EUROPEAN CHEMICALS AGENCY
BOARD OF APPEAL

DECISION OF THE BOARD OF APPEAL OF THE EUROPEAN CHEMICALS AGENCY

29 January 2020

(Substance evaluation – Legal basis – Potential risk)

Case number	A-008-2018
Language of the case	English
Appellants	Taminco BVBA, Belgium, and Performance Additives Italy S.p.A., Italy
Representatives	Claudio Mereu and Simon Englebert, Fieldfisher (Belgium) LLP, Belgium
Contested Decision	Decision of 13 February 2018 on the substance evaluation of zinc bis dimethyldithiocarbamate ('Ziram') 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 'REACH Regulation')

THE BOARD OF APPEAL

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

Registrar: Alen Močilnikar

gives the following

Decision

Background to the dispute

1. In 2012, Ziram (EC No 205-288-3, CAS No 137-30-4) was included in the Community rolling action plan ('CoRAP') for substance evaluation in 2012. This was on the basis of an opinion of the Member State Committee (the 'MSC') and due to initial grounds for concern relating to '*suspected Endocrine Disruptor; Risk characterisation ratio close to 1 (human health)*'. The Competent Authority of Denmark was appointed as the evaluating Member State Competent Authority (the 'eMSCA').

2. On 22 February 2013, following the substance evaluation of Ziram, the eMSCA submitted a draft decision (the 'first draft decision') to the Agency. The first draft decision required the Appellants to submit:

   - a developmental neurotoxicity study, in rats using oral exposure (OECD TG 426); and
   - '*information in the Chemical Safety Reports (CSRs), including:*
     a. *Justification that risks to workers are adequately controlled ([Section 6.4. of Annex I to] the REACH Regulation; section 10 of the CSR);*
     b. *Revision of the [Derived no-effect level ('DNEL')], based on dermal absorption and of the exposure estimations accordingly;*
     c. *Full documentation that all [Ziram] is consumed in the described production processes to ensure that consumers and downstream users are not exposed to residual free [Ziram].*'

3. On 4 April 2013, the Agency sent the first draft decision to the Appellants and invited them to provide comments pursuant to Article 50(1) of the REACH Regulation (all references to Articles and Annexes hereinafter concern the REACH Regulation unless stated otherwise).

4. On 5 May 2013, the Appellants provided comments to the Agency on the first draft decision.

5. On 10 July 2013 and 12 March 2015, the Appellants updated their dossiers (the 'dossier updates') with supplementary data on exposure.

6. On 21 June 2017, having assessed the Appellants' comments on the first draft decision and the dossier updates, the eMSCA submitted a second draft decision to the Agency. The second draft decision replaced the first draft decision. According to the second draft decision:

   '*In the updated registration dossier supplementary data on exposure was provided by the Registrant. The provided data was sufficient enough for the [eMSCA] to withdraw the initial requests based on the concerns related to human exposure. Thus the concern on the exposure was clarified and the [risk characterisation ratio ('RCR')] consequently reduced*.

   Furthermore, a study corresponding to the requested study (Developmental Neurotoxicity Study, OECD [TG] 426) had been performed, and the Registrant has now included it in the updated registration dossier.

   Based on the information in the updated dossier the [eMSCA] concludes, that [Ziram] may cause adverse effects on the developing nervous system manifested as increased activity before weaning and in adulthood, but no final conclusions can be drawn based on the available studies. The [eMSCA] has a residual concern that these adverse effects on the developing nervous system could be induced by an endocrine disrupting mode of action (MoA) (thyroid disruption). However, as [Ziram] may react via more than one MoAs, the [eMSCA] considers it to be very uncertain if further testing in order to clarify a potential endocrine MoA would lead to improved risk management.

In the course of the evaluation, from the public literature, the [eMSCA] identified specific additional concerns regarding involvement of [Ziram] in the development of Parkinson's [disease]. Consequently, the [eMSCA] considered that a revised testing strategy was required to clarify the concerns for developmental neurotoxicity and development of Parkinson's [disease].'

7. According to the second draft decision, '*the data available on [Ziram] raise concerns, but do not lead to clear conclusions regarding developmental neurotoxicty and development of Parkinson's [disease]*'.

8. In the second draft decision, the information requirements in the first draft decision (see paragraph 2 above) were removed and the Appellants were requested instead to provide information on:

'*Combined Developmental Neurotoxicity study (OECD TG 426) and Neurotoxicity study in rats (OECD TG 424), oral route of administration via feed, including additional endpoints to investigate effects linked to development of Parkinson's [disease] in the OECD TG 424 part of the study*'.

9. On 17 July 2017, the Agency sent the second draft decision to the Appellants and invited them to provide comments pursuant to Article 50(1).

10. On 22 August 2017, the Appellants provided comments to the Agency on the second draft decision. In particular, the Appellants argued that no relevant effects could be discerned from the existing data to justify the concern for Parkinson's disease. The Appellants however offered to re-examine the brain sections from an existing developmental neurotoxicity study for potential effects of Ziram on dopaminergic neurons, including immunohistochemical staining for possible α-synuclein accumulation.

11. On 7 September 2017, the eMSCA notified an amended version of the second draft decision to the competent authorities of the other Member States ('MSCAs') and the Agency in accordance with Article 52(1). The request for information (set out in paragraph 8 above) and the deadline to provide the information were not amended following an assessment of the Appellants' comments.

12. Some MSCAs submitted proposals for amendment to the amended version of the second draft decision in accordance with Articles 51(5) and 52(2).

13. On 13 October 2017, the Agency notified the Appellants of the proposals for amendment and invited them, pursuant to Articles 51(5) and 52(2), to provide comments on them.

14. The amended version of the second draft decision was further revised by the eMSCA following the proposals for amendment (the 'revised second draft decision').

15. On 9 November 2017, the Appellants submitted comments on the proposals for amendment.

16. The revised second draft decision was discussed at the MSC meeting of 11 to 15 December 2017. The MSC reached unanimous agreement on the revised second draft decision at that meeting. During the decision-making procedure, in response to a proposal for amendment, '*Parkinson's disease*' was changed to '*parkinsonian disorders*'. According to the minutes of the MSC meeting, the members of the MSC discussed '*…how to better reflect the neurotoxic (neurodegenerative effects) concern without linking [Ziram] to [Parkinson's] disease since there are over 100 neurodegenerative diseases. The term 'Parkinson's disease' was considered to be too specific and 'Neurodegenerative effects' was considered to be too general hence reference to '[parkinsonian] disorders' was instead to be considered*'.

17. On 13 February 2018, the Agency adopted the Contested Decision and notified it to the two addresses, who are the Appellants in these proceedings.

18. According to the Contested Decision, '*the data available on Ziram raise two concerns, but do not lead to clear conclusions regarding these two concerns: Developmental neurotoxicity and parkinsonian disorders*'.

19. According to the Contested Decision:

'*The term parkinsonian disorders is used here as defined in the scientific opinion of the [Panel on Plant Protection Products and their Residues (PPPR Panel)] (EFSA 2017): "Parkinson's disease is a chronic progressive neurodegenerative disorder with a higher prevalence in the aged male population… Although the clinical symptoms include slowness of movement, resting tremor, rigidity and disturbances in balance, it is recognized that additional non-motor symptoms can occur as a result of the progression of the disease. Some or all of the motor symptoms can, however, be observed in different disorders and the resulting syndrome is called 'parkinsonism'. When parkinsonism is the prominent part of the disorder, these are referred to as 'parkinsonian disorders' and include Parkinson's disease […]"*'.

20. According to the Contested Decision, '*Ziram is registered under [the] REACH [Regulation] at a tonnage band of 100 - 1 000 tonnes per annum. The registrations cover the manufacture, formulation and industrial use as a vulcanisation agent in rubber and latex production in the [European Union]. Thus, there is potential for exposure to workers and the environment*'.

21. The Contested Decision require the two addressees of the Contested Decision, the two Appellants in this case, to update their registration dossiers by 20 November 2020 with the following information:

'*Combined Developmental Neurotoxicity study (OECD TG 426) and Neurotoxicity study in rats (OECD TG 424), oral route of administration via feed, including additional investigations in the OECD TG 424 part of the study as specified in Appendix 3 [to the Contested Decision].*

The Developmental Neurotoxicity Study in rodents (OECD TG 426) shall be conducted according to the OECD test guideline. The adult animals from this study (F0) shall be kept and tested according to a Neurotoxicity study in rodents (OECD TG 424) with additional investigations as further specified in Appendix 3 of this decision: The number of investigated animals shall be sufficiently high, the dose levels shall be wide-ranged and a range-finding study may be necessary, the dosing period shall be at least 90 days for the OECD TG 424 part of the study in addition to the period for the OECD TG 426 part of the study, a number of specified functional tests at the right time shall be included, and specified histopathological methods and investigations shall be included in addition to the mandatory histopathological investigation presented in the guideline.'

Procedure before the Board of Appeal

22. On 14 May 2018, the Appellants filed this appeal.

23. On 18 July 2018, the Agency filed its Defence.

24. On 7 September 2018, the Appellants filed their observations on the Defence.

25. On 4 October 2018, PETA International Science Consortium Ltd. ('PISC') was granted leave to intervene in support of the Appellants.

26. On 29 October 2018, the Agency filed observations on the Appellants' observations on the Defence.

27. On 30 November 2018, the Chairman of the Board of Appeal at the time – Mercedes Ortuño - designated Christoph Bartos to act in the present case 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, the 'Rules of Procedure').

28. On 18 December 2018, PISC informed the Board of Appeal that it no longer wished to intervene in the case.

29. On 22 and 26 March 2019 respectively, the Appellants and the Agency replied to questions from, and provided documents requested by, the Board of Appeal. The Agency provided the draft substance evaluation report prepared by the eMSCA. The Appellants provided full study reports and study summaries/robust study summaries of the studies relied on during the proceedings.

30. On 5 June 2019, a hearing was held at the Appellants' request. At the hearing, the Parties made oral submissions and responded to questions from the Board of Appeal.

Form of order sought

31. The Appellants request the annulment of the Contested Decision.

32. In the alternative, the Appellants request the annulment of the additional investigation parameters of the OECD TG 424 study (number and sex of animals, dose level setting, dosing period, functional tests and histopathology).

33. The Appellants request the Board of Appeal to order the Agency to pay the costs of the appeal proceedings.

34. The Agency requests the Board of Appeal to dismiss the appeal as unfounded.

Reasons

35. The Appellants raise a number of pleas in law contesting the legality of the Contested Decision:

    1. Breach of Article 46 and the failure to identify a correct legal basis for the information requirement set out in the Contested Decision;

    2. Breach of Article 46 and the failure to meet the required legal standard for requesting information under substance evaluation;

    3. Failure to provide a statement of reasons;

    4. Error of assessment and inappropriateness of the Contested Decision; and

    5. Breach of the principle of proportionality and the principle of animal welfare, as well as Articles 13 and 25.

1. Breach of Article 46 and the failure to identify a correct legal basis

Arguments of the Appellants

36. The Appellants argue that, although the Agency can request additional information under Article 46, it must also identify a specific provision of Annexes VII to X justifying the need for that information. The Appellants argue that the Agency failed to do so in the present case and therefore breached Article 46 and failed to identify a correct legal basis for the Contested Decision.

Arguments of the Agency

37. The Agency argues that Article 46 is the correct legal basis for requesting information under substance evaluation without the need to identify an additional legal basis and without the need to refer to Annexes VII to X.

Findings of the Board of Appeal

38. Pursuant to Article 10(a)(vi) and (vii), a registration dossier must include study summaries or, if required under Annex I, robust study summaries, of the information derived from the application of Annexes VII to XI.

39. The information that must be provided for registration purposes includes the '*standard information*' set out, depending on the tonnage band at which the substance is registered, in Annexes VII to X (the 'testing Annexes'). Annex XI and Column 2 of

Annexes VII to X detail how the information required by the testing Annexes can be adapted for registration purposes.

40. Article 46(1) provides '*[if] the competent authority considers that further information is required, including, if appropriate information not required in Annexes VII to X, it shall prepare a draft decision…*' (emphasis added).

41. It is clear from Article 46(1) that the Agency may request information from registrants that goes beyond the standard information requirements set out in Annexes VII to X (see, for example, Case A-005-2014, *Akzo Nobel Industrial Chemicals and Others*, Decision of the Board of Appeal of 23 September 2015, paragraph 87).

42. Further information needed to clarify a concern can be requested pursuant to substance evaluation regardless of whether the specific information requested is included in the testing Annexes. However, any request for further information must comply with other legal requirements such as proportionality and legal certainty (Case A-015-2015, *Evonik Degussa and Others*, Decision of the Board of Appeal of 30 June 2017, paragraph 87).

43. It is uncontested by the Parties that the information requested in the Contested Decision goes beyond the standard information requirements of the testing Annexes. The Agency could therefore only request this information under substance evaluation. The Agency was not therefore required to identify in the Contested Decision a provision of the testing Annexes as the basis for its request for information.

44. The Appellants' plea that the Agency breached Article 46 and failed to identify a correct legal basis is therefore rejected.

2. Breach of Article 46 and the Agency's failure to meet the required legal standard for requesting information under substance evaluation

45. The Board of Appeal has developed criteria for requesting information under substance evaluation (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).

46. According to those criteria, 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 risk management measures.

47. In their appeal, the Appellants claim that the Agency failed to satisfy any of those criteria.

48. As stated in paragraph 18 above, the Contested Decision identifies two concerns: developmental neurotoxicity and parkinsonian disorders. The Board of Appeal will examine the Appellants' pleas in relation to each of these concerns in turn.

2.1. Concern for parkinsonian disorders

49. The Board of Appeal will first examine the Appellants' plea that the Agency failed to identify a potential risk of parkinsonian disorders being caused by exposure to Ziram. The term 'parkinsonian disorders' will be used in the following sections when referring to the concern or potential risk identified in the Contested Decision. 'Parkinson's disease' will be used where this term is used in the studies examined below.

2.1.1. Potential risk in relation to parkinsonian disorders

Arguments of the Appellants

50. The Appellants argue that the Agency has not demonstrated a '*real risk*' with regard to parkinsonian disorders.

51. The Appellants argue that the Contested Decision '*indicated that the data available on [Ziram] raise [a concern for parkinsonian disorders], but also acknowledged that this data do not lead to clear conclusions regarding [this concern]*'.

52. The Appellants contest the association made by the Agency between exposure to Ziram and the possible development of parkinsonian disorders from two epidemiological studies (Wang *et al.* (2011)[1] and Fitzmaurice *et al.* (2014)[2]).

53. The Appellants argue that in the Wang *et al.* (2011) study there is limited evidence of an association between exposure to Ziram and Parkinson's disease. According to that study, occupational and residential exposure to Ziram alone did not significantly increase the risk for Parkinson's disease. There was a significant increase in cases of Parkinson's disease only when there was co-exposure to Ziram and the pesticide Paraquat. However, since Paraquat '*is an acknowledged positive control substance for evoking Parkinson's disease in rats […], this is not a finding that can be used to associate Ziram exposure with Parkinson's disease cases*'.

54. The Appellants argue that the association between exposure to pesticides, which are known inhibitors of aldehyde dehydrogenase (ALDH), and Parkinson's disease seen in the Fitzmaurice *et al.* (2014) study was statistically significant only when there was combined residential and workplace exposure to Ziram. In addition, the results reported in this study are unreliable.

55. The Appellants argue that the epidemiological studies relied on by the Agency to support the conclusion that exposure to Ziram may cause parkinsonian disorders (Wang *et al.* (2011) and Fitzmaurice *et al.* (2014)) focus on exposure of the general public to Ziram from plant protection use. However, the registration of Ziram under the REACH Regulation is for '*industrial use of materials resulting in inclusion on a matrix in general rubber good industry*'. The Appellants argue that the only relevant exposure scenario from their registrations under the REACH Regulation relates to workers. The general public is not exposed to Ziram as a consequence of this industrial use.

56. The Appellants argue that the mechanistic studies relied on by the Agency in the Contested Decision (Chou *et al.* (2008)[3], Wang *et al.* (2006)[4] and Lulla *et al.* (2016)[5]) '*employ models with little metabolic competence and absent blood-brain barriers*'. These models are therefore not relevant to the *in vivo* situation in mammals. According to the Appellants, '*Ziram is completely metabolised in rats and its metabolites do not distribute to the brain, with less than 0.01 % of administered dose found in the brain*'. The Appellants argue that the mechanistic studies do not therefore demonstrate that parkinsonian disorders may be caused by exposure to Ziram.

Arguments of the Agency

57. The Agency argues that under substance evaluation it is necessary to establish a '*potential risk*' and not an '*actual risk*'.

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[1] Wang *et al.* 2011, *Parkinson's disease risk from ambient exposure to pesticides*. Eur J Epidemiol. (2011) 26: pp. 547 - 555.
[2] Fitzmaurice *et al.*, 2014. *Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease*. Neurology 2014; 82: pp. 419 - 426.
[3] Chou *et al.,* 2008, *Ziram causes dopaminergic cell damage by inhibiting E1 Ligase of the proteasome*. The Journal of Biological Chemistry Vol. 283, No. 50, December 12, 2008, pp. 34696 - 34703.
[4] Wang *et al.,* 2006. *Inhibitory effects of pesticides on proteasome activity: Implication in Parkinson's disease.* Neurobiology of Disease 23 (2006) pp. 198 - 205.
[5] Lulla *et al.* 2016. *Neurotoxicity of the Parkinson's disease –associated pesticide Ziram is synuclein-dependent in zebrafish embryos*. Environ. health perspect 124: pp. 1766 - 1775.

58. The Agency argues that the epidemiological studies it relies on to support the conclusion that exposure to Ziram may cause parkinsonian disorders '*suggest that exposure to some plant protection products, including [Ziram], is associated with increased relative risk for developing Parkinson's disease*'.

59. The Agency argues that although the Wang *et al.* (2011) study shows a statistically weak association between exposure to Ziram and Parkinson's disease, it still contributes to the conclusion that there is a concern for parkinsonian disorders in humans from exposure to Ziram.

60. The Agency argues that an opinion by EFSA[6] (the 'EFSA Opinion') suggests two possible adverse outcome pathways ('AOPs') linking Ziram with parkinsonian disorders. Some key events are common to the two suggested AOPs. In particular, the degeneration of dopaminergic neurons of the nigrostriatal pathway is a key event at the organ level, and impaired proteostasis is the key cellular event leading to this degeneration of neurons.

61. The Agency argues that the Fitzmaurice *et al.* (2014) study suggests that Ziram '*acts through inhibition of ALDH as a first step in a pathway leading to toxic aldehydes, protein aggregation and dopaminergic cell death*'.

62. The Agency argues that the mechanistic studies relied on in the Contested Decision (Chou *et al.* (2008), Wang *et al.* (2006) and Lulla *et al.* (2016)) support the view that Ziram might be capable of interfering decisively with the neuronal system. The Agency argues that, contrary to the Appellants' assertions, there is no evidence to suggest that the brain is not exposed to Ziram following exposure to the substance. The available data on Ziram does not exclude the possibility that sufficient amounts of Ziram pass through the brain and induce adverse effects.

63. The Agency argues that the chemical safety reports relating to Ziram indicate that there is potential exposure of workers and the environment from formulation, manufacture and industrial uses.

Findings of the Board of Appeal

64. As stated in paragraph 46 above, in order to request further information under substance evaluation, the Agency must, amongst other things, be able to demonstrate the grounds for considering that a substance constitutes a potential risk to human health or the environment.

65. With the objective in the REACH Regulation regarding the protection of human health and the environment in mind, proof of a real risk is too high a threshold to meet.

66. 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 judgment of 20 September 2019, *BASF Grenzach* v *ECHA*, T-125/17, EU:T:2019:638, paragraph 272 and 273, and Case A-023-2015, *Akzo Nobel Chemicals and Others*, Decision of the Board of Appeal of 13 December 2017, paragraph 99).

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

[6] *Investigation into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia.* EFSA Journal 2017; 15(3): 4691; (the 'EFSA Opinion').

68. The Appellants' argument that the Agency must demonstrate a '*real risk*' under substance evaluation is therefore rejected. The Board of Appeal will next examine whether the Agency has established a potential risk of parkinsonian disorders from exposure to Ziram.

69. As stated in paragraph 46 above, the identification of a potential risk is based on a combination of exposure and hazard information (see judgment of 20 September 2019, *BASF Grenzach* v *ECHA*, T-125/17, EU:T:2019:638, paragraph 438 and, for example, Case A-005-2014, *Akzo Nobel Industrial Chemicals and Others*, Decision of the Board of Appeal of 23 September 2015, paragraph 61).

70. With regard to potential exposure, Ziram is used as a vulcanisation agent in rubber and latex production. Ziram is registered at the 100 to 1 000 tonnes per year tonnage band (see paragraph 20 above). There is therefore, at least, potential for exposure of workers.

71. Since there is potential for exposure, the Board of Appeal will next examine whether the Agency has demonstrated a potential hazard related to Ziram.

72. To demonstrate the concern that exposure to Ziram may induce parkinsonian disorders the Agency relies on several epidemiological and mechanistic studies. The Contested Decision also discusses the relevance of the EFSA Opinion and a number of *in vivo* neurotoxicity studies.

Epidemiological studies

73. According to the Contested Decision, the epidemiological studies relied on by the Agency (Wang *et al.* (2011) and Fitzmaurice *et al.* (2014)) '*suggest that exposure to some pesticides, including Ziram, is associated with increased relative risk of developing Parkinson's [disease]*'.

74. When examining the available evidence from the two epidemiological studies it must be borne in mind that there can be confounding factors to consider in the assessment of any epidemiological study. The relevance of the results may also be uncertain especially when the target groups may be, as in the present case, exposed to many different chemicals (Case A-006-2014, *International Flavors & Fragrances*, Decision of the Board of Appeal of 27 October 2015, paragraph 97).

75. In the present case, the Contested Decision itself acknowledges the limitations of the Wang *et al.* (2011) and Fitzmaurice *et al.* (2014) studies. For example, the Contested Decision recognises '*the low number of cases included in the studies, the lack of accurate exposure estimates due to the long latency period of parkinsonian disorders and the fact that people often have been exposed to more than one pesticide during this period*'. The lack of clarity on the actual exposure to Ziram in the two studies is shown by the fact that exposure to Ziram was based on whether the study subjects' place of residence or workplace was located within a 500 meters radius of the areas in which the use of pesticides containing Ziram had been reported.

76. The Contested Decision also acknowledges that lifestyle, environmental and genetic risk factors among the exposed population may not be sufficiently accounted for in these epidemiological studies.

77. In addition, the Appellants and the Agency confirmed at the hearing that the Wang *et al.* (2011) study and the Fitzmaurice *et al.* (2014) rely on the same set of epidemiological data but represent that data differently with inconsistent findings. For example, the odds ratios (i.e. the comparison of the odds of developing the disease for those exposed to the substance and those unexposed to the substance) presented in the two studies are different although the study populations are the same. The shortcomings shown in this paragraph and the previous 3 paragraphs raise questions as to the value of the results of these epidemiological studies in demonstrating an association between Ziram exposure and parkinsonian disorders.

78. Furthermore, the Wang *et al.* (2011) study shows a weak association between exposure to Ziram and Parkinson's disease. In particular, a significant increase in the risk of developing Parkinson's disease is observed only where there is co-exposure to Ziram and other pesticides. As reported in the EFSA Opinion, '*the combined exposure to [paraquat, maneb and Ziram] at workplaces increased threefold the risk of [Parkinson's disease], whereas combined exposure to only [Ziram] and paraquat, excluding maneb exposure, was still associated with an 80% increase in risk*'.

79. According to the EFSA Opinion, '*[while] the available epidemiological studies support an association between pesticides and [Parkinson's disease], complimentary experimental research is needed to overcome the limitations inherent to those studies*'. Whilst the epidemiological studies may provide some useful information on the association between exposure to certain pesticides and parkinsonian disorders, it is not possible to make that association specifically with regards to Ziram.

80. In light of the shortcomings in the two epidemiological studies set out above, and in particular the lack of clarity as to exactly which substances the subjects of the study were exposed to and for how long, the epidemiological studies offer only weak evidence of an association between exposure to Ziram and the development of Parkinson's disease.

Mechanistic studies and the EFSA Opinion

81. The Agency argues that the association between exposure to Ziram and the development of parkinsonian disorders '… *is further supported by mechanistic studies lending support and biological plausibility to the epidemiological data*'.

82. According to the Contested Decision, mechanistic studies (Chou *et al.* (2008), Lulla *et al.* (2016) and Wang *et al.* (2006)) show that exposure to Ziram leads to both impaired proteostasis and degeneration of dopaminergic neurons. These are the same AOPs for Parkinson's disease suggested in the EFSA Opinion. The EFSA Opinion suggests that there are two relevant AOPs for Parkinson's disease. According to the Contested Decision, citing the EFSA Opinion, '*some key events are common in the two suggested AOPs, i.e. degeneration of dopaminergic neurons of the nigrostriatal pathway is a key event on organ level, and impaired proteostasis is the cellular key event leading to this degeneration of neurons*'. However, the EFSA Opinion does not conclude that there is a concern for Parkinson's disease related to exposure to Ziram, rather it discusses possible AOPs in relation to Parkinson's disease.

83. In addition, the Agency has not demonstrated in the Contested Decision that Ziram reaches the relevant parts of the brain to be able to cause any of the molecular initiating events (MIEs) identified in the mechanistic studies (for example ALDH inhibition). MIEs are the first steps in the AOPs leading to the adverse, toxic final effect, i.e. Parkinsonian disorder. In particular, the mechanistic studies do not take account of the existence of the blood-brain barrier in humans. In this respect, it should be noted that the test subjects used in the various mechanistic studies, for example zebrafish embryos, do not have blood-brain barriers. Whilst this does not rule out that the human brain might be exposed to Ziram, it is possible that the level of exposure in humans, if any, would be less than can be anticipated based on mechanistic studies using test subjects with no blood-brain barriers.

84. The Contested Decision also acknowledges that there is only limited toxicokinetic data to indicate whether the observations in the three mechanistic studies would be expected to occur *in vivo* under realistic exposure conditions. However, the Contested Decision concludes that '…*it is not unlikely that sufficient amounts of Ziram may pass through the brain and induce adverse effects*'. This likelihood is not, however, substantiated by the Agency.

85. In view of paragraphs 81 to 84 above, the mechanistic studies do not demonstrate a link between exposure to Ziram and parkinsonian disorders.

Neurotoxicity studies

86. In the Contested Decision, the Agency also assesses *in vivo* neurotoxicity studies. In relation to the *in vivo* neurotoxicity studies, the Contested Decision concludes that, '*since no neuropathological investigations specific to assessment of development of parkinsonian disorders were performed in already available* in vivo *studies, these studies cannot be used to negate this concern*'.

87. It is therefore clear that the Agency does not use the *in vivo* neurotoxicity studies discussed in the Contested Decision to demonstrate a concern. The Agency rather claims that the *in vivo* neurotoxicity studies presented by the registrants of Ziram do not rule out the possibility that exposure to Ziram may cause parkinsonian disorders. In this respect, it should be recalled that the burden of proof under the substance evaluation process rests on the Agency to demonstrate that a request for information is necessary (judgment of 20 September 2019, *BASF Grenzach* v *ECHA*, T-125/17, EU:T:2019:638, paragraph 276), and not on a registrant to prove that there is no concern. As the Board of Appeal has concluded that the epidemiological and mechanistic studies, together with the EFSA Opinion, do not demonstrate a sufficient link between exposure to Ziram and parkinsonian disorders, there is no need to examine the Agency's assessment of the *in vivo* neurotoxicity studies discussed in the Contested Decision.

2.1.2. Conclusion on the plea

88. In view of paragraphs 72 to 87 above, the Agency has not presented sufficient evidence that exposure to Ziram may cause parkinsonian disorders to justify the request for further information.

89. The Contested Decision is therefore annulled in so far as it relates to the neurotoxicity study (OECD TG 424). As a result, it is not necessary to examine the Appellants' other pleas related to the neurotoxicity study (OECD TG 424).

2.2. Concern for developmental neurotoxicity

90. The combined study requested in the Contested Decision consists of two studies to be performed, each following the principles of separate OECD test guidelines.

91. The requirement to provide an OECD TG 424 study, which was the first part of the combined study, has already been annulled. Therefore, if the Board of Appeal were to dismiss the Appellants' pleas regarding the second study and uphold the request for a developmental neurotoxicity study (OECD TG 426) alone, it may need to adopt its own decision by amending the Contested Decision and ordering the Appellants to perform the developmental neurotoxity study (OECD TG 426).

92. According to the case-law of the General Court of the European Union, where the examination of the pleas put forward by an appellant in proceedings before the Board of Appeal shows that the Agency decision in question is vitiated by errors, the Board of Appeal is competent, pursuant to Article 93(3), to replace that decision with its own decision or remit the case to the Agency for further action (see judgment of 20 September 2019, *BASF Grenzach* v *ECHA*, T-125/17, EU:T:2019:638, paragraph 117). As demonstrated in Section 2.1.1. of the present decision, the Contested Decision is partially erroneous. In light of the case law discussed above, this would allow the Board of Appeal to replace the Contested Decision.

93. However, before replacing a substance evaluation decision with its own decision, the Board of Appeal must examine whether the available evidence allows it to do so. In addition, when examining whether it can replace an Agency decision, the Board of Appeal must bear in mind the procedure for adopting Agency decisions under the substance evaluation process set out in Articles 50 to 52, and in particular the role of the various actors in that procedure (see judgment of 20 September 2019, *BASF Grenzach* v *ECHA,* T-125/17, EU:T:2019:638, paragraph 118).

94. Therefore, the Board of Appeal has to examine first whether the evidence available to it is sufficient to replace the Contested Decision with its own decision as regards the developmental neurotoxicity study (OECD TG 426).

95. The Appellants' registration dossiers contain the results of a developmental neurotoxicity study ([the '2009 study'][7]). According to the Contested Decision, that study was not performed according to OECD TG 426 as several standard parameters, such as startle response and cognitive function, were not assessed. However, it is not clear whether the deficiencies identified in the Contested Decision is an exhaustive list, whether these deficiencies make the study invalid, or whether these missing parameters contribute to the uncertainty in the interpretation of the changes in the locomotor activity and the developmental (neuro)toxicity of Ziram.

96. The Appellants argue that the [2009 study], taken together with the results of [a two-generation reproductive toxicity study ('the 1996 study')][8], cover all the required parameters of an OECD TG 426 study. As a result, in their opinion, the performance of an additional OECD TG 426 study would not provide any additional information.

97. The Contested Decision proposes different dosing levels for the combined study than those used in the existing [1996 study and 2009 study]. Lower dose levels are proposed with the aim of clarifying whether any effects observed are due to a secondary effect such as habituation.

98. The original dose setting in the [2009 study] was very close to the one suggested by the Agency for the combined study. Instead of the 0, 100, 200 and 400 ppm proposed in the Contested Decision, 0, 72, 207 and 540/340 ppm was used in the [2009 study]. In the [2009 study] there was some maternal toxicity at the 540 ppm level. As a result, the dose was reduced to 340 ppm during the lactation period.

99. However, by applying 400 ppm as the highest dose level, as proposed by the Agency, the Appellants risk performing a study without any maternal toxicity being induced at the highest dose. This can have two consequences. First, without some maternal toxicity at the highest dose, drawing a distinction between secondary effects and primary effects is difficult. Second, it is possible that the study will not be accepted as being valid because it does not fulfil the requirements of OECD TG 426. According to the test guideline, '*the highest dose level should be chosen with the aim to induce some maternal toxicity (e.g. clinical signs, decreased body weight gain (not more than 10%) and/or evidence of dose-limiting toxicity in a target organ)*'. The Agency has not justified whether it took these possible consequences into account when adopting the Contested Decision.

100. In light of paragraphs 95 to 99, the Board of Appeal does not possess sufficient information to be able to decide whether the performance of the OECD TG 426 study requested in the Contested Decision would, when performed without the OECD TG 424 study requested in the Contested Decision, provide information additional to that available from the [2009 study] and [1996 study]. It is therefore unclear whether a request to provide information from a new OECD TG 426 study on its own, as defined in the Contested Decision, would help to clarify whether Ziram is a developmental toxicant. As a consequence, it is also not clear whether conducting a new OECD TG 426 study would result in the unnecessary repetition of testing on vertebrate animals.

101. Furthermore, considering the important role of the various actors in the procedure for adopting a substance evaluation decision, the Board of Appeal considers that it is not appropriate to examine itself the open questions raised in paragraphs 95 to 100 above. It is therefore appropriate to remit the case to competent body of the Agency for further action.

[7] [Confidential].
[8] [Confidential].

102. Consequently, irrespective of whether there is a concern for developmental neurotoxicity, the Board of Appeal would be unable to replace the Contested Decision with its own decision requesting only an OECD TG 426 study. It is therefore unnecessary for the Board of Appeal to examine the Appellants' pleas related to the concern for developmental neurotoxicity and the requirement to perform an OECD TG 426 study.

3. Conclusion on the appeal

103. The Contested Decision is annulled in its entirety and remitted to the Agency for further action.

Refund of the appeal fee

104. 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.

105. As the appeal has been decided in favour of the Appellants, the appeal fee must be refunded.

Claim for the reimbursement of costs

106. In their Notice of Appeal, the Appellants requested the Board of Appeal to order the Agency to pay the costs of these proceedings.

107. The Rules of Procedure do not provide for the reimbursement of costs that are not, as provided in Articles 17 and 21(1)(h) thereof, related to the taking of evidence. Furthermore, Article 17a of the Rules of Procedure provides that the parties shall bear their own costs.

108. Consequently, and as in the present case no costs arose in relation to the taking of evidence, the Appellants' request for reimbursement of costs is rejected.

On those grounds,

THE BOARD OF APPEAL

hereby:

1. **Annuls the Contested Decision.**
2. **Remits the case to the competent body of the Agency for further action.**
3. **Decides that the appeal fee must be refunded.**

Sari HAUKKA
On behalf of the Chairman of the Board of Appeal

Alen MOČILNIKAR
Registrar of the Board of Appeal