*Increased DNA damage have been observed consistently in three* in vitro *alkaline comet assays […]. Although these studies had limitations, they consistently show that AC, ACH or AS may induce DNA damages*' (emphasis added).

108. Although the acknowledged deficiencies in the studies relied on by the Agency reduce their reliability, it is nonetheless possible under substance evaluation that such studies could be sufficient to demonstrate a concern. However, the Agency must carefully justify any decision to rely on studies with limited reliability to override the results of reliable, high quality studies with negative results. In the present case, the Agency has not provided an adequate justification for relying on positive results from less reliable *in vitro* and *in vivo* studies against the negative results from the more reliable *in vitro* studies provided by the Appellants.

109. Second, shortly before the MSC meeting, the Appellants were provided with the slides that the eMSCA later presented at the MSC meeting. Those slides introduced for the first time in the decision-making procedure the results of an *in vivo* micronucleus assay with AC (Paz *et al*. (2017)) to support the concern for genotoxicity (see paragraph 21 above). However, the Agency did not take into consideration data on an *in vitro* comet assay (Villarini *et al.* (2017)) introduced by the Appellants at the MSC meeting to support their

arguments that there is no concern for genotoxicity (see paragraphs 22 above). The Contested Decisions do not explain why documents introduced at a similar stage of the decision-making procedure (i.e. at and just before the MSC meeting) were treated differently. The Villarini *et al.* (2017) study may have been important to the decision-making of the MSC.

110. Third, the Agency argued during the present proceedings that the Paz *et al*. (2017) study is not decisive to its conclusions that there is a concern for genotoxicity. However, the Agency also argues that the study was introduced to address concerns raised in the proposals for amendment. The findings of the Paz *et al*. (2017) study may have been important in achieving agreement in the MSC. Contrary to the Agency's arguments, therefore, the references to the findings of the Paz *et al.* (2017) study in the Contested Decisions were not simply additions to strengthen a justification that was already sufficient in itself. The findings were a component of the Agency's argumentation supporting its conclusion that more information was required to clarify a concern for genotoxicity.

2.2. Read-across between AH and the three Substances

2.2.1. Rejection of the read-across

111. According to the Contested Decisions, the proposed read-across from the results of a study on AH (Lillford (2010)) to the three Substances was rejected because of differences in physico-chemical properties, potential lower systemic toxicity, and potential lower bioavailability. As a result, according to the Contested Decisions, the proposed read-across may underestimate the potential hazard for the three Substances.

112. However, the Agency has failed to demonstrate that in rejecting the Appellants' read-across from AH to the three Substances it took into account all the available evidence. This is irrespective of the substance or substances of concern (see paragraphs 90 to 98 above).

113. For example, first, the Agency does not adequately explain in the Contested Decisions why the alleged differences in the physico-chemical properties prevent the read-across from AH to the three Substances.

114. The Agency bases its rejection on differences in water solubility between AH and the three Substances, in other words on the grounds that the three Substances are soluble in water whereas AH is insoluble. The Parties agree that the aluminium 3+ ion released from aluminium compounds drives the toxicity of the three Substances. However, the Contested Decisions do not explain how the water solubility of the three Substances correlates with the bioavailability of the aluminium 3+ ion and consequently the possibility to read-across from one substance to another. In fact, the Agency itself acknowledges that '*although bioavailability appears to be generally correlated to solubility, insufficient data are available to directly extrapolate from solubility in water to bioavailability*'.

115. Second, the Agency also states that AH (and AO) '*are in forms of particulates*'. However, the Agency has not explained what this means and its relevance to the possibility to read-across from AH to the three Substances.

116. Third, the Contested Decisions state that '*differences in toxicity between soluble and insoluble aluminium compounds were also suggested by other studies such as sub-chronic toxicity in dogs (FAO/WHO, 2OO7)*'.

117. However, it is unclear whether the Agency has considered the results of the specific studies referred to in the FAO/WHO 2007 report[10] or whether it has just relied uncritically on the findings of the FAO/WHO 2007 report without looking at the actual

[10] Safety evaluation of certain food additives and contaminants: Prepared by the sixty seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series. 58: pp. 119 – 207.

studies in question and the relevance of them to the assessment of the read-across proposed by the Appellants.

118. Fourth, the Contested Decisions state that '*the results of Priest (2010)[11] show that the compounds administered as suspensions (hydroxide, oxide) were less bioavailable than the soluble compounds (AC) and (AS)*'. The Contested Decisions add that '*as [AH] [was] less bioavailable, toxicokinetics does not support the read-across with [this] salt.*' The Agency acknowledges that the Priest (2010) study, on which it relies, has '*some weaknesses*'.

119. However, the Poirier (2010) study[12], referred to in the Contested Decisions, and the Schönholzer (1997) study, relied on by the Intervener (Grace and Grace Silica) in these proceedings, indicate that the bioavailability of the three Substances and AH falls within the same range. In addition, according to the 2008 EFSA Opinion (see paragraph 64 above) '*there is no major difference in bioavailability between soluble and insoluble aluminium compounds*'.

120. There is therefore evidence which supports, and is contrary to, the conclusion of the Agency. The Agency has not explained why it gave pre-eminence to the results of the Priest (2010) study, even though it has some weaknesses.

2.2.2. Relevance of the Lillford (2010) study

121. The Agency argues that even if the read-across from AH to the three Substances had been possible it would not have altered the results of the substance evaluation. This is because, first, AH may be of lower bioavailability than the three Substances and, second, the Lillford (2010) study lacked proof of exposure to bone marrow.

122. The Agency's failings with regard to its conclusions on the bioavailability of AH and the three Substances have been examined in paragraphs 118 to 120 above.

123. With regard to the Agency's arguments on exposure of bone marrow to AH in the Lillford (2010) study, the Agency committed an error of assessment for the following reason.

124. The Agency concluded that the Lillford (2010) study was not relevant to the examination of the genotoxic potential of the three Substances because of the lack of exposure of bone marrow to AH. However, the Agency failed to address the fact that OECD TG 474 (mammalian erythrocyte micronucleus test) does not require proof of exposure of bone marrow where such exposure has been observed in other studies. In this respect OECD TG 474 states that '*[e]vidence of exposure of the bone marrow to a test substance may include a depression of the immature to mature erythrocyte ratio or measurement of the plasma or blood levels of the test substance. In case of intravenous administration, evidence of exposure is not needed. Alternatively, ADME [absorption, distribution, metabolism and excretion] data, obtained in an independent study using the same route and same species can be used to demonstrate bone marrow exposure'.* In the present case, there is evidence from an independent study of bone marrow exposure. In the Schönholzer (1997) study, a kinetic study in rats on four aluminium compounds including AH, aluminium was detected in plasma, indicating bone marrow exposure.

3. Improved RMMs

125. With regards to the possibility of improved RMMs, the Contested Decisions state:

> '*more information is required in order to determine the appropriate classification of aluminium salts for mutagenicity in somatic and germ cells. This request could also impact risk assessment by identifying a threshold-based mechanism (e.g. aneugenicity) of action to be considered for risk assessment and control of risk to humans*'.

---

[11] '*The bioavailability of ingested Al-26 labelled aluminium and aluminium compounds in the rat*' (2010).

[12] Aluminium neurotoxicity program, February, 2010. Techno synapse.

126. The Contested Decisions add that '*[t]he classification of the* in vivo *genotoxic potential and mode of action of [the three Substances] is requested for both risk assessment and classification and labelling*'.

127. The Contested Decisions also state that '*[f]urther [RMMs] such as classification and labelling or further testing on mutagenicity will be considered*'.

128. In summary, the possible improved RMMs identified in the Contested Decisions are (i) classification of the three Substances under 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') and (ii) identification of a threshold-based mode of action (e.g. for aneugenicity) for the three Substances.

129. However, for the following reasons, the Agency failed to demonstrate that the contested information requirement has a realistic possibility of leading to improved RMMs, an essential requirement in demonstrating that the requested information is necessary. Specifically, the Agency has not demonstrated that its conclusion that the contested information requirement is necessary is based on all the available evidence.

130. First, the sections of the Contested Decisions concerning the contested information requirement contain no examination of the available information on uses of the three Substances and the RMMs already in place for those Substances. In other words, it is not explained in the Contested Decisions why exposure to the three Substances is not already adequately controlled even if the three Substances are eventually shown to be genotoxic. Consequently, even if the results of the requested study led, for example, to a new classification, there is no examination in the Contested Decisions on whether the RMMs stemming from such a classification are already in place.

131. Second, if consumers are a population of concern, the Agency does not explain how the contested information requirement might lead to an improvement in the RMMs designed to protect them from exposure to the three Substances. This is particularly in view of the fact that there are a number of other legislative instruments aimed at regulating any risk related to exposure to aluminium. For example, the Contested Decisions do not mention Directive 98/83/EC, the objective of which is to protect human health from the adverse effects of any contamination of water intended for human consumption. This is also despite the following conclusion in the 2008 EFSA Opinion which is cited in the Contested Decisions:

    '*[Aluminium] compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation* in vitro*. Clastogenic effects were also observed* in vivo *when [aluminium] sulfate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the variety of genotoxic effects elicited by aluminium salts in experimental systems. Cross-linking of DNA with chromosomal proteins, interaction with microtubule assembly and mitotic spindle functioning, induction of oxidative damage, damage of lysosomal membranes with liberation of DNAase, have been suggested to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidized bases in experimental systems. <u>The Panel noted that these indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to aluminium via the diet</u>*' (emphasis added).

132. The Agency argues in the Defence that '*depending on the result obtained and subsequent classification or threshold-base, most probably the concentration levels specified for drinking water would be revised*'. However, this argumentation is not contained in the Contested Decisions and is, regardless, speculative and unsubstantiated.

133. Third, if workers are a population of concern, there is no examination in the Contested Decisions of the available information on worker exposure to the three Substances and the existing RMMs in relation to the concern for genotoxicity.

134. With regards to oral exposure of workers to the three Substances, the Contested Decisions state that '*dermal exposure may occur in workers*'. At the hearing, the Agency and the eMSCA argued that there is a concern that workers could ingest the three Substances by hand to mouth exposure after dermal exposure. However, the Agency did not demonstrate how the RMMs in place, for example wearing of gloves and washing hands after use, do not already address the concern.

135. Fourth, there is reference to uses of the three Substances in relation to some of the other information requirements in the Contested Decisions. However, it is unclear whether those uses are also relevant to the examination of the risks posed by the three Substances if they are found to be genotoxic.

Conclusion on the Appellants' plea that the Agency breached Article 46 and the principle of proportionality

136. As set out in paragraphs 84 to 135 above, the Agency has failed to demonstrate that the contested information requirement is necessary.

137. First, as set out in paragraphs 90 to 98 above, there is a lack of clarity, and in some respects consistency, in the three Contested Decisions regarding the substance or substances for which there is a genotoxicity concern.

138. Second, as set out in paragraphs 100 to 124 above, the Agency has failed to clearly demonstrate that, based on the evidence as a whole, there is a potential risk which requires further investigation under substance evaluation. In particular, the Agency has not demonstrated that it gave the appropriate importance to both reliable and unreliable *in vitro* and *in vivo* studies (see paragraphs 103 to 110). The Agency also failed to demonstrate that its rejection of the proposed read-across from AH to the three Substances was based on all the available evidence (see paragraphs 111 to 120).

139. Third, as set out in paragraphs 121 to 124 above, the Agency committed an error of assessment in concluding that, if the read-across from AH to the three Substance was accepted, the results of the study on AH (Lillford (2010)) were not relevant to the assessment of the genotoxicity of the three Substances.

140. Fourth, as set out in paragraphs 125 to 135 above, the Agency has not adequately examined, or explained, in the Contested Decisions how the contested information requirement could lead to improved RMMs.

141. In light of these failings, the Contested Decisions are annulled, with regard to all addressees of those decisions, in so far as they require information on a combined *in vivo* mammalian erythrocyte micronucleus test and an *in vivo* mammalian comet assay with additional specific investigation on oxidative DNA damage on the following tissues: liver, kidney, glandular stomach and duodenum (test methods EU B.12/OECD TG 474 and OECD TG 489 in rats, oral route).

142. Since the contested information requirement has been annulled, it is not necessary to examine the remainder of the Appellants' pleas and arguments.

Refund of the appeal fee

143. In accordance with Article 10(4) of Commission Regulation (EC) No 340/2008 on the fees and charges payable to the European Chemicals Agency pursuant to the REACH Regulation (OJ L 107, 17.4.2008, p. 6), the appeal fee shall be refunded if the appeal is decided in favour of an appellant.

144. As the appeals have been decided in favour of the Appellants, the appeal fees must be refunded.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Annuls the Agency's decisions of 21 December 2017 on the substance evaluation of aluminium chloride, aluminium chloride basic and aluminium sulphate in so far as they require information on a combined *in vivo* mammalian erythrocyte micronucleus test and an *in vivo* mammalian comet assay with additional specific investigation on oxidative DNA damage on the following tissues: liver, kidney, glandular stomach and duodenum (test methods EU B.12/OECD TG 474 and OECD TG 489 in rats, oral route).**
2. **Remits the case to the competent body of the Agency for further action.**
3. **Decides that the appeal fees must be refunded.**

Andrew FASEY
On behalf of the Chairman of the Board of Appeal

Marc GOODACRE
Acting as Registrar of the Board of Appeal