EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

11 December 2018

(Compliance check – Pre-natal developmental toxicity study (OECD TG 414) – Assessment of compliance with Column 1 of Section 8.7.2. of Annex IX – Setting of dose levels)

Case number	A-006-2017
Language of the case	English
Appellant	Climax Molybdenum B.V., the Netherlands
Representatives	David Scannell Brick Court Chambers, United Kingdom Raminta Dereskeviciute and Zanda Romata K&L Gates LLP, United Kingdom
Contested Decision	CCH-D-2114356486-40/01/F of 13 March 2017, adopted by the European Chemicals Agency (the 'Agency') pursuant to Article 41 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 and Rapporteur), Sari Haukka (Legally Qualified Member) and Henricus Spaas (Technically Qualified Member)

Registrar: Alen Močilnikar

gives the following

Decision

Background to the dispute

1. On 6 October 2010, the Appellant submitted a registration dossier for the substance disodium molybdate (EC No 231-551-7, CAS No 7631-95-0; the 'Substance') at the tonnage band of 100 to 1 000 tonnes per year.

2. The Appellant subsequently updated its registration dossier repeatedly, including the results of a pre-natal developmental toxicity study (W. Tyl *et al.*, *Developmental toxicity evaluation of sodium molybdate dihydrate (CAS No 10102-40-6) administered in the diet to CD® (Sprague Dawley) rats, RTI International, RTI Project No 0213540.000,* 2013; the 'Tyl (2013) study'). This study was commissioned by the International Molybdenum Association for the regulatory purposes of the Environmental Protection Agency – Office of Water of the United States of America.

3. On 27 June 2016, the Agency initiated a compliance check of the Appellant's registration dossier pursuant to Article 41 of the REACH Regulation (all references to Articles or Annexes hereinafter concern the REACH Regulation unless stated otherwise).

4. On 9 August 2016, the Agency notified a draft decision to the Appellant in accordance with Article 50(1).

5. On 28 September 2016, the Appellant submitted its comments on the draft decision.

6. On 13 March 2017, the Agency adopted the Contested Decision in accordance with Article 51(3).

Contested Decision

7. The Contested Decision finds that the dose levels used in the Tyl (2013) study (3, 10, 20 and 40 mg Mo/kg bw/day) were too low to comply with OECD test guideline 414. Consequently, according to the Contested Decision, the Tyl (2013) study does not satisfy the information requirement set out in Column 1 of Section 8.7.2. of Annex IX.

8. The dispositive part of the Contested Decision states:

   '*Based on Article 41 of [the REACH Regulation], ECHA requests you to submit information on*

   1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the [Substance].

   You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

   You are required to submit the requested information in an updated registration dossier by 20 March 2018. You shall also update the chemical safety report, where relevant.'

Procedure before the Board of Appeal

9. On 9 June 2017, the Appellant filed this appeal.

10. On 14 August 2017, the Agency submitted its Defence.

11. On 30 November 2017, PETA International Science Consortium (PISC) was granted leave to intervene in this case in support of the Appellant. PISC subsequently stated that it no longer wished to intervene in the case.

12. On 6 December 2017, the Appellant submitted observations on the Defence and responded to questions from the Board of Appeal.

13. On 13 April 2018, the Agency submitted observations on the Appellant's observations on the Defence and on its reply to questions from the Board of Appeal.

14. On 9 October 2018, a hearing was held at the Appellant's request. At the hearing, the Parties made oral submissions and responded to questions from the Board of Appeal.

Form of order sought

15. The Appellant requests the Board of Appeal to annul the Contested Decision and order the refund of the appeal fee.

16. The Agency requests the Board of Appeal to dismiss the appeal.

Reasons

17. The Appellant raises six pleas in law in support of its appeal, and numerous arguments in support of each of these pleas. The Board of Appeal will examine the Appellant's pleas in the following order:

    1. The fifth plea, alleging an error in the Agency's assessment of the Tyl (2013) study.
    2. The second and sixth pleas, alleging breaches of OECD rules and of the principle of good administration.
    3. The first, third and fourth pleas, alleging that the Contested Decision is not tailored to real information needs, that it breaches the principle of proportionality, and that it breaches the animal welfare provisions of the REACH Regulation.

1. The fifth plea, alleging an error in the Agency's assessment of the Tyl (2013) study

Arguments of the Appellant

18. By its fifth plea, the Appellant claims, in essence, that the Tyl (2013) study was conducted in accordance with OECD test guideline 414 and therefore satisfies the information requirement set out in Column 1 of Section 8.7.2. of Annex IX (reproductive toxicity). The Agency erred in finding that the dose levels used in this study were too low to identify the hazardous properties of the Substance, so that the information requirement was not fulfilled.

19. The Appellant explains that the Tyl (2013) study was preceded by a dose range-finding study performed with dose levels of 0, 1, 10 and 20 mg Mo/kg bw/day. The dose levels used in this dose range finding study were set on the basis of the information available at the time, in particular the following studies:

1. L. Fairhall *et al.*, *The toxicity of molybdenum*, 1945 U.S. Public Health Bulletin 293, p. 1-36 (the 'Fairhall (1945) study'). According to the Appellant, this study showed that a dose of 80 mg Mo/kg bw/day causes mortality in 25 to 50% of the animals.
2. T. Fungwe *et al.*, *The role of dietary molybdenum on estrus activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats*, 1990 Nutr. Res. 10, p. 515-524 (the 'Fungwe (1990) study'). According to the Appellant, this study showed that the Substance causes some developmental and/or maternal toxicity at dose levels as low as 1.6 mg Mo/kg bw/day. This study was relied on by regulatory authorities throughout the 1990s.
3. G. Hoffman *et al.*, *Sodium molybdate dihydrate: A 90-day oral dietary administration study in rats*, Study No 10-2225, Huntingdon Life Sciences, 2011 (the 'Hoffman (2011) study'). According to the Appellant, this study showed that a dose level above 60 mg Mo/kg bw/day would cause excessive toxicity. At the hearing, the Appellant added that effects were seen in this study already after two weeks of administration of the substance.

20. The dose-range finding study did not show any adverse effects at doses of 1, 10 and 20 mg Mo/kg bw/day. It was therefore decided to increase these dose levels in the Tyl (2013) study, using 3, 10, 20 and 40 mg Mo/kg bw/day.

21. More specifically, according to the Appellant:

    1. The highest dose level used in the Tyl (2013) study (40 mg Mo/kg bw/day) was set with the aim to induce some developmental and/or maternal toxicity but not death or severe suffering, as provided in OECD test guideline 414.
    2. The two intermediate dose levels used in the Tyl (2013) study (10 and 20 mg Mo/kg bw/day) were set with the aim to produce minimal observable toxic effects.
    3. The lowest dose level used in the Tyl (2013) study (3 mg Mo/kg bw/day) was set with the aim not to produce any evidence of either maternal or developmental toxicity.

22. In these circumstances, according to the Appellant, the Tyl (2013) study was carried out in accordance with OECD test guideline 414. The Tyl (2013) study consequently satisfies the information requirement set out in Column 1 of Section 8.7.2. of Annex IX.

23. In addition, the Appellant submitted with the Notice of Appeal certain documents to show that the dose levels used in the Tyl (2013) study were set correctly, namely:

    1. The final report of a two-generation reproductive toxicity study on sodium molybdate dihydrate in rats, dated 21 April 2017 (the 'OECD TG 416 (2017) study'). According to the Appellant, this study shows that the Substance causes maternal toxicity in rats at dose levels of 40 mg Mo/kg bw/day.
    2. F. Sullivan, *Expert opinion in response to ECHA's claim of failure of the prenatal developmental toxicity study on sodium molybdate dihydrate to be in compliance with the REACH Requirements*, 6 June 2017 (the 'Sullivan (2017) expert opinion'). According to the Appellant, this expert opinion shows that the Tyl (2013) study was performed in accordance with OECD test guideline 414 and is compliant with the REACH Regulation. Repeating the study using higher dose levels is not justifiable.
    3. J. Buschmann, *Critical review on ECHA notification on acceptance of a prenatal developmental toxicity study on sodium molybdate dihydrate*, 8 June 2017 (the 'Buschmann (2017) review'). According to the Appellant, this review shows that the Tyl (2013) study was performed in accordance with OECD test guideline 414.

Arguments of the Agency

24. The Agency objects to the admissibility of the OECD TG 416 (2017) study, the Buschmann (2017) review and the Sullivan (2017) expert opinion on the ground that these documents were not available before the adoption of the Contested Decision.

25. The Agency also argues that the available data do not support the Appellant's argument that the dose levels used in the Tyl (2013) study were expected to induce some developmental and/or maternal toxicity but not death or severe suffering, as provided in OECD test guideline 414.

26. More specifically, according to the Agency, the information on the basis of which the dose levels were set in the Tyl (2013) study did not provide sufficient evidence to limit the top dose level at 40 mg Mo/kg bw/day:

    1. The Fairhall (1945) study is not reliable because it contains no reliable information on dose levels. Moreover, the study was performed using various different substances, and in male rats rather than pregnant female rats.

    2. The Fungwe (1990) study had a considerably longer exposure duration than an OECD TG 414 study (starting six weeks before mating and pregnancy). Therefore, the results of that study cannot be used as such to determine the dose levels for an OECD TG 414 study. Moreover, the Fungwe (1990) study does not provide sufficient information to calculate the actual doses ingested by the animals.

    3. The Hoffmann (2011) study is a 90-day study, so that its results cannot be used as such to determine the dose levels for an OECD TG 414 study because the latter has a shorter exposure duration. Moreover, the effects observed in the Hoffmann (2011) study in non-pregnant female rats at a dose level of 60 mg Mo/kg bw/day (5.6% reduction in body weight and slight histopathological effects) do not constitute death or severe suffering within the meaning of OECD test guideline 414.

    4. The dose range-finding study was inadequate for setting a dose in the Tyl (2013) study as no maternal or developmental effects were observed up to its highest dose (20 mg Mo/kg bw/day).

27. The Agency further argues that the results of the OECD TG 416 (2017) study were not available when the Tyl (2013) study was carried out. Therefore, those results cannot be used to show that the dose levels used in the Tyl (2013) study were set correctly.

28. In any event, according to the Agency, the OECD TG 416 (2017) study does not show that the highest dose level used in the Tyl (2013) study was sufficiently high to induce some developmental and/or maternal toxicity but not death or severe suffering, as required by OECD test guideline 414. This is because the OECD TG 416 (2017) study was carried out over a considerably longer exposure duration than an OECD TG 414 study. Therefore the results of the OECD TG 416 (2017) study cannot be used as such to determine the dose levels for an OECD TG 414 study. Moreover, although the OECD TG 416 (2017) study showed some marginal maternal toxicity at 40 mg Mo/kg bw/day, the observed effects were too slight to constitute '*some developmental and/or maternal toxicity but not death or severe suffering*' within the meaning of OECD test guideline 414.

Findings of the Board of Appeal

1.1. Admissibility and probative value of certain documents

29. The Appellant filed the OECD TG 416 (2017) study, the Buschmann (2017) review and the Sullivan (2017) expert opinion with the Notice of Appeal.

30. The Agency objects to the admissibility of these documents on the ground that they constitute new evidence that was not available before the adoption of the Contested Decision.

31. Evidence filed with a notice of appeal which was not available to the Agency before the adoption of a contested decision is admissible if it supports facts already alleged during the decision-making procedure under Article 51 (see Case A-004-2015, *Polynt,* Decision of the Board of Appeal of 19 October 2016, paragraph 133).

32. The OECD TG 416 (2017) study, the Buschmann (2017) review and the Sullivan (2017) expert opinion support a fact already alleged during the decision-making procedure under Article 51, namely that the Tyl (2013) study complied with OECD test guideline 414.

33. The OECD TG 416 (2017) study, the Buschmann (2017) review and the Sullivan (2017) expert opinion are consequently admissible. The Agency's objection must be rejected.

34. It must however be added that the Appellant simply submitted the Buschmann (2017) review and the Sullivan (2017) expert opinion in support of its arguments in the Notice of Appeal. The authors of these documents were not admitted as experts and/or witnesses by the Board of Appeal in accordance with Article 16(2) to (6) 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').

35. Therefore, the Buschmann (2017) review and the Sullivan (2017) expert opinion cannot be attributed probative value as opinions of experts or statements of witnesses within the meaning of Article 16 of the Rules of Procedure.

36. Insofar as the Buschmann (2017) review and the Sullivan (2017) expert opinion are referred to in the Appellant's submissions, they must be considered as documents setting out arguments of the Appellant.

1.2. Substance

37. By its fifth plea, the Appellant claims that the Agency committed an error of assessment when it found that the dose levels used in the Tyl (2013) study were too low to comply with Column 1 of Section 8.7.2. of Annex IX.

38. When an appellant argues that the Agency committed an 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, and whether those facts support the conclusions that the Agency drew from them (see, to this effect, Case A-003-2015, *BASF Pigment*, Decision of the Board of Appeal of 1 August 2016, paragraphs 32 and 36).

39. The Board of Appeal will examine:

    1. the powers of the Agency when performing a compliance check under Column 1 of Section 8.7.2. of Annex IX,
    2. the criteria to be applied in the Agency's assessment of the Tyl (2013) study, and
    3. whether the Agency correctly applied those criteria in the circumstances of the present case.

1.2.1. Powers of the Agency when performing a compliance check

40. Under Article 41, the Agency can assess the quality and adequacy of information submitted in a registration dossier in order to determine whether this information satisfies the information requirements set out in, for example, Annex IX.

41. Column 1 of Section 8.7.2. of Annex IX requires registrants to perform a pre-natal developmental toxicity study in accordance with OECD test guideline 414 or test method B.31 of Commission Regulation (EC) No 440/2008 laying down test methods pursuant to the REACH Regulation (OJ L 142, 31.5.2008, p. 1; the 'Test Methods Regulation'). The wording of OECD test guideline 414 and test method B.31 in the Test Methods Regulation is identical.

42. The purpose of the information requirement set out in Column 1 of Section 8.7.2. of Annex IX is to generate information on the intrinsic hazard properties of a substance with respect to prenatal developmental toxicity.

43. It follows that the Agency has the power to conduct its own assessment in order to verify whether the information requirement set out in Column 1 of Section 8.7.2. of Annex IX has been met by means of a submitted study. This has not been disputed by the Parties.

1.2.2. Criteria to be applied in the assessment of the Tyl (2013) study

44. OECD TG 414 studies are designed to provide information concerning the effects of prenatal exposure to a substance on the pregnant test animal and on the developing organism.

45. As regards the period of administration, paragraph 13 of OECD test guideline 414 provides that, when the study is carried out using rats, a substance is administered to the animals daily for about 15 days. Dosing normally starts from implantation and the animals are terminated before delivery.

46. As regards the doses to be administered, paragraph 14 of OECD test guideline 414 states:

    '*At least three dose levels and a concurrent control should be used. Healthy animals should be assigned in an unbiased manner to the control and treatment groups. The dose levels should be spaced to produce a gradation of toxic effects. Unless limited by the physical/chemical nature or biological properties of the test chemical, the highest dose should be chosen with the aim to induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering. At least one intermediate dose level should produce minimal observable toxic effects. The lowest dose level should not produce any evidence of either maternal or developmental toxicity. A descending sequence of dose levels should be selected with a view to demonstrating any dosage-related response and no-observed-adverse-effect level (NOAEL) or doses near the limit of detection that would allow the determination of*

a benchmark dose. Two- to four-fold intervals are frequently optimal for setting the descending dose levels, and the addition of a fourth test group is often preferable to using very large intervals (e.g. more than a factor of 10) between dosages. Although establishment of a maternal NOAEL is the goal, studies which do not establish such a level may also be acceptable'.

47. Paragraph 14 of OECD test guideline 414 therefore provides, in essence, that a study should be carried out using dose levels set so as to induce:

    1. Some developmental and/or maternal toxicity but not death or severe suffering (highest dose),
    2. Minimum observable toxic effects (intermediate doses), and
    3. No effects (lowest dose).

48. As regards the limit dose, paragraph 17 of OECD test guideline 414 states:

    '*If a test at one dose level of at least 1000 mg/kg body weight/day by oral administration, using the procedures described for this study, produces no observable toxicity and if an effect would not be expected based upon existing data (e.g., from structurally and/or metabolically related compounds), then a full study using three dose levels may not be considered necessary*.'

49. Paragraph 17 of OECD test guideline 414 therefore provides, in essence, that a full study using three dose levels may not be necessary if it can be shown that a dose level of at least 1000 mg/kg bw/day produces no observable developmental and/or maternal toxicity.

50. Together, paragraphs 14 and 17 of OECD test guideline 414 provide for two situations.

51. On the one hand, there may be intrinsic physical/chemical or biological reasons that limit the highest dose level below the limit dose of 1000 mg/kg bw/day.

52. On the other hand, there may be data – such as an appropriate dose range finding study or similarly adequate and reliable scientific information – that demonstrate that a certain dose level under 1000 mg/kg bw/day will induce death or severe suffering in the animals concerned. The highest dose level should then be set below the dose level that is known to induce death or severe suffering, but still as high as possible in order to achieve the aim of inducing some developmental and/or maternal toxicity (potentially up to 1000 mg/kg bw/day if the reasons mentioned in the previous paragraph do not exist).

1.2.3. Assessment of the Tyl (2013) study

53. The Appellant argues, in essence, that available data show that the dose levels used in the Tyl (2013) study were set in accordance with OECD test guideline 414. The Appellant relies, in this regard, on the Fairhall (1945) study, the Fungwe (1990) study, the Hoffman (2011) study, the dose range-finding study that preceded the Tyl (2013) study, and the OECD TG 416 (2017) study.

1.2.3.1. The Fairhall (1945) study

54. According to the Appellant, the Fairhall (1945) study showed that 25% to 50% of rats die at doses of 78 to 86 mg Mo/kg bw/day. Based on this study a dose of 80 mg Mo/kg bw/day was expected to cause death or severe suffering.

55. However, as the Agency points out and the Appellant does not dispute, the Fairhall (1945) study was a long-term study carried out using various molybdenum compounds. An OECD TG 414 study, by contrast, is a short-term study (see paragraph 45 above). Given the difference in exposure duration, and the different molybdenum compounds used, it could not be assumed that the effects observed at a certain dose level in the Fairhall (1945) study would appear at the same dose level in an OECD TG 414 study.

56. Consequently, the Fairhall (1945) study did not constitute adequate information for setting the highest dose level in the Tyl (2013) study.

57. Moreover, as the Agency points out and the Appellant does not dispute, the actual dose intake of the animals in the Fairhall (1945) study is not known with certainty. It may have been considerably higher than 80 mg Mo/kg bw/day.

58. Consequently, the Fairhall (1945) study did not constitute reliable information for setting the highest dose level in the Tyl (2013) study.

1.2.3.2. The Fungwe (1990) study

59. According to the Appellant, the Fungwe (1990) study showed that the Substance caused adverse effects (increased resorption and decreased foetal bodyweight) at dose levels as low as 1.6 mg Mo/kg bw/day. Based on this study, doses between 1 and 20 mg Mo/kg bw/day were expected to cause the various degrees of toxicity required by OECD test guideline 414 (see paragraph 47 above).

60. However, the Fungwe (1990) study was a long-term study in which dosing started six weeks before mating and pregnancy. An OECD TG 414 study, by contrast, is a short-term study in which dosing starts after mating (see paragraph 45 above). Given these differences in exposure, it cannot be taken for granted that the effects observed at a certain dose level in the Fungwe (1990) study would appear at the same dose level in an OECD TG 414 study.

61. Consequently, the Fungwe (1990) study did not constitute adequate scientific information for setting the dose levels in the Tyl (2013) study.

62. Moreover, as the Agency points out and the Appellant does not dispute, the Fungwe (1990) study does not provide sufficient information to calculate actual intake. The dose levels may have been considerably higher than estimated. This is recognised in the published report of the Tyl (2013) study, which states:

'*The actual dose levels (mg Mo/kg bw/day) used [in the Fungwe (1990) study] are unclear because the authors reported only drinking water concentrations (0, 5, 10, 50 and 100 mg Mo/L) without data on maternal body weights and drinking water consumption; however, by making assumptions, [it was estimated that] the dose levels in the [Fungwe (1990) study] were approximately 0, 0.9, 1.6, 8.3 and 16.7 mg Mo/kg/day, respectively. These estimates, while tenuous, will be used throughout this article*.'

63. Consequently, the Fungwe (1990) study did not constitute reliable scientific information for setting the dose levels in the Tyl (2013) study.

1.2.3.3. The Hoffman (2011) study

64. According to the Appellant, the Hoffman (2011) study showed that a dose level of 60 mg Mo/kg bw/day produces extensive toxicity. Male rats suffered a 15.1% reduction in bodyweight and, although the reduction in bodyweight was less marked in the females (5.6%), 2 out of 10 females suffered renal toxicity. Based on this study, doses higher than 60 mg Mo/kg bw/day were assumed to cause severe suffering.

65. However, the Hoffman (2011) study was an OECD TG 408 study modified to include elements of an OECD TG 416 study. Dosing took place for 91 or 92 consecutive days. An OECD TG 414 study, by contrast, is a short-term study (see paragraph 45 above). Given these differences in exposure conditions, the findings of the Hoffman (2011) study cannot be considered to constitute a sound basis for assuming that the effects observed at a certain dose level in the Hoffman (2011) study would appear at the same dose level in an OECD TG 414 study.

66. Consequently, the Hoffman (2011) study did not constitute adequate scientific information for setting the highest dose level in the Tyl (2013) study.

67. Moreover, the effects seen in female rats at 60 mg Mo/kg bw/day in the Hoffmann (2011) study were slight (5.6% reduced body weight and slight histopathological effects) and all tissues were normal in the recovery animals at termination. Even after more than 90 days of continuous administration, these effects are so slight that they cannot be considered to demonstrate reliably that a dose level of 60 mg/kg bw/day would induce death or severe suffering in the animals concerned. Consequently, this does not demonstrate that the highest dose in an OECD TG 414 study should be lower than 60 mg/kg bw/day.

68. For the same reason, even if the Hoffman (2011) study showed some effects after two weeks of administration, those effects do not reliably demonstrate that the highest dose in an OECD TG 414 study should be lower than 60 mg/kg bw/day.

69. Consequently, even assuming that the Hoffman (2011) study constituted helpful scientific information for setting the highest dose level in the Tyl (2013) study, the results of that study would in any event not be sufficient to establish that the dose levels used in the Tyl (2013) study complied with OECD test guideline 414 so as to fulfil the information requirements of Column 1 of Section 8.7.2. of Annex IX.

1.2.3.4. The dose-range finding study

70. The Appellant explains that the dose levels used in the dose-range finding study (1, 10 and 20 mg Mo/kg bw/day) were set essentially on the basis of the Fairhall (1945) study, the Fungwe (1990) study, and the Hoffman (2011) study.

71. The Board of Appeal has already found above that the Fairhall (1945) study and the Fungwe (1990) study did not constitute sufficiently adequate and reliable scientific information that could be used in setting the highest dose level in an OECD TG 414 study. The Board of Appeal has also found that the Hoffman (2011) study did not constitute adequate information for that purpose and that, in any event, the results of that study are not sufficient to determine a dose level at which the Substance would induce death or severe suffering.

72. Indeed, the dose-range finding study showed no effects at any of the dose levels used (see paragraph 20 above). It therefore provided no information on the setting of the maximum dose level in an OECD TG 414 study, other than that the maximum dose level should be higher than 20 mg Mo/kg bw/day.

1.2.3.5. The OECD TG 416 (2017) study

73. According to the Appellant, the results of the OECD TG 416 (2017) study confirm that the highest dose level used in the Tyl (2013) study was properly selected to induce some developmental and/or maternal toxicity but not death or severe suffering.

74. However, even assuming that the results of the OECD TG 416 (2017) study could be used to establish that the earlier Tyl (2013) study complied with OECD test guideline 414, those results do not show that the highest dose level used in the Tyl (2013) study was set sufficiently high to induce some developmental and/or maternal toxicity but not death or severe suffering.

75. The OECD TG 416 (2017) study showed some maternal toxicity at a dose level of 40 mg Mo/kg bw/day (for example 9.7% reduction in body weight during gestation in the F1 generation). However, such an effect is too slight to show that the highest dose in an OECD TG 414 study should be 40 mg/kg bw/day.

76. Moreover, in the OECD TG 416 (2017) study, exposure to the Substance started ten weeks before mating and gestation. Therefore, it cannot be assumed that the effects observed at a certain dose level in the OECD TG 416 (2017) study constitute a sound basis for assuming that comparable effects would appear at the same dose level in an OECD TG 414 study.

77. In fact, the highest dose level in the Tyl (2013) study was 40 mg Mo/kg bw/day and did not result in any relevant effects, demonstrating the incomparability of the two studies. Consequently, the OECD TG 416 (2017) study provides insufficient evidence that the highest dose level used in the Tyl (2013) study was adequate to induce some developmental and/or maternal toxicity but not death or severe suffering.

1.2.4. Conclusion on the fifth plea

78. The Agency has the power to conduct its own assessment of whether the information requirement set out in Column 1 of Section 8.7.2. of Annex IX has been met by means of a submitted study (see paragraph 43 above).

79. On the one hand, there may be intrinsic physical/chemical or biological reasons that limit the highest dose level below the limit dose of 1000 mg/kg bw/day. On the other hand, there may be data – such as an appropriate dose range finding study or similarly adequate and reliable scientific information – that demonstrate that a certain dose level under 1000 mg/kg bw/day will induce death or severe suffering in the animals concerned. The highest dose level should then be set below the dose level that is known to induce death or severe suffering, but still as high as possible in order to achieve the aim of inducing some developmental and/or maternal toxicity (see paragraphs 51 and 52 above).

80. In the present case, the Fairhall (1945) study, the Fungwe (1990) study and the Hoffmann (2011) study do not constitute adequate and/or reliable scientific information for setting the dose levels in the Tyl (2013) study (see paragraphs 54 to 69 above).

81. The dose range finding study provided no information on the setting of the maximum dose level in the Tyl (2013) study, other than that the maximum dose level should be higher than 20 mg Mo/kg bw/day (see paragraphs 70 to 72 above).

82. The OECD TG 416 (2017) study does not show that the highest dose level used in the Tyl (2013) study was adequate to induce some developmental and/or maternal toxicity but not death or severe suffering (see paragraphs 73 to 77 above).

83. It follows that the Appellant has not established that there were any data that could justify limiting the highest dose level in the Tyl (2013) study to 40 mg Mo/kg bw/day.

84. Therefore, the Agency did not commit an error of assessment when it found that the Tyl (2013) study did not comply with the information requirement set out in Section 8.7.2. of Annex IX.

85. The fifth plea, alleging an error of assessment, must consequently be rejected.

2. The second and seventh pleas, alleging breaches of OECD rules and of the principle of good administration

Arguments of the Appellant

86. The Tyl (2013) study was relied on under the OECD Cooperative Chemicals Assessment Programme. According to the Appellant, the Agency is bound by the OECD's assessment under OECD Council Decision OECD/LEGAL/0194 of 12 May 1981 concerning the mutual acceptance of data in the assessment of chemicals (the 'MAD Decision'), in conjunction with paragraph 2 of Supplementary Protocol No. 1 to the Convention on the Organisation for Economic Co-operation and Development.

87. The Agency therefore breached OECD rules and the principle of good administration by failing to accept the Tyl (2013) study as a valid OECD TG 414 study.

88. The Appellant argues, moreover, that the Agency breached the principle of good administration in two ways. First, the Agency failed to take into account the fact that the Tyl (2013) study was accepted as a valid OECD TG 414 study by the OECD Cooperative Chemicals Assessment Programme. Second, the Member State Competent Authorities whose Member States have acceded to the MAD Decision breached their obligation, under international law, to accept the Tyl (2013) study under the MAD Decision.

Arguments of the Agency

89. The Agency does not dispute the fact that the OECD relied on the Tyl (2013) study under its Cooperative Chemicals Assessment Programme. However, the Agency argues that this is an OECD process that is unrelated to the MAD Decision.

90. According to the Agency, the MAD Decision is not an act of European Union law that is binding on the Agency. In any event, the MAD Decision does not prevent the Agency from conducting its own assessment as to whether the Tyl (2013) study complied with OECD test guideline 414.

Findings of the Board of Appeal

2.1. Breach of OECD rules

91. Paragraph I of Part I of the MAD Decision provides that '*data generated in the testing of chemicals in an OECD Member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other Member countries for purposes of assessment and other uses relating to the protection of man and the environment*'.

92. Paragraph 2 of Supplementary Protocol No 1 to the Convention on the Organisation for Economic Co-operation and Development states that '*[t]he Commissions of the European Economic Community and of the European Atomic Energy Community as well as the High Authority of the European Coal and Steel Community shall take part in the work of [the OECD]*'.

93. First, the European Union has neither acceded to the Convention on the Organisation for Economic Co-operation and Development, nor adhered to the MAD Decision.

94. Moreover, it is true that, according to case-law, rules of secondary Union law must be interpreted by taking into account relevant instruments of international law if all the Member States, but not the Union, have acceded to these instruments (see, to this effect, judgment of 11 July 2018, *Bosphorus Queen Shipping*, C-15/17, EU:C:2018:557, paragraphs 45 and 46). However, not all the Member States of the European Union have adhered to the MAD Decision.

95. It follows that the MAD Decision is not in itself binding on the Agency.

96. Second, according to the MAD Decision, studies must be accepted for purposes of assessment and other uses relating to the protection of human health and the environment if they have been carried out in accordance with OECD test guidelines.

97. This does not mean that the Agency cannot carry out its own assessment of whether the Tyl (2013) study was performed in accordance with OECD test guideline 414, and whether it satisfies the information requirement set out in Column 1 of Section 8.7.2. of Annex IX.

98. It follows that, even assuming that the Agency would be bound by the MAD Decision, the Agency would in any event have been entitled to conclude that the Tyl (2013) study did not comply with Column 1 of Section 8.7.2. of Annex IX.

99. Consequently, contrary to the Appellant's arguments, the Contested Decision did not breach OECD rules.

100. The second plea must therefore be rejected.

2.2. Breach of the principle of good administration

101. The principle of good administration, which is a general principle of European Union law, is set out in Article 41 of the Charter of Fundamental Rights. It entails, amongst other obligations, a duty for the administration to examine carefully and impartially all the relevant aspects in the individual case (judgment of 21 November 1991, *Technische Universität München*, C-269/90, EU:C:1991:438, paragraph 14).

102. The Appellant claims that the Agency breached the principle of good administration in two ways.

103. First, according to the Appellant, the Agency failed to take into account the fact that the Tyl (2013) study was relied on under the OECD Cooperative Chemicals Assessment Programme.

104. However, the mere fact that the Tyl (2013) study was relied on under the OECD Cooperative Chemicals Assessment Programme does not provide any information concerning whether that study complies with Column 1 of Section 8.7.2. of Annex IX.

105. Consequently, the fact that the Tyl (2013) study was relied on under the OECD Cooperative Chemicals Assessment Programme is not relevant to the Agency's own assessment of the Tyl (2013) study.

106. Second, according to the Appellant, the Member State Competent Authorities whose Member States have adhered to the MAD Decision breached their obligation, under international law, to accept the Tyl (2013) study under the MAD decision.

107. However, the Board of Appeal is not competent to determine whether Member State Competent Authorities breached their obligations under international law.

108. The seventh plea must therefore be rejected.

3. The first, third and fourth pleas, alleging that the Contested Decision is not tailored to real information needs, that it breaches of the principle of proportionality, and that it breaches the animal welfare provisions of the REACH Regulation

Arguments of the Appellant

109. According to the Appellant, the measured levels of human exposure (54 µg Mo/L serum for the most exposed workers, and 2 µg Mo/L serum for the general population) are much lower than the derived no-effect levels ('DNELs') identified on the basis of the Tyl (2013) study (3350 µg Mo/L serum for the most exposed workers, and 2000 µg Mo/L serum for the general population). The dose levels used in the Tyl (2013) study are therefore sufficiently high to conclude that the Substance poses no risk of pre-natal developmental toxicity.

110. Consequently, according to the Appellant, the Substance poses no risk to human health that would justify performing a new OECD TG 414 study with higher dose levels than those used in the Tyl (2013) study.

111. In support of this argument, the Appellant relies on K. Klipsch and L. Levy, *Risk characterisation report: Demonstration that the highest dose in the prenatal developmental toxicity study with sodium molybdate by Tyl (2013) is sufficiently high to demonstrate absence of risk to humans*, 6 June 2017 (the 'Klipsch and Levy (2017) report'). According to the Appellant, this report shows that the highest dose used in the Tyl (2013) study is sufficiently high to demonstrate an absence of risk to humans.

112. In addition, the Appellant argues that the highest dose level used in a new OECD TG 414 study would in any event have to be only about 60 mg Mo/kg bw/day, which would in all likelihood produce results similar to the Tyl (2013) study. This is because the Hoffman (2011) study shows that a dose level of 60 mg Mo/kg bw/day would induce excessive toxicity, whilst the Fairhall (1945) study shows that a dose level of 80 mg Mo/kg bw/day would cause mortality in 25 to 50% of the animals.

113. Consequently, according to the Appellant, the Contested Decision is disproportionate, not tailored to real information needs, and breaches the animal welfare provisions in the REACH Regulation.

Arguments of the Agency

114. The Agency argues that information on the measured levels of human exposure is irrelevant in the context of dose setting under Column 1 of Section 8.7.2. of Annex IX, in conjunction with paragraph 14 of OECD test guideline 414.

115. The Agency also objects to the admissibility of the Klipsch and Levy (2017) report on the ground that it was not available before the adoption of the Contested Decision.

116. The Agency adds that, in the absence of relevant and reliable scientific information that would allow accurate dose-setting, the highest dose level used should potentially be as high as 1000 mg/kg bw/day, unless reliable scientific information demonstrates that severe suffering or death occurs at a lower level.

Findings of the Board of Appeal

117. Although the Appellant raises its first, third and fourth pleas as separate pleas, all the arguments supporting these pleas follow the same line of thinking. The Board of Appeal will therefore examine these pleas and arguments together.

118. At the outset, it must be noted that, in the context of a compliance check concerning Column 1 of Section 8.7.2. of Annex IX, the role of the Agency is to verify whether a submitted study complies with OECD test guideline 414 or test method B.31 in the Test Methods Regulation, as the case may be (see paragraphs 40 to 43 above; see also, to this effect and by analogy, Case A-017-2014, *BASF*, Decision of the Board of Appeal of 7 October 2016, paragraph 76).

119. Once the Agency had correctly found that the Tyl (2013) study does not comply with the information requirement set out in Column 1 of Section 8.7.2. of Annex IX, it had no margin of discretion as to whether or not to find the existence of a data gap in the Appellant's registration dossier (see, to this effect and by analogy, *Polynt*, cited in paragraph 31 above, paragraph 140).

120. The consequence of the Agency's finding of a data-gap is that the Appellant must either perform an OECD TG 414 study pursuant to Column 1 of Section 8.7.2. of Annex IX or, alternatively, adapt this information requirement pursuant to Annex XI of the REACH Regulation.

121. These requirements are not discretionary requests for further information, such as those which the Agency adopts in the context of the substance evaluation procedure under Article 46. They are the direct and automatic consequence of the Agency's finding of a data-gap, flowing from Article 41 in conjunction with Articles 10(a) and 13(1).

122. It follows that the Appellant's arguments (see paragraphs 109 to 113 above), although formally directed against the Contested Decision, actually challenge the proportionality of the REACH Regulation.

123. The Board of Appeal is not competent to decide on the validity of the REACH Regulation (see, to this effect, Case A-001-2012, *Dow Benelux*, Decision of the Board of Appeal of 19 June 2013, paragraphs 56 to 59).

124. However, the Board of Appeal is competent to take a position on the interpretation of the REACH Regulation insofar as the Agency is competent to apply it (see, to this effect, Case A-013-2016, *BASF Personal Care and Nutrition*, Decision of the Board of Appeal of 12 December 2017, paragraphs 47 to 51).

125. The REACH Regulation must be interpreted, as far as possible, so as to comply with the principle of proportionality (see, to this effect, judgment of 13 January 2013, *McDonagh*, C-12/11, EU:C:2013:43, paragraph 44).

126. The Board of Appeal will therefore examine the Appellant's arguments in order to determine whether, in a case such as the present one, it is proportionate to interpret the REACH Regulation as meaning that, if the Agency finds that there is a data gap under Column 1 of Section 8.7.2. of Annex IX, the registrant concerned must submit an OECD TG 414 study or an adaptation under Annex XI.

127. The principle of proportionality requires that a measure should not exceed the limits of what is appropriate and necessary in order to attain the legitimate objectives pursued by the legislation in question. Where 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 9 June 2016, *Pesce and Others*, C-78/16 and C-79/16, EU:C:2016:428, paragraph 48).

128. The Appellant raises, in essence, two lines of argument in this regard.

3.1. An OECD TG 414 study or an adaptation under Annex XI is not necessary

129. The Appellant argues that, in the circumstances of the present case, submitting an OECD TG 414 study or an adaptation under Annex XI is not necessary because the Tyl (2013) study suffices to demonstrate the absence of a risk to human health (see paragraphs 109 to 111 above).

130. It must be noted that the Tyl (2013) study was commissioned for the regulatory purposes of the Environmental Protection Agency – Office of Water of the United States of America (see paragraph 2 above). It may be that, for those purposes, the Tyl (2013) study suffices to demonstrate the absence of a risk to human health.

131. However, under the REACH Regulation, the identification of a 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).

132. The REACH Regulation requires registrants to investigate the intrinsic properties of a substance separately from the exposure to that substance (see, to this effect, Case A-015-2014, *BASF*, Decision of the Board of Appeal of 28 June 2016, paragraph 58).

133. The levels and patterns of exposure to a substance may vary over time, depending for example on the uses of a substance, whilst the intrinsic properties of a substance remain the same.

134. It is therefore necessary, for the purposes of the REACH Regulation, that information on the intrinsic properties of a substance should be generated independently from information on the levels of exposure to that substance, so as to allow regulators, manufacturers and importers to determine the risk posed by a substance at any given moment in time.

135. This, in turn, is essential in order to attain the main objective of the REACH Regulation, which is to achieve a high level of protection of human health and the environment (judgment of 25 September 2015, *PPG and SNF* v *ECHA*, T-268/10 RENV, EU:T:2015:698, paragraph 83).

136. It follows that, contrary to the Appellant's argument, submitting an OECD TG 414 study or an adaptation under Annex XI is necessary even if the Tyl (2013) study suffices to demonstrate the absence of a risk to human health for the uses given to the Substance at the present moment.

3.2. The disadvantages of performing a new OECD TG 414 study are disproportionate to the objective pursued

137. The Appellant argues that the disadvantages of performing a new OECD TG 414 study are disproportionate to the objective pursued. The Appellant claims that, based on the Fairhall (1945) study and the Hoffmann (2011) study, the highest dose level used in a new OECD TG 414 study would in any event have to be only about 60 mg Mo/kg bw/day,

which would in all likelihood produce similar results as the Tyl (2013) study. Performing a new OECD TG 414 study would therefore add to the currently available data only for the range of 40 to 60 mg Mo/kg bw/day (see paragraph 112 above).

138. Contrary to the Appellant's argument, however, the REACH Regulation does not simply require the Appellant to perform a new OECD TG 414 study. The Appellant must submit an OECD TG 414 study or, alternatively, an adaptation under Annex XI.

139. In this regard, the Appellant has not established that there were any data to justify limiting the highest dose level in the Tyl (2013) study to 40 mg Mo/kg bw/day (see paragraph 83 above).

140. However – purely as an example – the Appellant might conduct a new and reliable dose range finding study to screen trends in effects at relevant dose levels in the range, potentially up to the limit value of 1000 mg/kg bw/day. Such a dose range finding study might show that a certain dose level between 40 mg Mo/kg bw/day and 1000 mg/kg bw/day produces death or severe suffering within the meaning of paragraph 14 of OECD test guideline 414. This might, in turn, form the basis of either an acceptable adaptation under Annex XI, or a new OECD TG 414 study with considerably higher dose levels than those used in the Tyl (2013) study. As the highest dose level used in the Tyl (2013) study did not reveal any effects, the minimum dose level used in a new study can be set at a level that is equal to or even higher than that level.

141. On the one hand, in case of a valid adaptation, this effort cannot be considered disproportionate since it is in any event a minimum requirement to justify a deviation from a standard information requirement.

142. On the other hand, in case of a new OECD TG 414 study, if the next dose levels are not limited by death or severe suffering at a level being only insignificantly higher than the new minimum level, then the full range of the study should provide meaningful new information over the entire range, so as to achieve the objective of the information requirements of Column 1 of Section 8.7.2. of Annex IX.

143. At the same time, the objective pursued by these requirements is of considerable importance (see paragraphs 134 and 135 above).

144. Consequently, contrary to the Appellant's argument, the disadvantages caused by requiring the Appellant to submit an OECD TG 414 study or an adaptation under Annex XI are not disproportionate to the objective pursued.

145. It follows from the above that the first, third and fourth pleas must be rejected.

146. There is therefore no need to examine the Agency's objection to the admissibility of the Klipsch and Levy (2017) report.

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

Refund of the appeal fee

148. Pursuant to Article 10(4) of Commission Regulation (EC) No 340/2008 on the fees and charges payable to the European Chemicals Agency pursuant to REACH (OJ L 107, 17.4.2008, p. 6), the appeal fee is refunded if an appeal is decided in favour of the appellant. As the appeal is dismissed, the appeal fee will not be refunded.

Effects of the Contested Decision

149. The Contested Decision required the Appellant to submit information on an OECD TG 414 study or, alternatively, an adaptation under Annex XI by 20 March 2018, which is twelve months and seven days from the date of its notification.

150. Pursuant to Article 91(2), an appeal has suspensive effect.

151. The Appellant must therefore provide the information required by the Contested Decision (see paragraph 8 above) by 17 December 2019.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Dismisses the appeal.**
2. **Decides that the information required by the Contested Decision (see paragraph 8 above) must be submitted by 17 December 2019.**
3. **Decides that the appeal fee is not refunded.**

Mercedes ORTUÑO
Chairman of the Board of Appeal

Alen MOČILNIKAR
Registrar of the Board of Appeal