Reports of Cases

JUDGMENT OF THE GENERAL COURT (Eighth Chamber)

16 December 2020 *

(REACH – Establishment of a list of substances identified with a view to their eventual inclusion in Annex XIV to Regulation (EC) No 1907/2006 – Supplement to the entry relating to the substance bisphenol A on that list – Articles 57 and 59 of Regulation No 1907/2006 – Manifest error of assessment – Weight of evidence approach – Exploratory studies – Intermediate uses – Proportionality)

In Case T-207/18,

PlasticsEurope, established in Brussels (Belgium), represented by R. Cana, É. Mullier and F. Mattioli, lawyers,

applicant,

v

European Chemicals Agency (ECHA), represented by M. Heikkilä, W. Broere and C. Buchanan, acting as Agents,

defendant,

supported by

Federal Republic of Germany, represented by J. Möller, D. Klebs and S. Heimerl, acting as Agents,

by

French Republic, represented by A.-L. Desjonquères, J. Traband, E. Leclerc and W. Zemamta, acting as Agents,

and by

ClientEarth, established in London (United Kingdom), represented by P. Kirch, lawyer,

interveners,

APPLICATION pursuant to Article 263 TFEU seeking the annulment of ECHA Decision ED/01/2018 of 3 January 2018, by which the existing entry relating to bisphenol A on the list of identified substances with a view to their eventual inclusion in Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and

* Language of the case: English.

Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ 2006 L 396, p. 1, corrigendum OJ 2007 L 136, p. 3), in accordance with Article 59 of that regulation, was supplemented to the effect that bisphenol A is also identified as a substance with endocrine disrupting properties that may have serious effects on the environment which give rise to an equivalent level of concern to those of other substances listed in Article 57(a) to (e) of that regulation, within the meaning of Article 57(f) thereof,

THE GENERAL COURT (Eighth Chamber),

composed of J. Svenningsen, President, T. Pynnä and J. Laitenberger (Rapporteur), Judges,

Registrar: E. Coulon,

gives the following

Judgment [1]

I. Background to the dispute

1 Bisphenol A (2,2-bis(4-hydroxyphenyl)propane or 4,4'-isopropylidenediphenol, EC 201-245-8, CAS 0000080-05-7) is a substance which is mainly used as a monomer for the manufacture of polymers such as polycarbonate and epoxy resins. It is thus used as an intermediate. In addition, bisphenol A can be used for non-intermediate purposes. This is the case, for example, where it is used in the manufacture of thermal paper.

2 On 12 January 2017, the European Chemicals Agency (ECHA) published on its website its decision ED/01/2017 of 4 January 2017 on the inclusion of bisphenol A in the list of substances identified with a view to their eventual inclusion in Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ 2006 L 396, p. 1, corrigendum OJ 2007 L 136, p. 3), as amended, as referred to in Article 59(1) of that regulation ('the Candidate List'), on the ground that that substance had been identified as toxic for reproduction within the meaning of Article 57(c) thereof.

3 On 21 March 2017, the applicant, PlasticsEurope, brought an action for annulment against ECHA Decision ED/01/2017 of 4 January 2017 concerning the inclusion of bisphenol A in the Candidate List. The applicant is an international professional association, established in Belgium and governed by Belgian law, which represents and defends the interests of over 100 member undertakings, made up of manufacturers and importers of plastic products. It has legal personality and capacity. Five of the applicant's member undertakings are active in placing bisphenol A on the market in the European Union and form part of the applicant's 'Polycarbonate/Bisphenol A' group. The members of that group market bisphenol A for both intermediate and non-intermediate uses. The Court dismissed that action by judgment of 11 July 2019, *PlasticsEurope* v *ECHA* (T-185/17, not published, EU:T:2019:492).

4 On 6 July 2017, ECHA adopted Decision ED/30/2017, whereby the existing entry relating to the substance bisphenol A on the Candidate List was supplemented to the effect that that substance was also identified as a substance with endocrine disrupting properties that may have serious effects on

1 Only the paragraphs of the present judgment which the Court considers it appropriate to publish are reproduced here.

human health which give rise to an equivalent level of concern to those of other substances listed in Article 57(a) to (e) of that regulation, within the meaning of Article 57(f) thereof. That decision was published on 7 July 2017. The Court dismissed the action brought by the applicant against that decision by judgment of 20 September 2019, *PlasticsEurope* v *ECHA* (T-636/17, under appeal, EU:T:2019:639).

5 On 29 August 2017, the Umweltbundesamt (Federal Environment Agency, Germany; 'the competent German authority') submitted, pursuant to pursuant to Article 59(3) of Regulation No 1907/2006, a dossier in accordance with Annex XV thereto ('the dossier prepared in accordance with Annex XV') in which it proposed that bisphenol A also be identified as an endocrine disruptor for which there is scientific evidence of probable serious effects to the environment, within the meaning of Article 57(f) of Regulation No 1907/2006.

6 On 5 September 2017, ECHA published the dossier prepared in accordance with Annex XV.

7 On the same day, in accordance with Article 59(4) of Regulation No 1907/2006, ECHA invited all interested parties to submit their comments on that dossier.

8 On 20 October 2017, the applicant submitted comments, on behalf of its members, on the dossier prepared in accordance with Annex XV.

9 The competent German authority subsequently produced a document dated 14 December 2017 and containing its responses to all the comments received by ECHA in the course of the public consultation.

10 Since comments had been received concerning the identification of bisphenol A, ECHA forwarded the dossier to the Member State Committee ('the MSC'), in accordance with Article 59(7) of Regulation No 1907/2006. In line with its working procedures on the identification of substances of very high concern, the MSC received the dossier prepared in accordance with Annex XV, a draft agreement of the MSC, and a working document ('the Support Document') containing the assessment of the intrinsic properties of bisphenol A in support of its identification under Article 57(f) of Regulation No 1907/2006.

11 At its 57th meeting, which took place from 11 to 15 December 2017, the MSC unanimously decided to identify bisphenol A as a substance of very high concern that meets the criteria set out in Article 57(f) of Regulation No 1907/2006. Four Member States abstained from the vote. Amongst those States, the United Kingdom of Great Britain and Northern Ireland set out the reasons for its abstention in a statement annexed to the minutes of the meeting. The grounds for the identification of bisphenol A were set out in an amended version of the Support Document, as adopted on 14 December 2017. The final version of the Support Document concluded, on the basis of an analysis of multiple studies, that bisphenol A meets the definition of endocrine disruptor as established by the Word Health Organisation (WHO) and interpreted by the European Commission's Endocrine Disrupters Expert Advisory Group. More specifically, the Support Document found that the *in vitro* and *in vivo* data analysed indicate that bisphenol A acts as an oestrogen agonist in certain species of fish, and as a thyroid antagonist in certain species of amphibian. Moreover, that document takes the view, in further support of its conclusions, that the analyses of various taxa of invertebrates show that it is possible that the serious effects of bisphenol A are the result of the endocrine mode of action. Lastly, it is stated in the Support Document that the effects of bisphenol A on fish and amphibians are regarded as giving rise to a level of concern equivalent to that of substances listed in Article 57(a) to (e) of that regulation, namely substances that are carcinogenic, mutagenic or toxic to reproduction ('CMR substances'), or persistent, bioaccumulative and toxic substances ('PBT substances') and very persistent and very bioaccumulative substances ('vPvB substances'). To those ends, the Support

Document relies, inter alia, on the severity and irreversible nature of the effects on organisms and populations, as well as the difficulties encountered in determining a safe level of exposure to bisphenol A.

12 On 3 January 2018, following the unanimous agreement of the MSC and in accordance with Article 59(8) of Regulation No 1907/2006, ECHA adopted Decision ED/01/2018 ('the contested decision'), whereby the existing entry relating to the substance bisphenol A on the Candidate List was supplemented to the effect that that substance was also identified, for reasons set out in the Support Document, as a substance with endocrine disrupting properties that may have serious effects on the environment which give rise to an equivalent level of concern to those of other substances listed in other substances listed in Article 57(a) to (e) of that regulation, within the meaning of Article 57(f) thereof.

13 On 15 January 2018, the Candidate List published on ECHA's website was updated in accordance with the contested decision.

II. Procedure and forms of order sought

14 By application lodged at the Registry of the General Court on 23 March 2018, the applicant brought the present action.

15 On 18 June 2018, the applicant requested that the Court join Cases T-185/17, T-636/17 and T-207/18 for the purposes of the oral phase of the procedure and, where appropriate, the decision which closes the proceedings, pursuant to Article 68 of the Rules of Procedure of the General Court.

16 The defence was lodged at the Court Registry on 19 June 2018.

17 By separate documents, lodged at the Court Registry on 9 July 2018, the applicant made a request, having regard to the fact that the French Republic and ClientEarth were interveners in Cases T-185/16 and T-636/16 and in the event that the present case were joined with those two cases, for confidential treatment of certain information communicated in the application and the defence lodged in the present proceedings vis-à-vis the French Republic and ClientEarth.

18 By documents lodged at the Court Registry on 18 July, 19 July and 24 July 2018, respectively, the Federal Republic of Germany, ClientEarth and the French Republic applied for leave to intervene in support of the form of order sought by ECHA.

19 On 26 July 2018, the President of the Fifth Chamber of the General Court decided not to join the present case to Cases T-185/17 and T-636/17.

20 By separate documents, lodged at the Court Registry on 27 August 2018, the applicant submitted three requests for confidential treatment of certain information communicated in the application vis-à-vis the Federal Republic of Germany, the French Republic and ClientEarth, respectively.

21 A reply was lodged on 10 September 2018.

22 By order of 2 October 2018, the President of the Fifth Chamber of the Court granted ClientEarth leave to intervene. By two orders of 9 October 2018, the President of the Fifth Chamber of the Court granted the Federal Republic of Germany and the French Republic leave to intervene.

23 Since the Federal Republic of Germany and the French Republic did not oppose, within the prescribed time limit, the confidential treatment of certain information communicated in the application, as requested by the applicant on 27 August 2018, the applicant's requests were granted vis-à-vis those intervening parties.

24 By written submission lodged at the Court Registry on 25 October 2018, ClientEarth opposed the applicant's request for confidential treatment of 27 August 2018.

25 On 30 October 2018, the rejoinder was lodged at the Court Registry.

26 On 23 November and 26 November 2018, the French Republic and the Federal Republic of Germany lodged their respective statements in intervention, drafted on the basis of a non-confidential version of the application, at the Court Registry.

27 After hearing the applicant in relation to the objections raised by ClientEarth concerning the request for confidential treatment, by order of 13 December 2018 the President of the Fifth Chamber of the Court rejected that request vis-à-vis ClientEarth.

28 On 28 January 2019, ClientEarth lodged its statement in intervention.

29 By documents lodged at the Court Registry on 14 March and 15 March 2019, ECHA and the applicant submitted their respective observations on the statements in intervention.

30 By document lodged at the Court Registry on 2 May 2019, the applicant requested a hearing, on the basis of Article 106(1) of the Rules of Procedure.

31 As the composition of the Chambers had been altered, the present case was assigned to a new Judge-Rapporteur sitting in the Eighth Chamber.

32 On 10 March 2020, the Court, by way of a measure of organisation of procedure, put questions to the main parties for written answer, to which they duly replied within the time limit prescribed.

33 On 7 April 2020, the Court, by way of a measure of organisation of procedure, asked the main parties whether, in the light of the health crisis associated with COVID-19, they nevertheless intended to be heard at a court hearing.

34 By way of a measure of organisation of procedure of 12 May 2020, the Court invited each party to submit its observations on the replies of the main parties to the Court's written questions of 10 March 2020. The parties complied with that request within the time limit prescribed.

35 By documents lodged at the Court Registry on 28 May and 1 June 2020 respectively, the applicant and ECHA requested that, for reasons associated with the health crisis due to COVID-19, the hearing – then listed for 22 June 2020 – be postponed to a later date. On 5 June 2020, the President of the Eighth Chamber decided not to grant those requests. On the same day, the Court asked ECHA to indicate whether it was able to take part in the hearing via video-conference. By documents lodged at the Court Registry on 10 June 2020, ECHA confirmed its participation in the hearing via video-conference.

36 By document lodged at the Court Registry on 9 June 2020, the applicant stated that, like ECHA, it wished to participate in the hearing via video-conference. However, the applicant stated that it would withdraw its request for a hearing in the event that its participation in a hearing held via video-conference were not technically possible at the same time as ECHA.

37 On 12 June 2020, in the light of the fact that it was technically impossible for the Court to hear both of the main parties at the same time in a hearing via video-conference and of the withdrawal, in that case, of the applicant's request for a hearing, the President of the Eighth Chamber ultimately decided to cancel the hearing. Having due regard to the answers provided by the parties to its questions and to their respective observations on those answers, the Court, considering that it had sufficient information available to it from the documents in the file, therefore decided to close the oral phase of the procedure.

38 The applicant claims that the Court should:

– declare the application admissible and well founded;

– annul the contested decision;

– order ECHA to pay the costs;

– take such other or further measure as justice may require.

39 ECHA contends that the Court should:

– dismiss the action in its entirety;

– order the applicant to pay the costs of both parties.

40 The Federal Republic of Germany and the French Republic contend that the Court should dismiss the action.

41 ClientEarth contends that the Court should:

– dismiss the action in its entirety;

– order the applicant to pay the costs of the proceeding.

III. Law

42 In support of its action, the applicant relies on four pleas in law. The first plea alleges the existence of several manifest errors of assessment in the identification of bisphenol A as a substance of very high concern under Article 57(f) of Regulation No 1907/2006, namely as a substance with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which give rise to an equivalent level of concern to those of other substances listed in of other substances listed in Article 57(a) to (e) of that regulation. By the second plea, the applicant alleges infringement of Article 59 of Regulation No 1907/2006, read in conjunction with Article 57(f) thereof. The third plea alleges infringement of Article 2(8)(b) of the regulation. By its fourth plea, the applicant alleges infringement of the principle of proportionality.

A. The first plea: manifest errors of assessment in the application of Article 57(f) of Regulation No 1907/2006

43 By its first plea, the applicant claims that, by adopting the contested decision, ECHA committed several errors of assessment in the light of the requirement set out in Article 57(f) of Regulation No 1907/2006, under which the identification of a substance as an endocrine disruptor of very high

concern must be based on 'scientific evidence of probable serious effects to … the environment' which give rise to 'an equivalent level of concern' to the effects covered by Article 57(a) to (e) of that regulation.

44 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contends that that plea should be rejected.

45 The arguments relied on in support of the first plea may be grouped into two separate parts. First, the applicant argues that ECHA committed a manifest error in the assessment of the evidence that it regarded as relevant for the purposes of the identification of bisphenol A, as it failed to take certain data into account and relied on exploratory studies. Second, the applicant relies on a manifest error of assessment in the identification of bisphenol A under Article 57(f) of Regulation No 1907/2006, by claiming in essence that the data evaluated by ECHA cannot substantiate the conclusions that it reached on the basis thereof.

1. The first part of the first plea: manifest error in the assessment of the relevant evidence in the examination referred to in Article 57(f) of Regulation No 1907/2006

46 By the first part of the first plea, which consists in two complaints, the applicant claims in essence that ECHA committed a manifest error in the assessment of the relevant evidence for the identification of bisphenol A as an endocrine disruptor that may have serious effects on the environment under Article 57(f) of Regulation No 1907/2006.

(a) The first complaint in the first part of the first plea: manifest error of assessment owing ECHA's alleged failure to take certain studies into account

47 In the first complaint in the first part of the first plea, the applicant claims that ECHA committed a manifest error of assessment by failing to examine, carefully and impartially, all the relevant facts of the individual case. In that connection, the applicant relies, inter alia, on the duty of care which requires that ECHA take all the relevant facts into account. It is argued that ECHA failed to take into account (i) the research programme known as 'Clarity-BPA' (Consortium Linking Academic and Regulatory Insights on Bisphenol A Toxicity; 'the Clarity-BPA programme'), which was still ongoing during the period in which bisphenol A was evaluated with a view to adopting the contested decision, and (ii) the results of a certain number of studies which the applicant regards as relevant. That, in the applicant's submission, had an impact on the validity of applying the weight of evidence approach to the evidence in the individual case and, therefore, calls the identification of bisphenol A as a substance of very high concern into question.

(1) The alleged failure to take the Clarity-BPA programme into account

48 The applicant claims, first of all, that ECHA failed to take the results of the Clarity-BPA programme into account. The draft report of the Clarity-BPA programme was published on 23 February 2018, that is only a few weeks after the identification of bisphenol A by ECHA.

49 The Clarity-BPA programme was launched in 2012 under the auspices of the National Toxicology Programme (United States; 'the NTP'), the National Center for Toxicological Research (United States; 'the NCTR'), the United States Food and Drug Administration ('the FDA') and the National Institute of Environmental Health Sciences (United States; 'the NIEHS'). That programme was launched in order to examine the divergent findings reached, up until that point, by a series of toxicological studies concerning bisphenol A. It was designed to examine, inter alia, the potential effects on human health of exposure to low levels of endocrine active agents, and take into account a wide range of doses and new relevant 'parameters' ('endpoints') which had never been used before.

50 The applicant takes the view that any of the findings of the Clarity-BPA programme affected the evidence available to ECHA and, consequently, should have been included in the application of the weight of evidence approach on which the identification of bisphenol A as an endocrine disrupting substance affecting the environment was based. The applicant claims that ECHA ought therefore to have awaited the publication of those results. Furthermore, the applicant takes the view that the fact that the Clarity-BPA programmed focused on the effects on human health rather than on the environment is not of crucial importance. The Clarity-BPA programme is also relevant for environmental purposes. Since any alleged effects on human health are assessed on the basis of animal data, data on human health and data on the environment cannot be completely and drastically separated from one another.

51 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

52 It should be observed that, as the Court has already ruled (judgment of 20 September, *PlasticsEurope* v *ECHA*, T-636/17, under appeal, EU:T:2019:639, paragraph 170), bearing in mind the dynamic and exploratory nature of scientific research generally, there will probably always be an ongoing study or a study about to begin on a substance examined pursuant to one of the points of Article 57 of Regulation No 1907/2006 according to the procedure referred to in Article 59 of that regulation. If ECHA had to await the completion of all the studies conducted on a certain substance, no substance could ever be identified as being of very high concern, which would be contrary to the main objective of that regulation, which is to ensure a high level of protection of human health and the environment, as laid down in Article 1(1) of Regulation No 1907/2006.

53 Moreover, although Regulation No 1907/2006 does not contain express provisions concerning the possibility of re-examining the inclusion of a substance on the Candidate List under Article 59 of Regulation No 1907/2006, it should be recalled that any decision adopted on the basis of that provision can, as a general rule, be re-examined in the light of new information available without any express provision being required (see, to that effect, judgment of 20 September, *PlasticsEurope* v *ECHA*, T-636/17, under appeal, EU:T:2019:639, paragraph 165).

54 In that connection, it should be observed that Article 58(8) of Regulation No 1907/2006 provides that substances included in Annex XIV to that regulation may be removed therefrom where, as a result of new information, they no longer meet the criteria of Article 57 of that regulation. That provision presupposes that ECHA can and, where necessary, must carry out a re-examination on the basis of new, relevant information. Given that the identification of a substance under Articles 57 and 59 of Regulation No 1907/2006 is carried out with a view to the eventual inclusion thereof in Annex XIV to that regulation, the right and, where appropriate, the obligation to carry out a re-examination on the basis of new information applies a fortiori, inter alia also during the period between (i) the identification of a substance under Article 57 of Regulation No 1907/2006 and its inclusion on the Candidate List and (ii) the subsequent inclusion in Annex XIV to that regulation. Consequently, any new information arising from a study that was still ongoing at the time of the identification of a substance as being of very high concern is therefore likely to be taken into account, where appropriate, even after the identification laid down in Articles 57 and 58 of Regulation No 1907/2006, and before the subsequent inclusion of that substance in Annex XIV to that regulation.

55 In the light of the foregoing, it must be found that ECHA committed no error of assessment by omitting to take the Clarity-BPA programme into consideration. ECHA was thus not required to take that programme into account, since it had not yet been completed at the time when the contested decision was adopted.

(2) The studies allegedly disregarded by ECHA

56 The applicant also claims that ECHA wrongly excluded high-quality studies obtained, in part, in accordance with internationally recognised protocols and scored as reliable on the Klimisch scoring scale (as described in an article by Klimisch, H.J., Andreae, M., and Tillmann, U., 'A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data', *Regulatory Toxicology and Pharmacology*, 1997, Elsevier, vol. 25, pp. 1-5) ('the Klimisch scoring system'). It is argued that by excluding those studies in the present case, ECHA committed a manifest error in its assessment of the relevant information. The applicant takes the view that that assessment was therefore arbitrary and inconsistent, thereby justifying the annulment of the contested decision.

57 First, according to the applicant, ECHA disregarded the Bjerregaard et al. (2008) study relating to brown trout, even though that study was sufficiently sound and substantiated and ought to have been given a reliability score of 2 in the Klimisch scoring system. The applicant argues that that study did not demonstrate any serious effects of bisphenol A on sex ratio or gonad development.

58 Second, the applicant claims that the Support Document does not refer to the Picard (2010c) study on the *Lumbriculus variegatus*, which used the test method approved by Test Guideline No 225 of the Organisation for Economic Co-operation and Development (OECD). The applicant takes the view that this study, which indicates a no-effect concentration level that is four orders of magnitude higher than in a study relied upon by ECHA, namely the Ladewig et al. (2006) study, which ought to have been given a score of 1 in the Klimisch scoring system. Furthermore, the applicant claims that ECHA wrongly excluded the Picard (2010a) study on *Leptocheirus plumulosus* and the Picard (2010b) study on *Chironomus riparius*. ECHA failed to state the extent to which these two studies were not relevant to the identification of bisphenol A.

59 Third, the applicant criticises ECHA for disregarding the Lee (2010) study on *Americamysis bahia*. This study – which, it is argued, complies with good laboratory practice – does not refer to the existence of any endocrine mediated effects of bisphenol A.

60 Fourth and last, according to the applicant, ECHA failed to take into account the Rhodes et al. (2008) study on *Pimephales promelas*, as published in Mihaich et al. (2012). This study was specifically designed and conducted with the aim of addressing certain deficiencies in scientific knowledge, highlighted in the European Union Risk Assessment Report on Bisphenol A, drawn up in February 2010 in accordance with Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances (OJ 1993 L 84, p. 1) ('the EU RAR'), as they may appear in the assessment of spermatogenesis included in the Sumpter et al. (2001) study conducted on the same species. ECHA should therefore have taken into account the results of the Rhodes et al. (2008) study, as published in Mihaich et al. (2008), according to which the observed effects of bisphenol A are the consequence of systemic toxicity rather than an endocrine mode of action.

61 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

62 As a preliminary point, it should be observed that ECHA enjoys a broad discretion in the identification of substances of very high concern under Article 57(f) of Regulation No 1907/2006. In that connection, it should be noted that this broad discretion of the authorities of the European Union, which implies limited judicial review of its exercise, applies not only to the nature and scope of the measures to be taken but also, to some extent, to the finding of the basic facts. However, even though such judicial review is of limited scope, it requires that the European Union authorities which have adopted the act in question must be able to show before the European Union judicature that in adopting the act they actually exercised their discretion, which presupposes that they took into consideration all the relevant

factors and circumstances of the situation the act was intended to regulate (see judgment of 30 April 2015, *Polynt and Sitre* v *ECHA*, T-134/13, not published, EU:T:2015:254, paragraph 53 and the case-law cited).

63 In the present case, the identification of the substance at issue as being of very high concern was made using the weight of evidence approach. Under point 1.2 of Annex XI to Regulation No 1907/2006, this approach is characterised by the fact that the hypothesis that a substance has or has not a particular dangerous property can be validly confirmed by evidence from multiple independent sources of information, while the information from each single source alone is regarded insufficient to support that hypothesis or finding. That approach presupposes that the competent authority examines all relevant information before identifying a substance as being of very high concern. Annex XV to Regulation No 1907/2006 thus provides that the dossier which initiates the authorisation procedure is to contain an examination of the relevant information from registration dossiers and, where appropriate, can rely on all other information available. It is therefore clear from Regulation No 1907/2006 that the identification of a substance using the weight of evidence approach must be made on the basis of complete data which allows the competent authority to exercise the discretion which it enjoys under Articles 57 and 59 of Regulation No 1907/2006 whilst taking into account all relevant evidence available at the time when the authority adopts its decision.

64 The approach taken by ECHA – that is, the weight of evidence approach – together with the discretion which it enjoys, including with a view to the finding of the basic facts (see, to that effect, judgment of 11 May 2017, *Deza* v *ECHA*, T-115/15, EU:T:2017:329, paragraph 164), mean, however, that it may exclude studies that it does not deem relevant for plausible reasons connected to the internal consistency of the assessment carried out. In that regard, it should be observed – as is noted, moreover, by ClientEarth – that bisphenol A is one of the most studied substances in the world. Consequently, the obligation incumbent on the institutions of the European Union to take all relevant evidence into consideration cannot mean that all the studies conducted, irrespective of the reliability or relevance thereof, must necessarily and without exception be included in ECHA's assessment. There can be a finding of a manifest error of assessment only if ECHA completely and wrongly disregarded a reliable study, the inclusion of which would have altered the overall assessment of the evidence in such a way that the final decision would have been implausible.

65 It is in the light of those preliminary observations that it is necessary to examine whether ECHA committed a manifest error of assessment on the ground that it failed to take into account the studies on which the applicant relies.

66 As regards, first, the Bjerregaard et al. (2008) study, it should be noted that ECHA did not regard it as particularly relevant, on the ground that the authors of that study had not, in ECHA's view, observed 'major changes in the gonad development for the fish' after exposure of brown trout egg and fry to E2 or bisphenol A, and that the authors stated that 'it is possible that the exposure period in the present study should have covered a larger part of the sex differentiation period of the brown trout if gonad differentiation should have been affected'. It is therefore clear from the study itself that the fact that no major change in gonad development was observed can be explained by the possibility that the study's exposure period covered too short a part of the sex differentiation period for brown trout. That possibility found by the authors of the study themselves was capable of leading ECHA to call into question the relevance of the results thereof. Accordingly, ECHA did not commit a manifest error by not finding that the Bjerregaard et al. (2008) study constituted relevant evidence.

67 As regards the Picard (2010a, 2010b, 2010c) studies, on *Leptocheirus plumosus, Chironomus riparius* and *Lumbriculus variegatus*, respectively, it should be noted that, as is apparent, moreover, from the applicant's contribution to the public consultation, the results of those studies were published in the Staples et al. (2016) publication which is itself amongst the evidence examined in the Support Document in support of the identification of bisphenol A. The Support Document cites the Staples et al. (2016) study on chironomids, in so far as that group of insects is a taxon relevant to the evaluation

of invertebrates. In that study, the impact on emergence is, it is argued, regarded as relevant for the population and possibly endocrine mediated. However, as ECHA explains, the effects observed on the species *Leptocheirus* and *Lumbriculus* were not at the heart of the evaluation of the endocrine disruptor in that study. Consequently, ECHA cannot be criticised for having failed to include the Picard studies in its assessment, especially given that, in any event, it took them into account through the Staples et al. (2016) study, on which it formally relied with a view to adopting the contested decision.

68 In so far as concerns the Lee (2010) study on *Americamysis bahia*, a species of invertebrate, it should be observed that it is apparent from the Support Document and from ECHA's observations on the applicant's answer in that regard to a question put by the Court that ECHA deliberately did not carry out an exhaustive analysis of the effects of bisphenol A on invertebrates and did not decisively base the identification of bisphenol A on evidence relating to invertebrates. ECHA took into account the fact that endocrine disruption in invertebrates was not sufficiently understood at scientific level. Furthermore, the applicant has failed either to explain or demonstrate the extent to which the results of that study – which does not set out any endocrine mediated effects – contradict the identification of bisphenol A as a substance of very high concern on the basis of evidence other than that relating to invertebrates, with the result that those results invalidate the weight of evidence in the assessment carried out. Accordingly, the decision not to rely on that study appears, ultimately, to be justified and within the scope of ECHA's discretion in the identification of relevant evidence. Consequently, that decision is not vitiated by a manifest error in that respect.

69 As regards, lastly, the Rhodes et al. (2008) study, as published in Mihaich et al. (2012), it should be observed that, contrary to the applicant's claim, this study was indeed taken into account by ECHA, as is clear from page 44 of the Support Document. In that document, no reference is made to any contradiction between that study and the Sumpter et al. (2001) study. On the contrary, the Support Document concludes that the Rhodes et al. (2008) study, as published in Mihaich et al. (2012) does indeed chime with the results of the Sumpter et al. (2001) study, which not only discusses effects on spermatogenesis, but also finds that vitellogenin is induced following exposure to bisphenol A. In so far as concerns the weaknesses on which the applicant relies as to the data on spermatogenesis in the Sumpter et al. (2001) study, it should be noted, as ECHA also observes, that, whilst it is true that certain weaknesses were included in the EU RAR, the authors of that report nevertheless regarded those data as unsuitable solely in the specific context of determining a predicted no-effect concentration. Thus, that aspect does not, per se, call into question the relevance of those data to the identification of bisphenol A on account of its intrinsic properties, namely its endocrine mode of action. The applicant's claim that ECHA failed to take into account the Rhodes et al. (2008) study, as published in Mihaich et al. (2012), is therefore unfounded.

70 In the light of the foregoing considerations, the applicant's argument that ECHA committed a manifest error of assessment on the ground that it failed to take into consideration the studies relied upon by the applicant and, accordingly, the first complaint in the first part of the first plea, must be rejected.

(b) The second complaint in the first part of the first plea: the taking into account of allegedly unreliable exploratory studies

71 By the second complaint in the first part of the first plea, the applicant claims that ECHA relied on numerous non-standard or exploratory studies, namely studies that were not conducted in compliance with nationally or internationally validated methods, whereas Regulation No 1907/2006 generally does not permit reliance on studies that follow non-validated methods, inasmuch as those studies cannot be regarded as reliable.

72 The applicant acknowledges that such non-standard or exploratory studies, which often relate to new species or new endpoints, are of a certain scientific interest in that they serve to extend knowledge. It argues that such studies are, however, vitiated by shortcomings, namely poor reproducibility, inter alia. That therefore calls their scientific reliability into question, precluding their being used for regulatory purposes.

73 In support of its argument, the applicant relies on Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council (OJ 2017 L 301, p. 1), which, it is claimed, provides that the identification of a substance as an endocrine disruptor must be based on either 'scientific data generated in accordance with internationally agreed study protocols' or 'other scientific data selected applying a systematic review methodology'.

74 Furthermore, the applicant relies on version 3.1 of the ECHA Guidance on Data-sharing of January 2017 which, it is argued, recommends that market participants providing information relating to a substance with a view to assessing the risks thereof preferably to use scientific studies with a score of 1 or 2 in the Klimisch scoring system. It is argued that by applying a higher standard of scientific reliability to information provided by market participants than to information on which it may rely for the identification of a substance as being of very high concern, ECHA is applying a 'double standard' which is unacceptable, according to the applicant.

75 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

76 It should be borne in mind that, in the present case, ECHA arrived at the identification of bisphenol A as a substance of very high concern under Article 57(f) of Regulation No 1907/2006 by following the weight of evidence approach, as described in paragraph 63 above. That approach requires that the competent authority take account of all relevant evidence for the identification of a substance as being of very high concern.

77 It is therefore clear, inter alia, from point 1.2 of Annex XI to Regulation No 1907/2006 that, in a weight of evidence approach, newly developed test methods which are not yet included in the test methods and therefore do not correspond to those defined in a Commission regulation, or an international test method recognised by the Commission or ECHA, may serve as evidence for those purposes.

78 Moreover, it follows from the third paragraph of point I of Annex XV to Regulation No 1907/2006 – which is applicable in the present case pursuant to Article 59(3) of that regulation, read in conjunction with the second indent of the first paragraph of point I of Annex XV – that, for all dossiers referred to in Article 59 of the regulation, the relevant information from registration dossiers is to be considered and that it is possible to use 'any other available information'.

79 Admittedly, it follows from the first subparagraph of Article 13(3) of Regulation No 1907/2006 that, for the purposes of the registration of substances, generally, where tests on substances are required to generate information on intrinsic properties of substances, those tests are to be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or ECHA as being appropriate.

80 However, it follows from the second subparagraph of Article 13(3) of Regulation No 1907/2006, read in conjunction with point 1.1.2 of Annex XI to that regulation, that the provisions referred to in paragraph 79 above do not constitute an absolute rule that from the outset prohibits ECHA from taking into consideration, for the purposes of the identification of substances of very high concern, studies which have not been conducted in compliance with validated methods.

81 Although the first subparagraph of Article 13(3) of Regulation No 1907/2006 requires that tests on substances be carried out in compliance with internationally validated methods, the second subparagraph of Article 13(3) of that regulation allows information to be submitted on the intrinsic properties of substances 'in accordance with other test methods provided that the conditions set out in Annex XI are met'. In that connection, point 1.1.2 of Annex XI to Regulation No 1907/2006 provides, inter alia, that data on environmental properties from experiments not carried out according to good laboratory practice or the test methods referred to in Article 13(3) of that regulation, are considered to be equivalent to such data generated, if certain conditions laid down in the same point, relating for example to exposure duration or key parameters, are met.

82 Furthermore, point 1.2 of Annex XI to Regulation No 1907/2006 states that 'there may be sufficient weight of evidence' from the use of newly developed test methods, not yet included in the international test methods referred to in Article 13(3) of that regulation 'leading to the conclusion that a substance has or has not a particular dangerous property'. Thus Regulation No 1907/2006 recognises that non-standard or non-validated data can be used to support findings as to the intrinsic properties of a certain substance where ECHA takes the weight of evidence approach in the identification of a substance as being of very high concern. It is inherent to that approach that the non-standard nature and, where applicable, the poor reliability of that data must be taken into consideration when weighting evidence with a view to making a finding as to the intrinsic properties of a substance, without the poor reliability of a certain study absolutely and generally precluding its being taken into account in the identification of a substance under Article 57(f) of Regulation No 1907/2006.

83 In the light of the foregoing considerations, it must be concluded that there is no prohibition in principle on ECHA taking into consideration 'non-standard' or 'exploratory' studies in order to substantiate, in the weight of evidence approach, findings based on standard studies that follow a validated test method for the purposes of the identification of a substance as being of very high concern under Article 57(f) of Regulation No 1907/2006.

84 That finding is in no way called into question by the applicant's argument that ECHA applies a double standard in so far as version 3.1 of its Guidance on Data-sharing of January 2017 recommends that registrants submit studies with a score of 1 or 2 in the Klimisch scoring system, if they believe that they are entitled to financial compensation from another registrant.

85 It should be noted in that connection that version 3.1 of the ECHA Guidance on Data-sharing of January 2017 contains only a mere recommendation, which is not legally binding, the sole aim of which is to identify those studies which are supposed to be the subject of financial compensation on account of their high quality in the context of the rules on data-sharing laid down in Articles 27 and 30 of Regulation No 1907/2006. That recommendation cannot, in itself, constitute a standard which guides ECHA in the selection of studies substantiating the identification of a substance as being of very high concern under Article 57(f) of that regulation. On the contrary, ECHA must satisfy the weight of evidence approach that it has elected to take, which means that it must take into consideration all the relevant evidence whilst weighting it in accordance with its scientific reliability, amongst other criteria.

86 Moreover, the applicant's argument that 'non-standard' or 'exploratory' studies are regularly vitiated by shortcomings that preclude the use thereof for regulatory purposes, must be rejected.

87 First, it is clear that, in the Klimisch scoring system on which ECHA relied in the present case, studies which are not fully compliant with validated methods can nevertheless be regarded as reliable with restrictions.

88 Furthermore, as the Federal Republic of Germany and ClientEarth both rightly point out, there are no validated methods for all questions relating to the endocrine properties of chemical substances. Studies which are compliant with validated methods are not necessarily the most relevant, inasmuch as they do not all explore the most sensitive parameters for the identification of endocrine properties. However, as the French Republic also observes in that connection, exploratory studies are regularly conducted with the specific aim of verifying a particular scientific hypothesis, with the result that they serve, in complementarity with standard studies, to identify such properties. Consequently, an approach which, as a general rule, excludes the use of non-standard or exploratory studies would make it impossible to identify substances which pose a risk to the environment. The precautionary principle, on which the provisions of Regulation No 1907/2006 are based pursuant to Article 1(3) thereof, means that, where there is uncertainty as to the existence or extent of risks to human health, protective measures may be taken without having to wait until the reality and seriousness of those risks become fully apparent (see, to that effect, judgment of 1 October 2019, *Blaise and Others*, C-616/17, EU:C:2019:800, paragraph 43).

89 Given that there is therefore no prohibition in principle on ECHA taking non-standard or exploratory studies into consideration in order to substantiate, in the weight of evidence approach, findings already made on the basis of standard studies and that, in any event, ECHA did not base its decision in the present case exclusively on non-standard or exploratory studies in order to justify the contested decision, as is clear from the Support Document, it must be concluded that the applicant's complaint, whereby ECHA committed a manifest error by not generally excluding non-standard or exploratory studies from the evidence supporting the identification of bisphenol A as being of very high concern under Article 57(f) of Regulation No 1907/2006, is unfounded and, in any event, ineffective.

90 In the light of the foregoing and without prejudice to the individual examination of the arguments put forward by the applicant concerning the reliability of certain studies submitted in the second part of the first plea, the second complaint in the first part of the first plea, and that part as a whole, must be rejected.

2. The second part of the first plea: manifest error of assessment in the identification of bisphenol A as a substance with endocrine disrupting properties for which there is scientific evidence that it may have serious effects on the environment which give rise to an equivalent level of concern to those of substances listed in Article 57(a) to (e) of Regulation No 1907/2006

91 By the second part of the first plea, the applicant claims that ECHA committed several manifest errors of assessment in the identification of bisphenol A as an endocrine disruptor that may have serious effects on the environment giving rise to an equivalent level of concern to those of other substances listed in Article 57(a) to (e) of Regulation No 1907/2006.

92 The second part consists essentially of three complaints. First, the applicant relies on a manifest error of assessment committed by ECHA in the assessment of the evidence for the identification of bisphenol A. Second, it disputes the fact that ECHA established that there was scientific evidence that bisphenol A may have serious effects on account of its endocrine mode of action. Third, it is claimed that ECHA committed a manifest error of assessment in the determination of the level of concern as referred to in Article 57(f) of Regulation No 1907/2006.

(a) The first complaint in the second part of the first plea: manifest error of assessment in the assessment of the evidence for the identification of bisphenol A as an endocrine disruptor with serious effects on the environment

93 By the first complaint in the second part of the first plea, the applicant claims that ECHA committed a manifest error of assessment in the assessment of the evidence on which it relied for the identification of bisphenol A under Article 57(f) of Regulation No 1907/2006, in so far as it took an arbitrary and

inconsistent approach in the assessment of the evidence and relied on studies containing multiple serious flaws which it failed to take into account in assessing the reliability thereof. Pursuant to Article 57(f) of Regulation No 1907/2006, only substances 'such as those having endocrine disrupting properties … for which there is scientific evidence of probable serious effects to … the environment' may be included on the Candidate List.

94 As a preliminary point, it should be observed that ECHA enjoyed discretion in the identification of the intrinsic properties of bisphenol A. In those circumstances, according to settled case-law, in order to establish that that agency has committed a manifest error in assessing complex facts such as to justify the annulment of an act, the evidence adduced by the applicant must be sufficient to make the factual assessments used in the act implausible. Subject to that review of plausibility, it is not the Court's role to substitute its assessment of complex facts for that made by the institution which adopted the act (see judgment of 9 September 2011, *France* v *Commission*, T-257/07, EU:T:2011:444, paragraph 86 and the case-law cited). Furthermore, the limits to the review by the Courts of the European Union do not, however, affect their duty to establish whether the evidence relied on is factually accurate, reliable and consistent, whether that evidence contains all the information which must be taken into account in order to assess a complex situation, and whether it is capable of substantiating the conclusions drawn from it (see judgment of 9 September 2011, *France* v *Commission*, T-257/07, EU:T:2011:444, paragraph 87 and the case-law cited).

95 It is in the light of those considerations that it is necessary to consider, in the present case, whether ECHA's assessment of the intrinsic properties of bisphenol A as an endocrine disruptor under Article 57(f) of Regulation No 1907/2006 is vitiated by a manifest error of assessment.

(1) The assessment of the evidence

96 The applicant claims that ECHA neither applied an existing systematic review method nor drafted a document to set out the principles for the selection of studies which it took into consideration for the purposes of assessing bisphenol A with a view to adopting the contested decision. It therefore took an arbitrary and inconsistent approach not only in selecting, but also in appraising the evidence. It is argued that ECHA relied, inter alia, on studies presenting numerous serious flaws that it failed to take into account when assessing their reliability.

97 Article 13 of and Annex XI to Regulation No 1907/2006 lay down the criteria relating to the identification of information, and ECHA's Guidance on Data-sharing requires, inter alia, that the reliability of a study be established using the Klimisch scoring system. It is argued that ECHA applied that scoring system incorrectly. Inter alia, it scored as very reliable or reliable with restrictions (1 or 2 in the Klimisch scoring system) studies which should, in the applicant's view, have been scored as not sufficiently documented or not valid (3 or 4 in the Klimisch scoring system). Nevertheless, those studies were subsequently relied upon by ECHA to substantiate its final determination.

98 Moreover, the applicant argues that the reliability assessment of several *in vivo* studies, as set out in the Support Document, is in clear contradiction with the reliability assessments carried out in the EU RAR. Those errors in the reliability assessment of the studies led to ECHA committing a manifest error in applying the weight of evidence approach correctly to all of the information gathered. In particular, ECHA failed to provide any justification for the different ways in which it weighed the items of evidence relied upon.

99 The applicant submits that it is also apparent from the bisphenol A hazard assessment protocol, as developed by the European Food Safety Authority (EFSA), that, for the purposes of selecting relevant studies for the assessment of its endocrine disrupting effects in the environment, precise and transparent scientific criteria must be laid down. Moreover, the applicant refers to Annex I to Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008

on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, p. 1), which, it is argued, requires that the quality and consistency of data be ensured appropriately in the context of the weight of evidence approach.

100 In support of its arguments, the applicant relies, by reference made to the judgment of 11 September 2002, *Pfizer Animal Health* v *Council* (T-13/99, EU:T:2002:209), on 'the principles of excellence, transparency and independence'.

101 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

102 It must be observed that, contrary to the applicant's claims, ECHA did apply a systematic review method, which is clear from Section 5.2 of the Support Document. It is stated in that section that the starting point for evaluating bisphenol A is the definition of an endocrine disruptor for the environment laid down by the WHO, as interpreted by the Commission's Endocrine Disrupters Expert Advisory Group. Furthermore, the Support Document indicates that the evaluation is to follow the guidelines for assessing chemical substances on account of their endocrine disrupting properties, drawn up by the OECD in its Guidance Document No 150.

103 Next, the Support Document explains that both *in vitro* and *in vivo* data were taken into consideration in order to establish the endocrine mode of action, the serious effects, the plausible biological link between those effects and the endocrine mode of action, and the environmental relevance. To those ends, the Support Document explains that two different types of effect were assessed separately, namely (i) the indicators of an endocrine mode of action and (ii) the consequences for apical endpoints. Given that, as stated in the Support Document, the indicators of an endocrine mode of action and the apical effects differed depending on the taxon, the assessment was based on studies of fish, amphibians and invertebrates, whilst stating that the data on invertebrates cannot be used to support the findings drawn principally from data on certain species of fish and amphibian. In other words, the data on invertebrates were not of autonomous, decisive significance in the findings made by ECHA for the purposes of adopting the contested decision.

104 It is also clear from the Support Document that the *in vitro* and *in vivo* data were taken into account in accordance with the weight of evidence approach, as laid down in Annex XI to Regulation No 1907/2006 and as described in paragraph 63 above. For those purposes, the studies used by ECHA were all evaluated as to their scientific reliability. The Support Document also gives a reliability score to each study, using the Klimisch scoring system. The Support Document thus sets out the criteria which it applies in order to determine whether a study can be regarded as reliable without restriction (1 in the Klimisch scoring system), reliable with restrictions (2 in the Klimisch scoring system), not reliable (3 in the Klimisch scoring system), or such that a score is not assignable (4 in the Klimisch scoring system).

105 In that connection, it should be noted that the Support Document contains, on page 22 thereof, a brief description of the scoring system applied which is not wholly identical to the Klimisch scoring system as described in the article cited in paragraph 56 above. Thus, as an example, according to that publication, a score of '1 = reliable without restriction' is given to studies conducted or data obtained in accordance with validated or internationally recognised guidelines, preferably in accordance with good laboratory practice, but equally to studies in which all the parameters are closely comparable to a guideline. According to the Support Document, the score of 1 is given to studies the design, conduct and documentation of which are of high quality, but are not necessarily in full compliance with guidelines adopted at international level such as, for instance, those adopted by the OECD. When questioned in the context of a measure of organisation of procedure on those differences in the definition of scoring criteria, ECHA nonetheless confirmed that it had used the Klimisch scoring

system exclusively for the identification of bisphenol A. Consequently, the differences in the brief description set out in the Support Document are purely terminological and do not alter the scoring system applied in the present case, which is the Klimisch scoring system.

106 Bearing in mind the reliability score given to a study, the Support Document distinguishes between key studies identified according to their reliability, and the relevance of that study. It is therefore clear from ECHA's replies to a question put by the Court that reliable studies (scores of 1 or 2 in the Klimisch scoring system) which offer the most information on endocrine mode of action and its effects are classed as key studies, whereas studies which are less reliable and contain less information on endocrine mode of action are used solely to support findings made principally on key studies and therefore contribute to the weight of evidence.

107 Accordingly, it should be found that ECHA applied a review method which systematically guaranteed that the identification of *in vivo* and *in vitro* data on different taxa as relevant evidence was made in full compliance with the principle of scientific excellence. Giving a score using the Klimisch scoring system to each study allowed ECHA in particular to weight the data depending on their scientific reliability. Such a weighting exercise is in fact inherent to the approach taken by ECHA for the identification of bisphenol A as a substance of very high concern under Article 57(f) of Regulation No 1907/2006, which is the weight of evidence approach.

108 As regards the Bisphenol A Hazard Assessment Protocol prepared by EFSA, it should be observed that this protocol, on which the applicant relies, cannot define criteria for assessing the intrinsic properties of bisphenol A, which ECHA is required to observe. That protocol is relevant only to the tasks allocated to EFSA, which are different to those incumbent on ECHA. The EFSA Protocol therefore focuses on assessing the risk associated with a specific use of bisphenol A, namely the risk arising from consumer exposure to a substance, particularly dietary exposure to bisphenol A from materials in contact with foodstuffs, in order to determine the tolerable daily intake of bisphenol A.

109 Furthermore, it must be observed that the fact that the reliability of certain studies was evaluated differently in the EU RAR and the Support Document cannot call into question, generally, the assessment of the intrinsic properties of bisphenol A carried out by ECHA. First, that report does not systematically evaluate the reliability of the studies used. In particular, it does not apply the Klimisch scoring system. Moreover, as the Support Document clearly indicates, the aim of the assessment in question is to assess the endocrine properties of bisphenol A, which distinction sets that assessment apart from others relating to bisphenol A, namely, in particular, the assessment apparent from the EU RAR, the aim of which is to define a predicted no-effect concentration for bisphenol A, and not an assessment of its intrinsic properties as an endocrine disruptor.

110 In that connection, it should also be noted that the Klimisch scoring system is admittedly a methodological tool used as a reference in the present case. However, it is only if ECHA had applied that reliability scoring system in a generally inconsistent manner, therefore affecting the weighting of the evidence, that that approach could be classed as being vitiated by a manifest error of assessment in the identification of bisphenol A as a substance of very high concern. The consistency of the application of the Klimisch scoring system must be assessed in the specific context of the identification of bisphenol A, as carried out by ECHA. The fact that other institutions gave a different reliability score to the same study can be explained, inter alia, by the specific context and the aim of that evaluation and does not necessarily call into question, in itself, the fairness of the overall score given by ECHA to a study.

111 In the light of the foregoing, the applicant's argument concerning an alleged absence of a systematic review method must be rejected.

(2) The in vitro *studies*

112 In the first place, as regards certain *in vitro* data relied upon in support of the finding relating to the *in vivo* data, the applicant takes the view that ECHA acknowledged certain shortcomings such as, inter alia, a missing control with E2-antagonist in the MCF-7 assays, and limited knowledge on how to interpret results from invertebrate *in vitro* data. The applicant claims that ECHA nonetheless failed to discuss the fact that those data are not conclusive in particular to support the findings made on the basis of the *in vivo* data.

113 The applicant argues that ECHA also failed to take into account, as ECHA itself has also accepted, the fact that the steroid-binding protein assay could not provide data on the receptor protein affinity of the compounds tested.

114 Moreover, the applicant claims that the *in vitro* studies which served as a basis for the finding as to the oestrogen receptor and androgen receptor pathway made in the Support Document are based neither on a test guideline validated by the OECD nor on a protocol validated by the Environmental Protection Agency (United States; 'EPA'). The Support Document further sets out only a small number of studies on androgenic activity and on thyroid hormone-like activity. Furthermore, the studies cited in the Support Document concerning transcriptional activation or reporter genes under control of oestrogen receptors, androgen receptors and thyroid receptors draw conclusions concerning bisphenol A, according to the applicant, whereas they contain no data relating to bisphenol A. The applicant claims that, in the document prepared by the competent German authority (see paragraph 9 above), ECHA acknowledged that those studies had been cited in error. However, it did not alter the findings substantiated by those studies.

115 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, rejects those arguments.

116 It should be observed that the Support Document is cautious in the assessment of the data drawn from the *in vitro* studies, the limited individual weight of which is acknowledged by ECHA. As an example, there is a finding on page 29 of the Support Document that it is not excluded that the effects observed in the MCF-7 assays were caused by an endocrine mode of action of bisphenol A. The Support Document concludes, on page 32, that all the *in vitro* data suggest that bisphenol A 'may' have an endocrine mode of action. The *in vitro* data, if considered alone, do not in fact serve to draw final conclusions on the mode of action of bisphenol A. Nonetheless, it is consistent that ECHA should use that data in the weight of evidence approach, inasmuch as those data support effects observed in the *in vivo* studies of fish and amphibians.

117 In that connection, it is clear that the applicant is not suggesting that the *in vitro* data contradict the effects observed *in vivo*. It confines itself to calling into question the relevance of certain *in vitro* data, without drawing any consequences for the weight of all of the evidence weighted. That approach does not preclude the *in vitro* data – despite their potentially less reliable and inconclusive nature per se – from supporting the conclusions drawn from the data that are deemed more reliable and conclusive.

118 As ECHA also notes, the general picture drawn by the available *in vitro* data fits very well with the conclusions drawn from the *in vivo* effects observed. Thus the weak anti-androgenic effects can, to a certain extent, support the occurrence of apical oestrogenic effects like a sex ratio skewed to females. As regards, more specifically, the plasma sex steroid-binding protein test, it is apparent from the Support Document that this test shows the ability of bisphenol A to displace E2 from the plasma sex steroid binding protein.

119 Consequently, the applicant's arguments do not demonstrate a manifest error of assessment in the evaluation of the *in vitro* studies which allegedly vitiated the identification of bisphenol A as an endocrine disruptor that may have serious effects on the environment under Article 57(f) of Regulation No 1907/2006.

(3) The in vivo *studies conducted on invertebrates*

120 In the second place, as regards the *in vivo* studies conducted to observe endocrine effects on invertebrates, the applicant claims that snail studies for freshwater compartment and worm studies with oligochaetes for sediment compartment contain erroneous assessments. It argues that those studies nevertheless played a causal role in the adoption of the contested decision.

(i) The Oehlmann et al. (2006) study on the snail Marisa cornuarietis

121 First, according to the applicant, the studies on the snail *Marisa cornuarietis* conducted by Oehlmann – namely, inter alia, Oehlmann et al. (2006) – are vitiated by significant shortcomings in their design and in the details provided, which weaknesses are also mentioned in the EU RAR and published in the Dietrich et al. (2006) study. The serious effects reported by Oehlmann have never been confirmed by any independent laboratory. In particular, the 'superfeminisation' effects observed by Oehlmann could not be reproduced in the Forbes et al. (2008) study which itself used a test design that was more sound and valid from a statistical perspective and relied on a strain of *Marisa cornuarietis* which is better suited to ecotoxicity assays. The lowest no-effect concentration observed by Forbes et al. (2008) was three to four times higher than in the Oehlmann studies. It is argued furthermore that, during the OECD validation process of what became Test Guideline No 242 concerning *Potamopyrgus antipodarum* reproduction tests, it was apparent that the test system could not be validated in respect of 'superfeminisation' effects. In that connection, the applicant observes that *Marisa cornuarietis* and *Potamopyrgus antipodarum* are key species which belong to the same taxonomic group, namely prosobranch molluscs. Consequently, in the applicant's view, it is 'very likely' that they have identical reproductive characteristics and endocrine systems.

122 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, rejects those arguments.

123 As regards the *in vivo* studies conducted on invertebrates, it should be observed, as a preliminary point, that it is clear from the Support Document itself that, in the absence of scientific consensus on the definition of a plausible biological link between the effects and the endocrine mode of action in those species of invertebrate, and on account of the fragmentary nature thereof, the data drawn from those studies served solely as supplementary evidence in support of conclusions drawn, in the first place, from studies on fish and amphibians.

124 As regards the Oehlmann studies, it is not disputed by ECHA that these contain certain flaws in their experimental design, which are explicitly described in the Support Document and were taken into account for the purposes of giving a reliability score to those studies. That document itself draws the conclusion therefrom that those studies should be treated with caution without disregarding the effects reported in those studies, which the Support Document regards as a possible indicator of the fact that *Marisa cornuarietis* responds extremely sensitively to bisphenol A.

125 However, as observed in paragraph 64 above, the weight of evidence approach does not preclude the identification of a substance also being based on data of low scientific reliability per se, where the latter fact is taken into consideration in weighting the data. In the present case, the Oehlmann studies, like all data drawn from studies on invertebrates, are not key data in the assessment of the endocrine mode of action of bisphenol A, but were used only in support of that assessment. It also

follows that the fact that the effects reported by Oehlmann could not be reproduced in the Forbes et al. (2008) study cannot call into question, in particular, the conclusions drawn from the key studies on endocrine mode of action conducted on fish and amphibians.

126 Moreover, the Support Document examines the reasons which may explain the fact that the effects reported in the Oehlmann studies could not be reproduced. These include the different species used and the masking effect of a high reproduction rate, together with the fact that seasonality was not taken into consideration in the Forbes et al. (2008) study. According to the Support Document, the effects observed in the Oehlmann studies could, moreover, be attributed to metabolites that can be seen in the relevant concentrations in semi-static conditions but not in flow-through conditions such as those used by Forbes. Furthermore, as the Federal Republic of Germany and ClientEarth observe, the Forbes studies were not intended to reproduce the Oehlmann studies.

127 Consequently, the manner in which ECHA dealt with the Oehlmann studies is not vitiated by errors in the light of the requirements of the weight of evidence approach.

(ii) The Duft et al. (2003) and Jobling et al. (2004) studies on the snail Potamopyrgus antipodarum

128 Second, the applicant submits similar observations in so far as concerns the studies on the snail *Potamopyrgus antipodarum* conducted by Duft et al. (2003) and by Jobling et al. (2004). In that connection, the applicant claims that the results relating to the effects of bisphenol A set out in those studies could not be confirmed by other definitive studies, in particular Forbes et al. (2007), Forbes et al. (2008), Warbritton et al. (2007a) and Warbritton et al. (2007b).

129 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, rejects those arguments.

130 It should be noted that, according to the Support Document, ECHA took into account the effects observed by Duft et al. (2003) and by Jobling et al. (2004) on the snail *Potamopyrgus antipodarum* in the weight of evidence approach as being data used solely to support conclusions on the endocrine mode of action in fish and amphibians. Those studies found a stimulation of embryo production at reduced concentrations which ECHA treated as indicative of a mode of action comparable to that of an oestrogenic mode of action. ECHA therefore gave a lower relative value to that study, as it did to all studies on invertebrates, in the overall weighting of the available data. That being so, the purely indicative nature of the effects reported by Jobling et al. (2004) and Duft et al. (2003) cannot be called into question by the fact that they were not confirmed by the studies on which the applicant relies.

131 Lastly, the applicant has failed, in any event, to submit evidence that would invalidate the effects reported by Jobling et al. (2004) and Duft et al. (2003) and be such as to show that the results presented by those authors could not be used as evidence supporting the conclusions on the endocrine mode of action of bisphenol A.

(iii) The Ladewig et al. (2006) study on Lumbriculus variegatus

132 Third, the applicant argues that ECHA wrongly relied on a study on the annelid worm *Lumbriculus variegatus* conducted by Ladewig et al. (2006). The applicant claims that the aim of that study was not to produce reliable data for risk assessment but rather to present a new technical approach. Furthermore, it should also be noted that the high quality Picard (2010c) study indicates a no-effect concentration level that is four orders of magnitude higher than that of the exploratory Ladewig et al. (2006) study.

133 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, rejects those arguments.

134 In that connection, it is clear that the Support Document explicitly finds that the potential underlying mode of action of bisphenol A is not clear from the Ladewig et al. (2006) study. ECHA therefore did indeed take into consideration the limited evidential weight of that study in the identification of the endocrine disrupting properties of bisphenol A in the weight of evidence approach. Given, moreover, that the studies on invertebrates were used solely to support that identification in the weight of evidence approach, the alleged flaws in the assessment of the Ladewig et al. (2006) study – assuming that these are established – cannot in any event constitute a manifest error of assessment vitiating the identification of bisphenol A under Article 57(f) of Regulation No 1907/2006.

135 In the light of the foregoing considerations, the arguments raised in relation to the studies conducted on invertebrates must be rejected.

(4) The in vivo *studies on amphibians*

136 In the third place, the applicant claims that ECHA based its decision on certain studies of species of amphibian constituting sound evidence, whereas the MSC acknowledged the reduced availability of the data and the poor quality thereof. More specifically, the existing *in vitro* data do not correspond to the *in vivo* findings in that regard. The *in vitro* data – which, it is argued, are weak and limited – prove there to be interactions with the thyroid hormone receptor and suggest that bisphenol A is an antagonist of that receptor, whereas the *in vivo* data which find there to be accelerated development in amphibians argues in favour of bisphenol A being a thyroid hormone receptor agonist. Consequently, it is argued, the mechanism resulting in accelerated amphibian development remains unclear.

137 Moreover, according to the applicant, the *in vivo* data on amphibians contains serious shortcomings. Thus, in the Heimeier et al. (2009) study on *Xenopus laevis*, which the Support Document regards as a key study and which has been scored as being reliable with restrictions (2 in the Klimisch scoring system), the control animals were at development stage 54 on the relevant Nieuwkoop and Faber scale at the beginning of the study and reached stage 56 only 21 days later, whereas the relevant test method – namely OECD Test Guideline No 231 on amphibian metamorphosis assays – requires that control animals be at development stage 51 at the beginning of the study and that they reach at least development stage 57 after 21 days. Consequently, the applicant disputes the reliability of the study as a whole which should, in the applicant's view, have been given a reliability score of 3 in the Klimisch scoring system and, for that reason, could not constitute sound evidence in the present case. Furthermore, it argues that ECHA failed to take those comments into account during the public consultation on the dossier prepared in accordance with Annex XV.

138 In its observations on the answer to a written question put by the Court sent in that connection to ECHA, the applicant further notes that the observations set out in the Heimeier et al. (2009) study can also be explained by a flawed study design, namely the disregard of the daily feeding regime. Moreover, the applicant claims that the same observations were made in the negative controls which were not exposed to bisphenol A. Lastly, according to the applicant, the Iwamuro et al. (2003) study on the same species could not support the findings as to the existence of a thyroid mode of action, given that the effects were observed only at a concentration equivalent to acute toxicity, which does not comply with the amphibian metamorphosis assay set out in OECD Test Guideline No 231.

139 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, rejects those arguments.

140 It should be observed, first of all, that the Support Document finds that bisphenol A acts as a thyroid antagonist in amphibians. In that connection, it relies, inter alia, on thyroid mode of action indicators, as laid down by OECD Test Guideline No 231, in the light of which the *in vivo* studies conducted on *Xenopus laevis* were evaluated. Those indicators include delayed development as an indicator of an antagonist thyroid mode of action, provided that no systematic toxicity can be observed.

141 Contrary to the applicant's claim, the *in vivo* studies on which the Support Document relies as key studies, namely Heimeier et al. (2009) and Iwamuro et al. (2003), both set out – as ECHA confirmed in reply to a written question put by the Court – such a delay in development which, according to OECD Test Guideline No 231, suggests that bisphenol A neutralises the effects of the T3 thyroid hormone.

142 In so far as concerns, in particular, the Heimeier et al. (2009) study, the Support Document clarifies the differences between the latter study and OECD Test Guideline No 231. In the light of those differences, the reliability score of 2 in the Klimisch scoring system appears to be consistent. Admittedly, this study diverges from that guideline. Nevertheless, ECHA convincingly – or, at the very least, plausibly – sets out the reasons for which it regarded that study as being very well documented. Furthermore, the classification thereof as a key study does not appear to be vitiated by an error, given that, according to the methodology followed by ECHA in the present case, studies given a reliability score of 2 in the Klimisch scoring system can serve as key studies in so far as the effects reported are of particular relevance.

143 In that connection, it must also be held that the differences with OECD Test Guideline No 231 cannot, per se, call into question the significance of the observation of antagonistic activity on thyroid hormones. That observation, made in the Heimeier et al. (2009) study is confirmed by other *in vivo* studies contained in the Support Document, including the Iwamuro et al. (2003) key study on the same species. Admittedly, it follows from that study itself that it was conducted at relatively high concentrations, which is not necessarily in compliance with the recommendations contained in OECD Test Guideline No 231. However, it is only in its observations on ECHA's answers to questions put by the Court that the applicant claims that the Iwamuro et al. (2003) study was conducted at a toxic concentration. In that regard, according to OECD Test Guideline No 231, it is solely in the absence of toxicity that the delay in development is a strong indicator of anti-thyroid activity. However, it is clear that the applicant has not substantiated that claim with detailed factual evidence. In those circumstances, bearing in mind the fact that ECHA gave that study a reliability score of 2 in the Klimisch scoring system, which takes account of the fact that that study is not fully compliant with a validated method, the taking into account of the Iwamuro et al. (2003) study by ECHA does not constitute a manifest error of assessment. Moreover, the conclusions drawn from the Heimeier et al. (2009) and Iwamuro et al. (2003) studies are substantiated by various other studies on species of amphibian which the Support Document regards as being supporting studies. It is therefore apparent from the Support Document, as well as from ECHA's answer to a written question put by the Court, that the Goto et al. (2006) study reports a spontaneous inhibition of the metamorphosis of *Xenopus (silruna) tropicalis* and *Rana rugosa* caused by exposure to bisphenol A which blocks thyroid hormone – particularly the T3 hormone – receptors. The fact that this study was conducted at a single concentration only, as the applicant observes, was taken into account by the Support Document, inasmuch as it gives that study a reliability score of 2 in the Klimisch scoring system and does not class it as a key study.

144 Furthermore, the thyroid mode of action hypothesis is supported by the *in vitro* assays, taken into account by the Support Document, which showed that bisphenol A disrupted the hypothalamic-pituitary-thyroid axis and reported antagonist activity on the thyroid hormone receptors responsible for the delay in development observed in the *in vivo* studies.

145 In the light of the foregoing, it must be held that the applicant's arguments disputing ECHA's use, in the present case, of studies on amphibians, and particularly the Heimeier et al. (2009) study on *Xenopus laevis*, cannot demonstrate a manifest error vitiating the conclusions that ECHA drew therefrom in relation to the thyroid mode of action of bisphenol A. Consequently, those arguments cannot invalidate the weight of evidence which led ECHA to the identification of bisphenol A under Article 57(f) of Regulation No 1907/2006.

(5) The in vivo *studies on fish*

146 In the fourth place, the applicant claims that certain studies on the oestrogenic effects of bisphenol A in species of fish do not substantiate ECHA's finding on the intrinsic properties of bisphenol A as an endocrine disruptor that may have serious effects on the environment.

(i) The Chen et al. (2015) study on zebrafish (Danio rerio)

147 First, the applicant claims that the Chen et al. (2015) multi-generational study on zebrafish (*Danio rerio*), referred to on pages 41, 42 and 53 of the Support Document as being a 'key study', is not reliable for the purposes of assessing the endocrine properties of bisphenol A, on the ground that it is vitiated by considerable disadvantages and, in particular, poor replication, a lack of control, analytical inconsistencies and insufficient documentation, with the result that ECHA could not rely on that study in the present case. In that connection, the applicant refers to the statement made by the United Kingdom at the 57th meeting of the MSC, according to which there was not enough information to validate the results of that study. It is argued that the latter was not conducted in accordance with validated test methods which require that assays be carried out at multiple levels of exposure.

148 Furthermore, the applicant claims that the Chen et al. (2015) study is the only study relied upon by ECHA which reports effects at low concentrations, whereas the majority of studies on the endocrine mode of action of bisphenol A report effects at acutely toxic concentrations, which prevents the effects of a specific mode of action being determined reliably, as any effect observed could also be the consequence of an acutely toxic concentration rather than an actual mode of action of bisphenol A.

149 Moreover, according to the applicant, there is uncertainty as to the effects reported by the Chen et al. (2015) study concerning the sex ratio in fish, which ECHA recognised as being a key criterion in determining the endocrine disrupting properties of a substance. That effect was established, it is claimed, by means of a visual inspection which (i) was not reliable in respect of zebrafish on account of the fact that they present few distinct secondary sexual characteristics and (ii) was not confirmed by a histological inspection, namely by a precise determination of sex through the study of cells and tissues. In that respect, in order to constitute a statistically robust assessment, as OECD Test Method No 240 suggests, a large and representative sample should have been the subject of such a histological inspection. The Chen et al. (2015) study does not, the applicant argues, contain details as to the exact number of fish inspected.

150 Lastly, the applicant observes that the data relating to bisphenol A in respect of *Oryzias latipes*, namely the species of fish which was the subject of the greatest number of research studies on the potential change in sex ratios, indicate that no change in sex ratios was generally observed. Only two studies, namely the Yokota et al. (2000) and Na et al. (2002) studies, report changes in sex ratios, although the results of those studies are contradictory. By contrast, six other studies, namely the Metcalfe et al. (2001), Kashiwada et al. (2002), Sun et al. (2014), Bhandari et al. (2015), Kang et al. (2002) and Tabata et al. (2001) studies, did not find any change in sex ratios.

151 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

152 In response to the arguments relating to the Chen et al. (2015) study, it should be noted that the flaws relied upon by the applicant and by the United Kingdom in its statement annexed to the minutes of the 57th meeting of the MSC in relation to that study on zebrafish (*Danio rerio*), arising, inter alia, from the fact that it was conducted using a single concentration, are expressly acknowledged on pages 42 and 43 of the Support Document. That document clearly states that the Chen et al. (2015) study does not comply with good laboratory practice. Furthermore, according to page 53 of the Support Document, the reliability score of 2 in the Klimisch scoring system given to that study takes into account the fact that the study was conducted at a single concentration only. That score is therefore in line with ECHA's methodology which applies the Klimisch criteria described in paragraph 104 above. In that connection, it should be borne in mind that certain, even considerable, shortcomings in studies are not in themselves sufficient to exclude them from the outset. Lastly, those shortcomings must be assessed having regard to the ability of those studies nevertheless to substantiate the conclusion that they are called upon to support. In the context of the broad discretion conferred on ECHA, as described in paragraph 62 above, and more specifically in the weight of evidence approach, differences of opinion concerning such questions are not sufficient to exclude a study or findings based thereon. Such a consequence follows only if ECHA has completely and erroneously disregarded evidence which, if included, would have altered the overall assessment of the evidence in such a way that the final decision would have been implausible.

153 In the light of the foregoing, it cannot be established that ECHA's treatment of the Chen et al. (2015) study is vitiated by a manifest error of assessment. The shortcomings of that study were admittedly highlighted but, with supporting explanations, were not regarded as being so serious as to justify the study being considered unreliable and irrelevant having regard to its findings. Since it may therefore be regarded as a reliable study, and taking into account the fact that this study reports multiple effects of bisphenol A, ECHA also did not commit a manifest error of assessment by classing it as a key study in accordance with its own methodology.

154 In that connection, it should be observed more specifically, as ClientEarth does in its statement in intervention, that the fact that the study was conducted at a single concentration does not per se preclude it being taken into account in the identification of bisphenol A, as the identification of a substance as being of very high concern is based on its intrinsic properties.

155 As regards the effects on sex ratios observed in the Chen et al. (2015) study, it should be observed, first, that the applicant does not dispute that the Support Document regards sex ratios as an endpoint that can serve as an indicator of an endocrine mode of action. As stated in the Support Document, such an approach complies with OECD Test Guideline No 150, according to which there are no cases in which sex ratios are altered that are not caused by an endocrine disruptor.

156 It is apparent from the Support Document and the parties' written submissions that the visual observations of sex ratios were in fact subject to verification by double-blind histological examinations. Nevertheless, ECHA was not able to indicate the exact number of fish that were subject to such a histological inspection. Consequently, it cannot be established whether a sufficiently large and representative sample was subject to such a histological verification, as recommended by OECD Test Method No 240. Nonetheless, it should be noted that the Support Document does not suggest that ECHA treated that study as a study in full compliance with validated methods. However, ECHA gave that study a reliability score of 2 in the Klimisch scoring system so as to reflect the methodological deficiencies vitiating it, without calling into question its overall reliability. Similarly, it is apparent from page 42 of the Support Document, in so far as concerns that study, that there were no significant differences between the results of the visual inspection, on the one hand, and those of the histological inspection, on the other. Consequently, it is apparent that, in so far as a histological inspection was carried out, the results thereof did not contradict those of the visual inspection It follows that the fact that the extent of the histological inspection in the Chen et al. (2015) study is not more amply documented is not sufficient to call into question the results reported by that study.

157 As regards the question of the reproducibility of the effects on sex ratios, as reported by Chen et al. (2015), the following observations should be made.

158 In the first place, it is apparent from the Support Document that, admittedly, neither the Segner et al. (2003a) key study nor the Keiter et al. (2012) study, which were also conducted on the *Danio rerio* at concentrations higher than those applied in the Chen et al. (2015) study, observed any effects on sex ratios. It should also be noted that ECHA was not able to provide, in response to a written question put by the Court, the underlying reasons that may explain that absence of effects on sex ratios. Nevertheless, those studies report other indicators confirming the existence – or, at the very least, the probability – of an endocrine mode of action of bisphenol A, namely in particular, vitellogenin induction. As a consequence, the absence of observations of effects on sex ratios does not, in itself, show there to be a sufficient contradiction to allow the findings of the Chen et al. (2015) study to be called into question at scientific level.

159 In the second place, effects on sex ratios were also observed in another species of fish: *Oryzias latipes*, in the Yokota et al. (2000) key study. It is true that not only does that study concern a different species of fish, but it was also conducted at a higher concentration than in the Chen et al. (2015) study. Consequently, it cannot directly corroborate the findings drawn from the Chen et al. (2015) study on that point. Nonetheless, those two studies, taken together, contribute to the weight of evidence in so far as concerns the effects of bisphenol A on sex ratios in fish populations. In the present case, the various elements put forward by ECHA constitute a body of evidence which supports its hypothesis. However, the evidence put forward by the applicant is not such as to render the weight of that body of evidence completely implausible.

160 Lastly, as regards the six studies on *Oryzias latipes* cited by the applicant (see paragraph 150 above), which did not find there to be any effects on sex ratios, it must be observed that that can be explained, as ECHA argues with regard to the Kang et al. (2002) and Tabata et al. (2001) studies, by the fact that the fish observed in those studies had not been exposed during the sensitive stage in their development. Consequently, the absence of effects on sex ratios in those studies does not necessarily contradict the effects reported in the Yokota et al. (2000) or the Chen et al. (2015) studies. In so far as concerns, second, the Metcalfe et al. (2001), Kashiwada et al. (2002), Sun et al. (2014) and Bhandari et al. (2015) studies, it should be observed that, whilst they do not report any effects on sex ratios, they may nevertheless support the findings drawn from the Chen et al. (2015) study on the endocrine mode of action of bisphenol A. Thus the Metcalfe et al. (2001) study reports testis-ova, morphological changes in the testicles in male fish and accelerated ovogenesis in females. The Kashiwada et al. (2012) study reports vitellogenin induction, while the Sun et al. (2014) study reports reduced hatching and a high level of vitellogenin. As regards the Bhandari et al. (2015) study, it is apparent from the Support Document that that study reports cross-generational reproductive abnormalities, having regard to fertilisation and embryo survival rates, caused by exposure to bisphenol A.

161 In the light of the foregoing, it is clear that, in the weight of evidence approach, the doubts expressed with regard to the Chen et al. (2015) study and, in particular, the verification and reproducibility of the effects on sex ratios, even assuming these to be justified, are not such as to demonstrate that ECHA's finding that bisphenol A has an oestrogenic mode of action in fish is vitiated by a manifest error of assessment.

162 In any event, the Chen et al. (2015) study is not confined to reporting effects on sex ratios, which is the crux of the applicant's criticisms. That study also reports other indicators of an oestrogenic mode of action, namely effects on the number and quality of sperm and larval malformation and mortality. The fact that that study was conducted at a low concentration cannot per se call into question the findings made regarding the oestrogenic mode of action. As noted in paragraph 63 above, information taken into account in the weight of evidence approach can, moreover, be deficient in respect of a specific endpoint, without that precluding that the conclusion be drawn from an overview of the available data showing similar effects. In the present case, it is particularly the Segner et al. (2003a)

study – the classification of which as a key study is not, moreover, disputed by the applicant – which, according to the Support Document, reports other indicators of an oestrogenic mode of action in *Danio rerio*, namely vitellogenin induction, testis-ova and reduced fertility. Furthermore, the Chen et al. (2015) study is not alone in demonstrating effects on sex ratios. Such effects are also reported, inter alia, in the Yokota et al. (2002) key study, the evaluation of which by ECHA is not disputed by the applicant. Lastly, other studies on *Danio rerio* and *Oryzias latipes* report other indicators of an endocrine mode of action and support the conclusions drawn from the key studies, such as, inter alia, the Yokota et al. (2000) study on *Oryzias latipes*, but also the Segner et al. (2003a) study.

163 Accordingly, it must be stated, for the sake of completeness, that, even if the Chen et al. (2015) study could not have been taken into account, ECHA would not have committed a manifest error of assessment by basing its decision on the weight of many other studies, which have not been challenged by the applicant, relating to the endocrine mode of action of bisphenol A.

(ii) The Shioda and Wakabayashi (2000) study on Oryzias latipes

164 Second, the Shioda and Wakabayashi (2000) study on *Oryzias latipes* – which, according to the Support Document, reports long-term effects following short-term exposure to bisphenol A, particularly on egg hatching – cannot, in the applicant's view, support the hypothesis of an oestrogenic mode of action, bearing in mind the low reliability thereof which, furthermore, was acknowledged in the Support Document.

165 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

166 As a preliminary point, it is clear that the Support Document gives the Shioda and Wakabayashi (2000) study a reliability score of 2 in the Klimisch scoring system, which suggests that ECHA regarded the study as being reliable with restrictions. At the same time, the Support Document states, on page 40, that the study is 'of low reliability'.

167 When questioned about this apparent contradiction concerning the Shioda and Wakabayashi (2000) study which is, on the one hand, given a score of 2 in the Klimisch scoring system and, on the other hand, classed as a 'low reliability' study, ECHA explains this as a typographical error and claims that the Support Document should be read and understood as meaning relatively 'lower' reliability, which reflects the fact that only a limited number of organisms were tested. The study remains relevant and valid, nonetheless.

168 Whilst it is true that the same wording can also be found in the dossier prepared in accordance with Annex XV initially proposing the identification of bisphenol A, even assuming that the Shioda and Wakabayashi (2000) study on *Oryzias latipes* ought indeed to have been regarded as being of low reliability, the fact that ECHA also relied on that study cannot constitute a manifest error of assessment to the point of vitiating the identification of bisphenol A as a substance of very high concern, as found in the contested decision.

169 It must be observed that ECHA treated the effects reported by the Shioda and Wakabayashi (2000) study as being merely supplementary indications of a mode of action that support conclusions drawn from studies which were given greater weight and which constituted key studies. That is also illustrated by the fact that the brief examination of the Shioda and Wakabayashi (2000) study in the Support Document is introduced by the words 'in addition' and can be found at the end of the section devoted to the analysis of the effects on *Oryzias latipes* (see page 40 of the Support Document). In particular, ECHA did not regard it as being a key study in the data weighting. The weight of evidence approach does not preclude ECHA from also relying on information that is of low reliability, provided that the weighting of the information takes that low reliability into consideration.

170 It should next be observed that, above all, the applicant has failed to explain the extent to which the effects reported in the Shioda and Wakabayashi (2000) study contradict the conclusions that ECHA drew regarding the identification of bisphenol A from other studies showing long-term effects following exposure to bisphenol A such as, in particular, the Bhandari et al. (2015) study conducted on the same species.

171 Consequently, the argument put forward with regard to the Shioda and Wakabayashi (2000) study cannot lead to the conclusion that the identification of bisphenol A is vitiated by a manifest error of assessment.

*(iii) The Lahnsteiner et al. (2005) study on brown trout (*Salmo trutta fario*)*

172 Third, according to the applicant, the Lahnsteiner et al. (2005) study on brown trout, referred to, inter alia, on page 57 of the Support Document, also has serious flaws, such as poor quality of test fish, poor replication, a lack of analytical confirmation or novel endpoints without validation. It is argued that, as a consequence of the foregoing, the EU RAR concluded that this study was inadequate for regulatory purposes. In spite of that finding, that study was relied upon in the Support Document, and given a reliability score of 2 in the Klimisch scoring system. The applicant takes the view that that study should have been given a score of 3 in the Klimisch scoring system, that is to say 'not reliable'.

173 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, rejects that argument.

174 In that connection, ECHA admittedly does not dispute the fact that the Lahnsteiner et al. (2005) study contains data characterised by low reliability. Nevertheless, as already noted in paragraph 64 above, it is inherent to the weight of evidence approach that the database used may contain deficient data relating to a certain endpoint. Thus the low reliability of certain data contained in a study used by ECHA does not, per se, preclude ECHA using such a study in the assessment of a substance. In such cases, however, it is for ECHA to take into consideration the low reliability of that data in the weighting of the various data available.

175 In the present case, it is apparent from the Support Document that ECHA confined itself to relying on the reliable endpoints contained in the Lahnsteiner et al. (2005) study, such as the effects observed on egg production and sperm fertility. However, in particular, the endpoint associated with delayed ovulation, for which only six fish were examined, was not taken into account. Consequently, the score of 2 in the Klimisch scoring system (reliable with restrictions) does not appear to be vitiated by a manifest error of assessment, in so far as ECHA relied solely on certain data that it considered to be reliable.

176 As regards the applicant's argument that ECHA could not rely on the Lahnsteiner et al. (2005) study on the ground that it was not used in the EU RAR, it should be pointed out that the aim of the latter report was to determine a predicted no-effect concentration. However, the evaluation of the Lahnsteiner et al. (2005) study, as carried out by ECHA, is part of a different regulatory context pursuing a different aim, namely that of identifying substances of very high concern under Article 57(f) of Regulation No 1906/2007.

177 In any event, it is clear that, according to the Support Document, the data on brown trout were used solely in support of the findings on endocrine mode of action drawn from *in vivo* studies conducted on other species of fish, namely *Oryzias latipes*, *Danio rerio* and *Pimephales promelas*. It follows that, even assuming that the criticisms put forward by the applicant against the Lahnsteiner et al. (2005) study are well founded, they cannot in any case invalidate the identification of bisphenol A as an endocrine disruptor on the basis of those data primarily taken into account.

178 In the light of the foregoing, the arguments put forward by the applicant in relation to the Lahnsteiner et al. (2005) study on brown trout cannot substantiate the conclusion as to a manifest error of assessment vitiating the identification of bisphenol A as an endocrine disruptor under Article 57(f) of Regulation No 1906/2007.

(iv) The Bowmer and Gimeno (2001) and Mandich et al. (2007) studies on Cyprinus carpio

179 Fourth, the applicant relies on the low reliability of two studies on *Cyprinus carpio*.

180 First, according to the applicant, the Mandich et al. (2007) study on *Cyprinus carpio*, referred to on pages 36 and 48 of the Support Document, was given a score of 1 in the Klimisch scoring system, whereas, in the applicant's view, it is a study that must be regarded as exploratory, given that it does not fully comply with OECD Test Guideline No 240 in so far as concerns certain endpoints on which ECHA nonetheless relied. Furthermore, the applicant argues that that study contains certain shortcomings such as, in particular, insufficient documentation, a lack of detail on histopathology, an absence of data on control fish, poor reproducibility and poor supporting statistics. Bearing in mind those factors, an appropriate assessment of that study would, in the applicant's view, have led to a reliability score of 3 in the Klimisch scoring system (that is to say, 'not reliable').

181 Second, the study conducted by Bowmer and Gimeno (2001), as referred to on pages 36 and 48 of the Support Document, is supported only by a detailed summary. The applicant claims that in spite of the fact that this study has not been published in full, that evidence was been given a score of 2 in the Klimisch scoring system, that is, 'reliable with restrictions', whereas an appropriate scientific assessment would suggest a reliability score of 4, that is to say, 'insufficient documentation'.

182 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

183 In that connection, it should be recalled, as a preliminary point, that the weight of evidence approach does not preclude ECHA from relying on studies containing certain shortcomings affecting the reliability thereof, where ECHA takes these into consideration in the weighting of the data on which it relies. Furthermore, it is clear that the data on *Cyprinus carpio* were used only to support the conclusions drawn from the studies conducted on other species of fish, namely *Danio rerio* and *Oryzias latipes*, in particular. Consequently, none of the studies conducted on *Cyprinus carpio* were used as a key study in the weighting of data for the identification of bisphenol A as an endocrine disruptor.

184 As regards, first of all, the Mandich et al. (2007) study, it should be observed that the Support Document finds that that study complies only in part with OECD Test Guideline No 240. In particular, it contains no indication that the endpoints relating to vitellogenin induction or gonad histopathology were analysed in accordance with that validated test guideline. The Support Document finds that study to be reliable without restriction by giving it a reliability score of 1 in the Klimisch scoring system, without differentiating between the various endpoints. Given that that score is, in principle, reserved for studies conducted in full compliance with internationally validated methods, the score given to that study appears to be incorrect. Nevertheless, as noted in paragraph 182 above, ECHA did not find that that study was a key study for the identification of bisphenol A. It served solely as a supporting study in the context of the weight of evidence approach. That study was therefore not decisive for the identification of bisphenol A as a substance of very high concern, but rather simply supported that identification. It follows that, even supposing that ECHA wrongly assessed the reliability of that study, such an error would not call into question the conclusions drawn in particular from key studies as evaluated by ECHA in the Support Document.

185 Next, as regards the Bowmer and Gimeno (2001) study, it should be observed that it is apparent from the Support Document that (i) only one of the two assays used in that study was carried out in compliance with good laboratory practice, as defined by the OECD and (ii) only an extended summary is available. In the light of those considerations, the score of 2 in the Klimisch scoring system (reliable with restrictions) given to that study does not appear to be vitiated by a manifest error of assessment. That said, it is clear that, as is the case for the Mandich et al. (2007) study, the Bowmer and Gimeno (2001) study was used solely to support the identification of bisphenol A. Consequently, even if the score given to that study were to prove to be mistaken, such an error would not call into question the conclusions drawn, in particular, from the key studies.

186 In the light of the foregoing, the arguments put forward with regard to the studies conducted on *Cyprinus carpio* must be rejected as unfounded and, bearing in mind all of those factors, it must be held that the arguments raised in respect of certain *in vivo* studies conducted on certain species of fish have failed to demonstrate the existence of a manifest error of assessment vitiating the assessment of those studies which would mean that they could not serve to support the finding of an oestrogenic mode of action of bisphenol A in fish, reached by means of the weight of evidence approach.

(6) Conclusion on the first complaint in the second part of the first plea

187 In the light of the foregoing, it is clear that, in exercising its discretion for the identification, in the present case, of bisphenol A as an endocrine disruptor that can have serious effects on the environment, ECHA followed a clear and systematic methodology whilst respecting the principle of excellence for the purposes of appraising the diverse evidence on which it relied. In the context of the weight of evidence approach, ECHA carried out a weighting of *in vivo* and *in vitro* data drawn from a multitude of scientific studies whilst taking the reliability of each study into account. That weighting led ECHA to identify an endocrine mode of action in the first place on the basis of certain *in vivo* studies on certain species of fish and amphibian, whereas other *in vivo* data – namely, in particular, those on certain species of invertebrate – and *in vitro* data were used in support of those findings.

188 It is the weight of the evidence drawn from the aforementioned data that permitted ECHA to reach its conclusions with regard to the intrinsic properties of bisphenol A as an endocrine disruptor. In particular, those findings were not drawn from a single individual study, and even less so from a single study used as a supporting study. It must be found that the applicant's criticisms of certain studies used by ECHA are confined to calling into question the individual relevance or inconclusive nature of those studies, without however demonstrating a material contradiction in the effects reported or a clear inconsistency in the weighting which would invalidate the weight of the evidence.

189 The first complaint in the second part of the first plea must therefore be rejected.

(b) The second complaint in the second part of the first plea: manifest error of assessment, in that ECHA failed to establish that there was scientific evidence of bisphenol A having serious effects on the environment on account of its endocrine disrupting properties

190 By the second complaint in the second part of the first plea, the applicant claims that ECHA committed a manifest error of assessment, as it failed to establish that there was scientific evidence of bisphenol A having serious effects on the environment on account of its endocrine disrupting properties. The applicant states that, pursuant to Article 57(f) of Regulation No 1907/2006, only substances which have endocrine disrupting properties 'for which there is scientific evidence of probable serious effects to … the environment' can be identified as being of very high concern.

191 The applicant takes the view that the evidence relied upon in the Support Document does not provide a clear hypothesis to demonstrate an endocrine disrupting mode of action in the environment for bisphenol A, but relies solely on the description of individual observations in the context of endocrine

disruption, while the scientific arguments are vague and unsubstantiated. The data which supports the existence of low oestrogenic activity for fish and amphibians are not, in the applicant's opinion, sufficient to identify a substance of very high concern under Article 57(f) of Regulation No 1907/2006. The applicant argues that the evidence is, on the contrary, either extremely poor or highly speculative. The latter criticism applies in particular to the suggested mode of action in fish and amphibians. Nor, it is claimed, is there sufficient evidence obtained, for example by means of *in vitro* studies, to identify bisphenol A as having an endocrine disrupting mode of action.

192 In support of its argument, the applicant refers to the observations submitted by the Kingdom of Denmark and the United Kingdom at the public consultation. It claims, more specifically, that the United Kingdom expressed its hesitation as to the conclusion that bisphenol A definitely causes its effects via endocrine disruption.

193 Furthermore, the applicant observes that ECHA's claim that an effect is associated to an endocrine disrupting mode of action does not provide, by itself, sufficient evidence to fulfil the criteria set out in Article 57(f) of Regulation No 1907/2006. The applicant states, generally, that an association between two aspects alone does not, in its view, prove the scientific evidence required.

194 Moreover, the fact that certain serious effects were acknowledged as 'EATS [estrogen, androgen, thyroid and steroidogenic]-mediated' is not sufficient scientific proof for an endocrine mode of action of bisphenol A *in vivo* resulting in serious effects. According to the applicant, the existence of other potential mechanisms should have been examined and excluded. Given that the majority of the *in vitro* assays on endocrine mechanisms assess molecular initiating events only, other data relating to suspected undesirable effects would have been necessary before it was possible to presuppose that certain effects were 'EATS-mediated'. Furthermore, the mere assertion that certain effects are known to be 'EATS-mediated' is too general, and does not explain which effects are concerned, or how or by whom those effects are known to be 'EATS-mediated', or in what way it allowed ECHA to find that there was a biologically plausible link. Consequently, ECHA should have conducted a detailed analysis of the mode of action.

195 The applicant claims that the Support Document does not establish the key biochemical, cellular, and molecular events in the proposed mode of action, or the temporal and dose-response concordance between them, but rather confines itself to postulating their existence in a hypothetical scenario. In doing so, ECHA failed to satisfy the criteria that it identified itself in the Support Document.

196 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

197 In that connection, it is necessary to examine whether ECHA failed to apply the required standard of proof to establish that bisphenol A causes serious effects on the environment on account of its endocrine mode of action.

198 As a preliminary point, it is clear that in paragraph 173 of the judgment of 11 May 2017, *Deza* v *ECHA* (T-115/15, EU:T:2017:329), the Court held that the probability that a substance may have serious effects on the environment was sufficient to establish a causal link within the meaning of Article 57(f) of Regulation No 1907/2006. In particular, such an approach is in accordance with the precautionary principle, on which the provisions of Regulation No 1907/2006 are based, pursuant to Article 1(3) thereof.

199 Furthermore, the Court stated in paragraph 94 of the judgment of 20 September 2019, *PlasticsEurope* v *ECHA* (T-636/17, under appeal, EU:T:2019:639), that 'the facts and evidence relied upon in the examination of a substance [had to] serve to establish that it [was] "plausible" that the mode of action of that substance [could] lead to certain serious effects [and that, by] contrast, Article 57(f) of Regulation No 1907/2006 does not require absolute proof of a causal relationship'.

200 In the light of those considerations, the following observations must be made. In the Support Document, ECHA clearly sets out the methodology followed in order to determine whether there is indeed a plausible biological link between the endocrine mode of action of bisphenol A and the serious effects. Following that methodology, ECHA assessed (i) indicators of an endocrine mode of action and (ii) effects of apical endpoints as evidence substantiating the finding that bisphenol A causes serious effects on account of its endocrine mode of action. In that connection, the Support Document regards the *in vivo* studies in particular as being relevant to determining whether the serious effects are caused by the endocrine mode of action or whether they are solely the consequence of general systemic toxicity.

201 As an example, pages 33 to 35 of the Support Document explain, more specifically, in relation to studies on fish, first, the relevant indicators of an endocrine mode of action, namely, in particular, vitellogenin induction or histological changes and, second, the apical endpoints which, according to the OECD Guidance No 150 for evaluating endocrine disruptors, may be regarded as indicators of an antagonist of oestrogenic hormone receptors, namely, in particular, a reduction in secondary sexual characteristics and the skewing of sex ratios towards females during sexual development. In that regard, the Support Document explains that, in conjunction with the indicators of endocrine activity, the endpoints allow it to be found that there exists an oestrogenic mode of action.

202 It is in the light of those considerations that the Support Document concludes, in respect of *Oryzias latipes* and *Danio rerio*, that there is a direct link between the oestrogenic mode of action and the serious effects observed. Those conclusions were drawn from scientific studies analysed in the Support Document, all of which observed vitellogenin induction in *Oryzias latipes* and *Danio rerio*. Changes in sex ratios were also observed in *Oryzias latipes*, inter alia, in the Yokota et al. (2000) key study, and in *Danio rerio* in the Chen et al. (2015) study.

203 Similarly, in respect of amphibians, the studies analysed in the Support Document, in particular the Iwamuro et al. (2003) and Heimeier et al. (2009) studies, prove there to be a thyroid mode of action which manifested itself by a disruption of the hypothalamic-pituitary-thyroid axis and a delay in development, which led ECHA to conclude that there exists a plausible biological link between the mode of action and serious effects.

204 In the light of the foregoing, it must be held that, contrary to the applicant's claims, the evidence on which ECHA relied was neither too vague nor too speculative. It was in fact based on the observation of cellular and molecular biochemical events. Those data led ECHA to find that it was biologically plausible that bisphenol A caused its effects on account of an endocrine mode of action. Contrary to what the applicant appears to claim, ECHA did not confine itself to 'associating a certain effect with a certain mode of action'.

205 Moreover, in the present case, ECHA based its decision primarily on certain key studies concerning certain species of fish as well as certain species of amphibian in order to demonstrate the existence of a plausible biological link. A variety of *in vivo* and *in vitro* studies support that conclusion. The plausibility of the existence of a causal link, found by ECHA in the Support Document, therefore cannot be called into question by the mere fact that there remain uncertainties regarding a limited set of data considered in isolation, for example certain elements drawn from the Chen et al. (2015) study, as described above. Even if the studies containing the alleged shortcomings which are relied upon by the applicant had been disregarded by ECHA, the weight of the remaining evidence as a whole would nonetheless have been sufficient to substantiate the conclusion put forward by ECHA as to the plausibility of a causal link between the endocrine mode of action and the serious effects observed.

206 None of the applicant's arguments call that conclusion into question.

207 First of all, as regards the argument that ECHA confined itself, in its assessment, to assuming, without a detailed analysis, that certain effects of bisphenol A were caused by endocrine mediation, it is admittedly true that the Support Document does presume, in the part describing the methodology used, that some of the effects are endocrine-mediated. Nevertheless, the Support Document substantiates that presumption by referring to scientific publications. Thus, on page 34, the Support Document explains that the skewed sex ratios towards females is the known result of oestrogenic or anti-androgenic exposure during sexual development, whilst citing three reference sources which include publications by the OECD and the WHO International Programme on Chemical Safety. In doing so, ECHA began with a hypothesis that appears to be at least plausible from a scientific perspective and, consequently, meets the standard of proof as to the existence of a biologically plausible causal link between the mode of action and serious effects.

208 Second, as regards the applicant's argument that the data supporting the existence of weak oestrogenic activity did not suffice to identify an endocrine disruptor, it should be observed, first, that the applicant has failed to define what it means by weak endocrine activity and, consequently, what data it regards as insufficient. Second, the weight of evidence approach allows and requires that all relevant data which supports a hypothesis be taken into account. ECHA was therefore entitled to base its findings also on data demonstrating weak effects only. Third, the degree of the effects observed is not a criterion necessary to establishing a causal link between an endocrine mode of action and its effects. Such a causal link may also be established plausibly on the basis of weak effects.

209 Lastly, as to the applicant's argument that the United Kingdom expressed its hesitation in relation to the conclusion that bisphenol A undeniably causes its effects through endocrine disruption, it should be noted that that observation on the part of the United Kingdom was in fact made in the light of the data contained in the studies on invertebrates. It follows from page 135 of the Support Document that ECHA did not rely conclusively on the data concerning invertebrates, but confined itself to finding that it was possible that the effects of bisphenol A were caused by endocrine disruption. More specifically, ECHA acknowledges that, in the absence of scientific consensus on the definition of a plausible biological link between the effects and the endocrine mode of action in those species of invertebrate, that evidence can serve only as supplementary evidence, supporting the conclusions drawn in the first place from the studies on fish and amphibians. Accordingly, ECHA cannot be criticised for excluding hesitations such as those expressed by the Kingdom of Denmark and the United Kingdom during the consultation on the draft identification.

210 In the light of all the foregoing, the second complaint in the second part of the first plea in law must be rejected

(c) The third complaint in the second part of the first plea: manifest error of assessment in the identification of an equivalent level of concern

211 By the third complaint in the second part of the first plea, the applicant claims that ECHA committed a manifest error of assessment in the identification of the criteria laid down in Article 57(f) of Regulation No 1907/2006 by finding that bisphenol A gave rise to 'an equivalent level of concern' to those of other substances set out in Article 57(d) and (e) of Regulation No 1907/2006, namely (i) PBT substances and (ii) vPvB substances.

212 First, the applicant submits that the ready biodegradability of bisphenol A, together with the fact that the potential concentration in the environment does not exceed the safe threshold preclude that substance giving rise to a level of concern equivalent to that of PBT or vPvB substances, on account of the fact that it does not accumulate in the environment. In that connection, the applicant relies on Section 1.1 of Annex XIII to Regulation No 1907/2006, under which a substance does not fulfil the persistence criterion if it is biodegradable. It is argued that the high level of concern associated with PBT and vPvB substances is primarily driven by their accumulation in the environment, due to their

persistent and bioaccumulative properties. Although meeting the PBT and vPvB properties is not a precondition to being an endocrine disruptor in the meaning of Article 57(f) of Regulation No 1907/2006, the applicant takes the view that reference should be made to properties that are relevant to the identification of PBT and vPvB substances, namely persistence and bioaccumulation. In support of its argument, the applicant relies on observations made by various Member States, and in particular the Kingdom of the Netherlands and the United Kingdom, on the dossier prepared in accordance with Annex XV, emphasising the ready and immediate biodegradability of bisphenol A. The applicant claims that ECHA responded to those observations by asserting that bisphenol A was readily biodegradable. Nevertheless, ECHA failed to call into question its own conclusions with regard to the equivalent level of concern. The applicant claims furthermore that ECHA failed to demonstrate the existence of an equivalent level of concern by reference to criteria other than persistence or bioaccumulation.

213 In addition, the applicant refers to the determination of a predicted no-effect concentration of bisphenol A in the context of the EU RAR which, it argues, illustrates the possibility of determining a safe level of exposure to bisphenol A. ECHA, however, reached the speculative conclusion that it appeared difficult to find a safe level, but failed to provide any justification for that conclusion, which – according to the applicant – constitutes a manifest error of assessment vitiating the contested decision.

214 Next, inasmuch as ECHA also based its decision on the serious nature of effects as well as the irreversible nature thereof, the applicant maintains that such findings are based on unreliable studies. Moreover, ECHA cannot, in the applicant's view, rely on the serious nature of effects to justify the level of concern, given that, under Article 57(f) of Regulation No 1907/2006, the serious nature of effects is already taken into account in order to determine whether bisphenol A is a substance for which there is scientific evidence of probable serious effects to the environment.

215 Lastly, in the applicant's view, the mere fact that the MSC unanimously accepted that there existed such a level of concern was insufficient and could not compensate for a lack of scientific evidence for that assertion.

216 ECHA, supported by the Federal Republic of Germany, the French Republic and ClientEarth, contests those arguments.

217 In that connection, it should be borne in mind from the outset that Article 57(f) of Regulation No 1907/2006 requires, as regards the identification of substances other than those meeting the classification criteria referred to in Article 57(a) to (e) of that regulation, that it be established, on a case-by-case basis, on the basis of scientific evidence, that (i) the substances concerned can have serious effects on human health or the environment, and (ii) those effects give rise to an equivalent level of concern to those of other substances referred to in Article 57(a) to (e) of Regulation No 1907/2006, namely CMR, PBT and vPvB substances. Those conditions are cumulative, so that the identification of a substance as being of very high concern must be rejected if either of those conditions is not met (judgment of 15 March 2017, *Hitachi Chemical Europe and Polynt* v *ECHA*, C-324/15 P, EU:C:2017:208, paragraph 26).

218 As regards the second condition laid down in Article 57(f) of the REACH Regulation, there must be scientific evidence that those effects 'give rise to an equivalent level of concern' to those of CMR, PBT or vPvB substances. As the Court of Justice notes in paragraph 32 of the judgment of 15 March 2017, *Hitachi Chemical Europe and Polynt* v *ECHA* (C-324/15 P, EU:C:2017:208), Article 57(f) of Regulation No 1907/2006 does not lay down any criterion and does not provide any clarification as regards the nature of the concerns that may be taken into consideration for the purposes of identifying a substance other than CMR, PBT or vPvB. Under those circumstances, it is necessary to ascertain whether ECHA committed a manifest error of assessment in its determination of the level of concern.

219 First of all, it should be observed that the Support Document contains, through a weight of evidence approach, a series of considerations which led ECHA to find there to be probable serious effects giving rise to an equivalent level of concern. The Support Document relies, inter alia, on the serious nature of the effects on reproduction and sexual development in fish and amphibians, together with the irreversibility of those effects, which potentially have long-term consequences for the population, even after brief exposure to bisphenol A. Moreover, the Support Document explains that (i) bisphenol A acts on a wide variety of ecologically important species and (ii) exposure to that substance is not confined to certain environments but is instead ubiquitous. Lastly, ECHA relies on the difficulty in determining and quantifying a safe exposure threshold.

220 It is clear that the applicant does not call those findings into question in their entirety. In fact, it confines itself to (i) discussing the possibility of establishing a safe level of exposure to bisphenol A, and (ii) claiming that the ready and immediate biodegradability of bisphenol A – which, moreover, is not disputed by ECHA – precludes the finding of a level of concern equivalent to that of PBT and vPvB substances, inter alia.

221 As regards, first, the possibility of determining a safe level of exposure, it should be noted that, admittedly, a predicted no-effect concentration was determined in the EU RAR.

222 As ECHA explains in its observations on the applicant's reply to a written question put by the Court, contrary to the work carried out for the purposes of establishing a predicted no-effect concentration, the identification of a substance under Article 57(f) of Regulation No 1907/2006 is not a question of risk analysis, but rather an assessment of the dangers inherent to the intrinsic properties of a substance. Thus the possibility of inferring a safe level in context must be assessed in relation to the dangers that bisphenol A poses to the environment on account of its endocrine mode of action. It is in that context that ECHA took account of the uncertainties highlighted in deriving a safe level. In that connection, the Support Document refers, inter alia, to the difficulties arising from the fact that certain effects can be observed only during certain life stages, time windows or seasons. Furthermore, difficulties were identified on account of the fact that bisphenol A affects a wide variety of organisms though different endocrine modes of action.

223 In the light of those uncertainties – which are, at the very least, plausible – ECHA took a cautious approach to the question of the possibility of determining a safe level of exposure to bisphenol A. That caution is particularly justified in the light of the precautionary principle on which the provisions of Regulation No 1907/2006 are based pursuant to Article 1(1) thereof. That principle, which is a general principle of EU law, means that, where there is uncertainty, appropriate measures may be taken without having to wait until the reality and seriousness of those risks become fully apparent (see, to that effect, judgments of 1 October 2019, *Blaise and Others*, C-616/17, EU:C:2019:800, paragraph 43, and of 19 September 2019, *GE Healthcare* v *Commission*, T-783/17, EU:T:2019:624, paragraph 45). Consequently, ECHA cannot be criticised for having justified the level of concern arising from the effects of bisphenol A on account of its endocrine mode of action, in particular, by relying on the uncertainties that it had identified for the determination of a safe level of exposure to bisphenol A.

224 Next, as regards the argument that the ready and immediate biodegradability of bisphenol A precludes the determination of an equivalent level of concern to those of other substances listed in Article 57(a) to (e) of Regulation No 1907/2006, first, it should be found that that argument is contradictory. On the one hand, the applicant rightly acknowledges that it is not necessary that a substance have PBT or vPvB properties in order to be regarded as an endocrine disruptor for the purposes of Article 57(f) of Regulation No 1907/2006. On the other hand, it takes the view that reference should be made to properties relevant to the identification of PBT and vPvB substances in order to establish an equivalent level of concern. In that context, the applicant has failed, however, to explain which criteria would, in its view, allow the identification of a substance as an endocrine disruptor without that substance being both a PBT and vPvB substance.

225 That interpretation of Article 57(f) of Regulation No 1907//2006, put forward by the applicant, would essentially make that provision a mere duplication of the provisions of Article 57(a) to (e) of that regulation, which would render the provisions of Article 57(f) of that regulation ineffective. In particular, such an interpretation would run counter to the main purpose of Regulation No 1907/2006, set out in Article 1(1) thereof, namely that of ensuring a high level of protection of human health and the environment, in so far as that interpretation would give rise to a situation in which substances of a very high level of concern which do not possess the properties referred to in Article 57(a) and (e) of Regulation No 1907/2006 could not be identified as such. According to the very wording of Article 57(f) of that regulation, that provision covers, in particular, substances 'which do not fulfil the criteria of [Article 57(d) and (e) of the regulation]'.

226 Second, the applicant has failed to explain the extent to which the ready biodegradability of bisphenol A, in itself, would invalidate ECHA's conclusions on the level of concern to which bisphenol A gives rise. It is apparent from the Support Document that ECHA found that even brief exposure to bisphenol A may suffice to cause serious, irreversible long-term effects on organisms and populations. Accordingly, the ready and immediate biodegradability of bisphenol A cannot affect the level of concern, as identified by ECHA.

227 Third, it should be borne in mind that ECHA arrived at the determination of a level of concern on the basis of the weight of evidence. Thus the argument that ECHA relied on unreliable studies, which corresponds to the first complaint of the first plea, must also be rejected. The weight of the studies assessed allowed ECHA to conclude, without committing a manifest error of assessment, that the effects caused by bisphenol A on account of its endocrine mode of action are irreversible inasmuch as they are transmitted from one generation to the next, as observed by the various multi-generational studies conducted on species of fish analysed in the Support Document.

228 Lastly, as regards the serious nature of the effects caused by bisphenol A on account of its endocrine mode of action, it should be noted that Article 57(f) of Regulation No 1907/2006 admittedly requires that it be proved that bisphenol A causes serious effects to the environment. Nevertheless, that does not prevent ECHA from considering the serious nature of those effects by comparison to the seriousness of the effects caused by the substances set out in Article 57(a) to (e) of that regulation. In particular, such an approach does not constitute a double counting of evidence, but simply an analysis of that evidence from a different angle.

229 Having regard to that evidence, it is clear that the applicant has failed to demonstrate how ECHA could have committed a manifest error of assessment in establishing an equivalent level of concern.

230 In the light of all the foregoing, the third complaint in the second branch of the first plea in law must be rejected, as must that branch and plea in their entirety.

…

IV. Costs

272 Under Article 134(1) of the Rules of Procedure, the unsuccessful party is to be ordered to pay the costs if they have been applied for in the successful party's pleadings. Since the applicant has been unsuccessful, it must be ordered, in accordance with the form of order sought by ECHA and ClientEarth, to bear its own costs and to pay those incurred by both of the latter.

273 In accordance with Article 138(1) of the Rules of Procedure, the Member States which have intervened in the proceedings are to bear their own costs. Consequently, the Federal Republic of Germany and the French Republic must be ordered to bear their own costs.

On those grounds,

THE GENERAL COURT (Eighth Chamber)

hereby:

1. **Dismisses the action;**

2. **Orders PlasticsEurope to bear its own costs and pay those incurred by the European Chemicals Agency (ECHA) and ClientEarth;**

3. **Orders the Federal Republic of Germany and the French Republic to bear their own costs.**

Svenningsen Pynnä Laitenberger

Delivered in open court in Luxembourg on 16 December 2020.

[Signatures]