

CHRONICALLY UNDERRATED?

A review of the European
carcinogenic hazard
assessment of 10 pesticides

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This report, commissioned by Pesticide Action Network (PAN) Germany and by the Health and Environment Alliance (HEAL), examines how EU Member States (acting as “Reporting Member States”, RMS) and the European Food Safety Authority (EFSA) assess the risk that pesticides cause human cancer. It does so by comparing the actual risk assessments performed with the recommendations that follow from OECD guidelines on the performance of carcinogenicity studies and the guidance provided by the European Chemicals Agency (ECHA), as well as with the requirements imposed by EU instruments themselves, in particular the 2008 and 2009 regulations on the conditions under which pesticides can be placed on the market.¹

The report reaches conclusions that are particularly disturbing. Had the protocols been properly followed, three of the ten substances (folpet, pirimicarb and thiacloprid) would have been classified as “presumed to have carcinogenic potential for humans”, rather than as “suspected human carcinogen”; in other terms, the risks to human health have been underestimated. For three other substances (captan, chlorpropham and dimoxystrobin), the study finds that no conclusion can be reached, due to a lack of information. Finally, for one substance (phosmet), whereas EFSA reached the conclusion that it was not carcinogenic, it did so despite the absence of reliable data. In other terms, in seven cases out of ten, the assessments made by the EFSA appear to be unconvincing at best, and arguably to have been adopted in violation with the rules it should have followed. The health of European consumers, it seems, has routinely been sacrificed on the altar of the interests of the industry.

These findings are important for three reasons.

First, they provide a clear demonstration that time and again vested interests seem to prevail in the process of market authorisation of pesticides, and the precautionary principle is set aside.

The saga of the re-authorisation of glyphosate-based herbicides, in autumn 2017, already alerted the European public opinion to the reality of this risk. This was reflected by a resolution the European Parliament adopted in which it considers that “the Commission’s draft implementing regulation fails to ensure a high level of protection of both human and animal health and the environment, fails to apply the precautionary principle, and exceeds the implementing powers provided for in Regulation (EC) No 1107/2009”.² Moreover, the proposal to re-authorize glyphosate was made just as the European Citizens’ Initiative “Stop Glyphosate”, calling on the Commission “to propose to member states a ban on glyphosate, to reform the pesticide approval procedure, and to set EU-wide mandatory reduction targets for pesticide use”, was pending examination, after receiving the required support of more than one million citizens from at least 7 EU Member States.³

In other terms, the decision to renew the approval of the active substance glyphosate for the period 2018–2022 violated not only the requirement imposed on the EU to take into account the protection of human health in its policies,⁴ as well as the precautionary principle; but it also appeared to violate the principle of democracy.⁵

¹ Regulation (EC) No 1272/2008 of 16 December 2008 on classification, labelling and packaging of substances and mixtures and Regulation (EC) No 1107/2009 of 21 October 2009 concerning the placing of plant protection products on the market.

² European Parliament resolution of 24 October 2017 on the draft Commission implementing regulation renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Implementing Regulation (EU) No 540/2011, para. 1.

³ <https://ec.europa.eu/citizens-initiative/public/initiatives/successful/details/2017/000002>

The second reason why this report is important is because it illustrates how there is a second loser in the current system: apart from consumers' health being sacrificed, science is set aside. The re-approval of glyphosate took many observers by surprise, because the data presented by EU authorities themselves clearly pointed to a carcinogenicity classification similar to that of the International Agency for Research on Cancer (IARC), the World Health Organization's cancer agency, which in 2015 classified glyphosate as 'probably carcinogenic to humans'.⁶ Similar methods as for glyphosate were used to brush aside evidence on carcinogenicity for three pesticides assessed in 2017 and 2018.

The limited length of the approval period of glyphosate (until 2022) represents a half-hearted acknowledgement of the uncertainty surrounding its re-approval. In the face of this uncertainty, the correct attitude is not to put the European population at risk. It is to abstain from taking such a risk, until any doubt is alleviated and until convincing answers are provided to the concerns raised about the toxicity of the products that are to be placed on the market. This is required under the precautionary principle, referred to above. As confirmed by the Court of Justice, "where it proves to be impossible to determine with certainty the existence or extent of the alleged risk because of the insufficiency, inconclusiveness or imprecision of the results of studies conducted, but the likelihood of real harm to public health persists should the risk materialise, the precautionary principle justifies the adoption of restrictive measures".⁷

Third, finally, the present report confirms the importance of the judgment delivered on 7 March 2019 by the General Court of the European Union to make publicly available the documents it relied on in order to arrive at its conclusion that glyphosate-based herbicides do not cause a cancer risk.⁸ The Court of Justice based itself on the presumption that the disclosure of information which "relates to emissions into the environment" is deemed to be in the overriding public interest: the protection of the commercial interests of a particular natural or legal person, the Court concluded, may not be invoked to preclude the disclosure of that information.

The glyphosate dossier -- with the European Citizens' Initiative, the court case, the Bayer-Monsanto acquisition, and the concerns raised in the general public about the risks associated with the pesticide that is the most widely used in the EU -- had a particularly high profile. This new review prepared by Peter Clausing sends a powerful message: the glyphosate saga is not an isolated instance; in the EU, pesticides are routinely used that endanger human health, and the procedures in place to protect the European population are notoriously insufficient. We have the choice, either to keep our eyes wide shut, or to take action in order to close this gap. While the report does not allege corruption, it does denounce a corrupt system that must be reformed and far better take into account the concerns expressed both by the scientific community and European citizens. I am grateful that this report allows an informed debate on how to improve it.

Olivier De Schutter

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⁴ According to Article 9 TFEU, "In defining and implementing its policies and activities, the Union shall take into account requirements linked to the (...) protection of human health". Article 12 TFEU states further that "Consumer protection requirements shall be taken into account in defining and implementing other Union policies and activities". Article 168(1) TFEU provides in turn that "A high level of human health protection shall be ensured in the definition and implementation of all Union policies and activities". The requirement to ensure a high level of human health protection also follows from Article 35 of the Charter of Fundamental Rights.

⁵ De Schutter (2017): Why the Commission's renewal of the authorization to place glyphosate on the EU market should be annulled. Footnote 8.

⁶ Available on: <http://monographs.iarc.fr/ENG/Monographs/vol112/index.php>

⁷ Judgment of 10 April 2014, Acino AG v. Commission, Case C-269/13 P, EU:C:2014:255, para. 58; judgment of 17 December 2015, Neptune Distribution, C 157/14, EU:C:2015:823, para. 82.

⁸ Judgment of 7 March 2019 in Cases T-716/14, Anthony C. Tweedale v European Food Safety Agency (EFSA), and T-329/17, Hautala and Others v EFSA.

EXECUTIVE SUMMARY

The controversy around the assessment of glyphosate as a carcinogenic hazard revealed that the European authorities' main justification for concluding that glyphosate is not carcinogenic was associated with a flawed and distorted use of guidelines and guidance documents.⁹ This observation raised the question whether such flaws were unique for glyphosate or also applied to other pesticides. Thus, we performed a review of the carcinogenicity sections of the draft Renewal Assessment Reports (RARs) of ten different pesticides for which the draft RARs were completed between 2015 and 2018. According to the EU pesticide database,¹⁰ nine of them were already classified as category 2 carcinogens (suspected human carcinogens), while one was classified as non-carcinogenic.

Our investigation focused on compliance with Organisation for Economic Cooperation and Development (OECD) guidelines and guidance documents of the section describing the carcinogenicity studies in rats and mice. EU directives 1272/2008 and 1107/2009 were our point of reference and we also took into account European Chemicals Agency (ECHA) guidance (2015, 2017). Furthermore, we reviewed the description of additional studies used to claim a mode of action making the observed carcinogenic effect irrelevant for humans.

Only for three of the ten pesticides was our own evaluation identical to the authorities' assessment. Two of them, chlorotalonil and diuron, were "upgraded" by the Reporting Member State (RMS) and/or the European Food Authority (EFSA) and proposed to be classified as category 1B carcinogens (presumed to have carcinogenic potential for humans) in the future. For the third pesticide, forchlorfenuron, we came to the same conclusion as the RMS, i.e. to keep the existing category 2 classification.

Strikingly, information in the RARs was insufficient for three of the ten pesticides (captan, chlorpropham, dimoxystrobin) to make a judgment, indicating a severe lack of detail and a widespread deficiency in transparency concerning carcinogenicity studies.

Similar to glyphosate, there was disagreement between the authorities' and our assessment for three pesticides (folpet, pirimicarb, thiacloprid), which in our view should be classified as category 1B. For phosmet, the RMS accepted a clearly insufficient study, drawing the wrong conclusion that phosmet is not carcinogenic.

Misuse of historical control data to dismiss study results was the flaw most frequently observed.

There is an urgent need for a more stringent application of guidelines and guidance documents and for more transparency and detail in the RARs. According to our analysis, for at least four of ten compounds, the authorities' hazard classification was too weak or based on a flawed database.

⁹ Clausung et al. (2018): Pesticides and public health: an analysis of the regulatory approach to assessing the carcinogenicity of glyphosate in the European Union. *J. Epidemiol. Community Health* 72, 668–672.

¹⁰ http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance_selection&language=EN

1. INTRODUCTION

In 2015, a controversy erupted concerning the assessment of glyphosate's carcinogenic hazard. The International Agency for Research on Cancer (IARC) came to the conclusion that glyphosate is probably carcinogenic for humans (category 2A, equivalent to category 1B – presumed human carcinogen – as defined in the EU regulation 1272/2008), whereas the German Federal Institute for Risk Assessment (BfR), on behalf of the RMS Germany, came to the conclusion that glyphosate is not carcinogenic.

It was repeatedly claimed by BfR and EFSA that this divergent assessment was – at least partly – due to the fact that BfR/EFSA assessed more studies than IARC. However, a peer-reviewed paper (Clausing et al., 2018) revealed that the European authorities' main justification for their conclusion of non-carcinogenicity was associated with a flawed and distorted use of their own guidelines and guidance documents.

The purpose of this report is to assess whether this violation and/or flawed use of guidelines and guidance documents applicable to carcinogenicity assessments was unique for the case of glyphosate or also occurred with other pesticide active ingredients. With an emphasis on category 2 pesticides (suspected human carcinogen), we reviewed the use of current guidelines and guidance documents (ECHA 2015, EU 2008, EU 2009, OECD 2009a, OECD 2009b, OECD 2012) for Renewal Assessment Reports (RARs) of eight pesticides prepared after 2015. Two further pesticides (diuron and chlorotalonil) were not included in this analysis, because the Reporting Member State (RMS) already proposed a category 1B classification.

2. METHODOLOGY

Official documents (Renewal Assessment Report, Volume 1 and Volume 3 B.6, and the respective EFSA conclusion) were retrieved from EFSA's "Register for Questions" website. The document parts related to the carcinogenicity assessment were reviewed. The review focused on the description of the individual rodent carcinogenicity bioassays (rat and mouse studies) and the "mode of action" discussion, if any. Points of reference were

- 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 (European Commission 2008)

- Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EC and 91/414/EC
- OECD Guidance Document 116 on the conduct and design of chronic toxicity and carcinogenicity studies (OECD 2012)
- OECD Test Guideline 451, Carcinogenicity Studies (OECD 2009a)
- OECD Test Guideline 453, Combined Chronic Toxicity/Carcinogenicity Studies (OECD 2009b)
- ECHA Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (ECHA 2015)¹¹

All individual rodent bioassays, as described in the authorities' documents, were assessed concerning the use of the statistical method, the survival rate, the description of tumour incidences observed in the study, and use of historical control data for interpretation of observed tumour incidences. The use of a weight of evidence approach, insofar as this was discussed in the authorities' documents, was also taken into account.

It should be noted that the ability to make an independent evaluation of the authorities' assessment hinges on the level of detail provided in the official reports. Only for compounds with enough detail was a critical assessment possible.

2.1. STATISTICAL METHOD

In the scientific community, it is well known that statistical significance of an increase tumour incidences is not the only criterion for concluding whether a pesticide is carcinogenic or not. Specifically for that reason it is important to make a proper statistical evaluation and at the same time take into account biological relevance and other weight of evidence aspects. However, taking into account other aspects for the final conclusion applies for both situations – presence and absence of statistical significance. This view is explicitly supported by OECD guidance document no. 116, saying, “Similarly declaring a result non-significant . . should not be interpreted as meaning the effect is not biologically important” (OECD 2012, p. 118). Moreover, from the flow diagram on page 123 of this guidance document, it becomes obvious that for the statistical analysis of tumour incidences, so-called trend tests are preferred over pairwise comparisons. Trend tests are more powerful than pairwise comparisons (OECD 2012, p. 127). Furthermore, statistical tests can be applied as one-sided or two-sided comparisons. A one-sided comparison has twice as much statistical power as a two-sided comparison, because the test is performed only in one pre-specified direction. In other words, in a one-sided comparison, the statistical analysis evaluates whether the pesticide causes an increase of tumour incidences, and not whether a pesticide has therapeutic properties (decreasing a tumour incidence). Thus, for risk assessments, the application of one-sided comparisons makes sense.

¹¹ It should be noted that the carcinogenicity part of the updated version of this guidance (ECHA 2017) is identical to the 2015 version, except for very minor changes and a new section on classification of substances containing CMR constituents, additives or impurities

In the case of glyphosate, Clausen et al. (2018) criticized the double attenuation of the power of statistical analysis of carcinogenicity studies as applied by the European authorities. They preferred pairwise comparisons instead of trend tests and exclusively applied two-tailed tests instead of one-sided tests.

This weakened the strength of evidence, even before taking into account biological relevance or weight of evidence. According to regulation (EC) 1272/2008, “Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance.”

2.2. SURVIVAL RATE

Carcinogenicity studies are long-term studies (covering about 75% of the life expectancy of rodents), and for the validity of a study it is crucial that sufficient animals survive until the end of the 18- or 24-month study period. Therefore, OECD guidance document no. 116 recommends:

“For a negative result to be acceptable in a rat carcinogenicity bioassay, survival in the study should ideally be no less than 50% in all groups at 24 months, while for ‘life span studies’, studies continued to end of life/death of the animals’ survival at study termination should not be less than 25%. In a mouse study, survival in all groups in the study should be no less than 50% at 18 months. It is the responsibility of the study director to use rodent strains that would ensure adequate survival at 18/24 months. Additionally, no more than 10% of any group should be lost due to autolysis, cannibalism, or management problems.” (OECD 2012, p.80)

In other words, studies with a survival rate of less than 50% in any of the groups after 24 months in rats or 18 months in mice should not be accepted by the authorities as proof of no carcinogenicity.

2.3. HISTORICAL CONTROL DATA (HCD)

HCD (the use of tumour incidence data from control group animals of earlier studies) can support the interpretation of data from the carcinogenicity study under consideration. However, OECD guidance 116 emphasizes that “the concurrent control group is always the most important consideration in the testing for increased tumour rates”. Importantly, strict rules concerning the use of HCD should be followed. This includes that HCD should come from the same laboratory and the same strain of animals and should have been generated within a maximum of 5 years prior to the actual study. Finally, the median and the Interquartile Range (IQR) should be used, but not the arithmetic mean and the “simple” range.

In other words, a number of restrictions apply before HCD should be used to dismiss the findings of a study.

3. RESULTS

3.1. CAPTAN

RMS: **Austria**; Year of RAR: **2018**; Proposed category: **2**

The classification of captan as a category 2 carcinogen was based on the results of two rat and two mouse studies. According to the RAR, no tumours were observed in rats, but duodenal tumours were seen in both mouse studies.

3.1.1. ASSESSMENT

For the 1982a rat study the RMS stated (RAR Volume 3 B.6, p.111):

“The incidence of microscopic neoplastic and non-neoplastic lesions was comparable between treatment groups and the controls. There were no statistically or toxicologically significant increases in any tumour type, total tumours, total benign tumours or total malignant tumours.”

However, no details on tumour incidences were given, nor was the method of statistical evaluation described. Furthermore, no information was provided on the survival of the animals at the end of the 2-year study period. The 1983 rat study prompted a similar statement in the RAR, but with regard to neoplastic changes, it is not mentioned which statistical method was used.

Due to this lack of information an assessment of the two rat studies is impossible.

A life-time mouse study (1981) using dietary concentrations of 0, 6,000, 10,000 or 16,000 ppm was terminated at week 113. A statistically significant increase in duodenal neoplasms was described, but without details on the statistical analysis. An increased incidence of duodenal tumours was also seen in the second mouse study (1983). Therefore, captan was classified as a category 2 carcinogen. The mode of action proposed for these duodenal tumours appears plausible: Damage of intestinal villus cells, resulting in enhanced cell replication and subsequent tumours due to the formation of thiophosgene – a degradation product of captan with irritant properties (RAR, volume 1, p. 41).

However, in the 1981 mouse study, the RMS mentioned a second tumour type (lymphosarcoma), which according to the RAR was increased in females of the high-dose group, though supposedly not statistically significant. Scant information was provided: “The number of thymic lymphosarcomas was slightly increased ($p < 0.09$) in high dose females (4/26) compared to the control (0/30)” (RAR, Volume 3 B.6, p. 119). No information on the incidences in the other dose groups or in male animals is given, and it is not known which

statistical method was used to establish the error probability of $p < 0.09$. It is also not known what the incidences of 4/26 and 0/30 refer to, because the total number of females was 80 in each group, and according to Table 6.5-5, there were 10 and 33 surviving females at the study's termination in the control and high dose group, respectively. It is disturbing that no detailed data are available, because the cause of death determined for animals dying during the study "was attributed to lymphosarcoma/myeloproliferative disease or duodenal neoplasms" (RAR, Volume 3 B.6, p. 116). According to these data, lymphosarcoma was considered an important outcome in this carcinogenicity study, but from the limited details provided in the RAR, it cannot be assessed whether the study has been properly assessed.

In a followup study (1983), presumably using the same strain of CD-1 mice, the animals were exposed to dietary concentrations of 0, 100, 400, 800 or 6,000 ppm captan. The diets were "administered for approximately 22 months". No reason was given for the shorter-than-normal study duration (24 months being the usual duration), no exact time point or reason for the study's termination was given, and concrete information about mortality was restricted to a remark that during the first 14 months of the study, mortality for high-dose males was higher (35%) as compared to control males (15%). The duodenal tumours were confirmed at the dietary concentrations of 6,000 ppm and were also seen at 800 ppm. The crucial flaw of this study is that only selected tissues were examined histopathologically, and lymphatic tissues were not included, except for those with macroscopic lesions and the mesenteric lymph nodes of animals with gastrointestinal lesions. In other words, lymphosarcoma were not systematically assessed.

3.1.2. CONCLUSION

Based on the information in the RAR it is impossible to make an independent evaluation of the claim that no toxicologically significant increases in rats were seen. For the mouse studies, while a plausible mode of action was provided for duodenal tumours, the observed increase of lymphosarcoma in the 1981 mouse study was insufficiently evaluated. In the 1983 mouse study such an evaluation was not possible due to a flawed study design. It cannot be excluded that captan would qualify as a category 1B carcinogen according to Regulation (EC) 1272/2008.

3.2. CHLORPROPHAM

RMS: **The Netherlands**; Year of RAR: **2017**; Proposed category: **2**

The proposal to classify chlorpropham as a category 2 carcinogen was based on the results of two rat and two mouse carcinogenicity studies. One further rat study, one further mouse study, and one study in golden hamsters were convincingly described as inappropriate for assessment.

3.2.1. ASSESSMENT

The RAR did not provide any details about the statistical methods used to evaluate tumour incidences in any of the carcinogenicity studies. In addition, while compliance with OECD guidelines no. 451 or 453 was claimed (except that some technical deviations were mentioned), the statement made for mouse study 2 and rat study 2 that “microscopy [was carried out] of approximately 40 tissues” (emphasis added) does not create confidence that RMS did properly check guideline compliance, because microscopic examination of at least 43 different tissues is mandatory. Besides, histopathological examination was not described at all in the RAR for mouse study 1 and rat study 1.

According to the RAR, no tumours were observed in the two mouse studies, but a significant increase in benign interstitial tumours in the testes (Leydig cell tumours) was observed in one rat study. In the other rat study there was a higher frequency and severity of Leydig cell hyperplasia in the highest dose group.

Except for the Leydig cell tumours in rat study 1 and the higher/more severe incidence of Leydig cell hyperplasia in rat study 2 (which potentially could lead to Leydig cell tumours), no tumour incidence was tabulated for any of the studies. Data were presented in the narrative part of rat study 2 for another tumour type (thyroid cell adenomas). Incidences did not differ between groups.

The applicant claimed that the observed increases in Leydig cell tumours are not relevant for humans, based on the proposed mode of action, i.e. “dopamine agonism”. The RMS did not agree with this proposal, but failed to sufficiently take into consideration mechanistic evidence from the scientific literature. Summarizing the paper by Orton et al. (2009), the RMS stated, “Chlorpropham was reported to have shown anti-androgenic activity in the yeast based androgenicity screen at concentrations ranging from 0.5–15.6 μM ”, and cautioned that “Yeast-based assays may not be predictive for human or environmental species” (RAR Volume 3 B.6, p. 291). However, it failed to take note of a more recent publication (Kugathas et al. 2016), demonstrating anti-androgenic activity of chlorpropham in a model of SC5 mouse Sertoli cells. This is a mammalian model and therefore more predictive of human health effects. At the same time, it is in line with the results from the yeast-based assay.

3.2.2. CONCLUSION

Due to insufficient information in the RAR, we were unable to perform an in-depth evaluation of the assessment made by the RMS. It is known from glyphosate (for which the original reports of the carcinogenicity studies became accessible) that the authors of the RAR failed to detect or report statistically significant increases of certain tumour types (Portier and Clausen 2017). Therefore, from the data available, it cannot be excluded that such a failure also exists in the present case. Moreover, the scientific literature was insufficiently

taken into consideration by the RMS. An important paper published by Kugathas et al. in April 2016, corroborates the anti-androgenic activity of chlorpropham described earlier, using a yeast-based assay (Orton et al. 2009). The paper by Orton et al. was considered of limited relevance by RMS. Importantly, the new publication by Kugathas et al. supports a possible anti-androgenic mode of action in mice that is, therefore, relevant for humans. In contrast, the applicant claimed that the observed Leydig cell tumours are due to an interference with the dopaminergic system in the mouse brain, and, therefore, not relevant for humans. The RMS or the EFSA should have taken into account the publication by Kugathas et al. (2016), leading to the conclusion that human relevance of the observed Leydig cell tumours cannot be excluded.

3.3. DIMOXYSTROBIN

RMS: **Hungary**; Year of RAR: **2017**; Proposed Category: **2**

The proposed classification of dimoxystrobin as a category 2 carcinogen was based on one rat and one mouse carcinogenicity study. In addition, tumour findings in a rat chronic toxicity study were taken into consideration.

3.3.1. Assessment

An increase of duodenal adenoma and adenocarcinoma was observed in the study using B6C3F1 mice. The RAR states that dimoxystrobin has no irritant properties. Rather, the duodenal tumours were explained as the result of an adaptive cell proliferation of the duodenal epithelium, to compensate for a reduced iron uptake in the duodenum. It was proposed that dimoxystrobin interferes with duodenal receptors (Dcytb and Ferroportin) involved in iron absorption. The applicant provided convincing evidence (additional mechanistic studies) for this reversible threshold mechanism. At the same time, the RMS dismissed liver tumour findings in the rat study. The incidences of the liver tumours are shown in the table below.

Liver tumours in the 2-year rat carcinogenicity study (50 animals per sex per group in all groups)

SEX	MALES				FEMALES			
Dose (ppm)	0	50	150	500	0	50	150	500
Liver adenoma	2	3	7	3	1	1	2	4*
Liver adenocarcinoma	3	3	1	4	0	0	1	0
Combined	5	6	8	7	1	1	3	4**

* marginally statistically significant (Cochran-Armitage trend test, $p=0.0529$, one-sided),

** borderline significant (Cochran-Armitage trend test, $p=0.0642$, one-sided) own calculation.

In female rats, there was a dose-dependent, significant increase for the incidences of liver adenoma and adenocarcinoma combined. In addition, male rats exhibited a non-significant tendency for an increase. The RMS not only failed to apply a statistical evaluation, it also used flawed HCD to dismiss the finding instead of putting emphasis on the concurrent control as recommended by OECD (2012). The report of this study dates back to the year 2000, but RMS, while using the HCD range, which often can be misleading and therefore is discouraged by OECD (2012), referred to a total of 29 studies covering a period of more than 20 years (between 01 January 1992 and 07 July 2015) instead of the maximum last five years prior to the study under evaluation as stipulated by OECD (2012). Furthermore, while OECD (2012) recommends using the interquartile range (instead of the simple range), scientifically even more sound methods are available to integrate HCD, instead of just referring to the HCD range (Fung et al. 1996, Tarone 1982, Yanagawa et al. 1985). In other words several restrictions for using HCD were violated to be able to dismiss the significant tumour findings.

3.3.2. CONCLUSION

The applicant and RMS convincingly presented a reversible threshold mechanism for the duodenal tumors observed in mice which enables the application of dose-response considerations in the evaluation of carcinogenic hazards. However, RMS failed to acknowledge the statistically significant increase in liver tumours and used flawed HCD to dismiss this increase, which they also erroneously considered non-significant. Without access to the full reports of both rat and mouse studies and detailed information about HCD, it is impossible to exclude that dimoxystrobin could qualify as a category 1B carcinogen.

3.4. FOLPET

RMS: **Austria**; Year of RAR: **2018**; Proposed category: **2**

The classification of folpet as a category 2 carcinogen was based on two rat and two mouse carcinogenicity studies. RMS concluded, “Folpet was not carcinogenic in rats”, and “Folpet was carcinogenic in mouse, duodenal carcinomas and adenomas were produced” (RAR, Volume 1, p.40).

3.4.1. ASSESSMENT

Concerning the duodenal tumours in mice, a mode of action similar to that of captan was proposed: the formation of thiophosgene, leading to tumour formation because of its irritant properties (see captan assessment above for further details). For folpet too, the mode of action proposed for duodenal tumours in mice appears plausible and acceptable.

However, several other tumour incidences were significantly increased according to the RAR,

namely benign fibro-epithelial mammary gland tumours, malignant lymphoma and C-cell adenoma of the thyroid in the study using Fischer F344 rats, malignant lymphoma and stomach papilloma in the study using B3C6F1 mice, benign b-squamous papilloma in the 1994 study using CD-1 mice, and a significant increase in the total number of malignant neoplasms (not specified in the RAR) in the 1982 study using CD-1 mice. All of these statistically significant increases were dismissed with questionable arguments and the classification as a category 2 carcinogen was solely based on the finding of duodenal tumors together with its mode of action. Therefore, it is worth looking at these dismissals more closely.

Additional tumours with significantly increased incidences in the Fischer F344 rat study (60 animals per sex per group)

SEX	MALES AND FEMALES COMBINED				FEMALES			
Dose (ppm)	0	500	1,000	2,000	0	500	1,000	2,000
Mammary gland, benign fibro-epithelial tumour p-value	9	6	11	15* 0.0298	7	5	8	12 0.0476 @
Malignant lymphoma p-value	0	3	4	5* 0.0316	0	2	2	3 0.0923
Thyroid C-cell adenoma p-value	10	2	4	10 0.2637	4	0	2	8* 0.0227

* significantly different according to RAR at $p = \text{or} < 0.05$
#Cochran-Armitage trend test, one-sided

@ additional significance according to own calculations, using Cochran-Armitage trend test, one sided

Inappropriate use of HCD

Because of the findings described above, RMS requested from the applicant: “If available .. contemporaneous historical control data (from the same species, strain and laboratory) for these tumour types” (RAR Volume 3 B.6, p. 171).

But instead of providing appropriate HCD as requested by RMS, the applicant used two publications from the U.S. National Toxicology Program (Haseman et al. 1984; Haseman et al. 1985) to argue that the increased tumour incidences are irrelevant, which was accepted by the RMS (RAR Volume 3 B.6, p. 172). In addition to using inappropriate HCD, the applicant’s argument contains a number of errors and/or false claims. Nevertheless it was accepted by the RMS. The errors and/or false claims include:

- The publication used by the applicant itself (Haseman et al. 1984, p.134) states: “Supplemental comparisons with historical control rates may occasionally be made and should generally be limited to data from the same laboratory. For certain uncommon or rare tumors use of program-wide rates may be appropriate” (emphasis added). Even within the National Toxicology Program, which has made efforts to standardize the conduct of carcinogenicity studies with the aim of making HCD more comparable, the use of “program-wide” tumour incidences (HCD combined from

several locations of the National Toxicology Program) were only considered appropriate for rare tumours. The three tumour types listed in the table above are definitely not rare tumours.

- The statement, “Folpet .. is not present systemically” (RAR Volume 3 B.6, p. 172), contradicts the applicant’s own data, where it is stated: “In the rat, absorbed Folpet is converted to phthalamic acid via phthalimide” (emphasis added, RAR Volume 3 B.6, p. 12). In other words, folpet in fact is available systemically.
- For thyroid C-cell adenoma and carcinoma, besides using inappropriate HCD, the applicant presented a non-transparent mix of percentages and absolute incidences from the entire study (i.e. with early mortalities) and/or at study termination.

Significantly higher tumour incidence in the CD-1 rat study not recognized or ignored

In the 1985 study using CD-1 rats, an incidence of 1, 5, 4, and 8 of interstitial cell tumours in the testes was observed for the control, low, mid, and high dose group, respectively (RAR Volume 3 B.6, p. 171, p. 177, table 6.5.1-20). This is a statistically significant increase ($p=0.0348$, Cochran-Armitage trend test, two-sided, own calculations) – a finding that was neither mentioned by the applicant in its dossier nor detected by the RMS.

Significant increase of non-duodenal tumours in mouse studies dismissed

In the 1985 study using B6C3F1 mice, a significant increase in malignant lymphoma (Peto’s test for trend, $p<0.01$) was seen in female mice and – according to the RAR – “an increased trend among late decedent males” (RAR Volume 3 B.6, p. 171, p. 180). RMS stated that the study author considered this lesion as having only a “dubious relationship to treatment” with no further comment or explanation why this trend should be considered “dubious” – especially given that the same type of tumour was seen in the study using Fischer 344 rats. In addition, the incidence of stomach papilloma was significantly increased in female mice. A significantly increased incidence of stomach papilloma was also seen in the 1994 study using CD-1 mice.

3.4.2. CONCLUSION

The applicant focused on a mode-of-action explanation for duodenal tumours, enabling the determination of a dose without carcinogenic effect, and, thus, making possible a category 2 classification of folpet. However, increased incidences of non-duodenal tumours were observed in two rat and two mouse studies – findings that were either ignored or dismissed by the applicant using flawed arguments. RMS failed to follow up on these deficits and accepted the misleading arguments of the applicant. With the caveat that access to the full study reports and additional information would be needed for a final conclusion, the available data warrant a classification of folpet as a category 1B

carcinogen, also because a significant increase in malignant lymphoma was observed in both species, rats and mice.

3.5. FORCHLORFENURON

RMS: **Spain**; Year of RAR: **2016**; Proposed category: **2**

The proposal to classify forchlorfenuron as a category 2 carcinogen was based on two rat studies and one mouse study, all of 24 months' duration. In addition, a supplementary 18-month study in mice with two dose levels was performed. The RMS concluded that the compound was not carcinogenic in the rat. For mice, the RMS concluded, "it cannot be excluded that the mechanism of formation of renal tumours proposed could be relevant for humans" (RAR, Volume 1, p. 21).

3.5.1. ASSESSMENT

A 1996 rat study was performed using Crl:CD BR rats. The only information about carcinogenicity in this study consisted of the statement, "There was no evidence of a treatment-related increase in either sex" (RAR Volume 3 B.6, p. 88). According to the methods description for this study, the quoted statement refers to a statistical evaluation via pairwise comparisons (Chi-square test), without specification whether a one-sided or a two-sided test was used. Therefore, it is impossible to assess the validity of this claim. Likewise, in the 1987 study using Wistar rats, data on tumour incidences were not provided, so that the conclusion that the compound was not carcinogenic in rats cannot be scrutinized. For the 1987 mouse study using Crj:CD-1 mice, a significant association between treatment and the development of renal adenoma (both sexes) and adenocarcinoma (males only) was identified (incidences shown in RAR Volume 3 B.6, p. 98, table 6.5.2.2.-1).

3.5.2. CONCLUSION

If the statement is true that no carcinogenic effects were seen in the rat studies (which cannot be assessed, because no data were provided), then the classification of forchlorfenuron as a category 2 carcinogen (based on the significant increase in renal adenocarcinoma in male mice in one study) is correct. However, because the crucial data were not provided, this classification remains obscure.

3.6. PHOSMET

RMS: **Spain**; Year of RAR: **2017**; Proposed category: **not carcinogenic**

The assessment was based on one rat and one mouse carcinogenicity study. The RMS concluded

that phosmet is not carcinogenic.

3.6.1. ASSESSMENT

Referring to the rat study, RMS stated (RAR, Volume 3 B.6, p.101): “Although initially the study was considered not acceptable due to the high mortality observed at 24 months in all groups, in EPCO meeting for mammalian toxicology (EPCO 33, Sep 2005), the experts concluded that it was adequate for the assessment of carcinogenicity.”

This is a flawed conclusion in clear violation of OECD Guidelines 451 and 453 and OECD Guidance 116. In all the groups of this rat study, the mortality rate was higher than the 50% limit defined in these documents as acceptable, this study should not be considered valid for carcinogenicity testing. Therefore, a new study should have been required. In accordance with Regulation EC 1107/2009 and Regulation 283/2013, market approval for phosmet should have been withheld until the results of a valid carcinogenicity study in rats were available.

It is incomprehensible and completely non-transparent as to why the RMS came to the conclusion that the rat study was adequate for the assessment of carcinogenicity. In fact, in the RAR, the cut-off criterion for high mortality is cited (Volume 3 B.6, p. 103): “however the validity criteria in OECD 453 Guideline for long-term studies is ‘survival of all groups should be no less than 50% at 24 months for rats.’” On the same page, reference is made to a UK criterion: “UK competent authorities state that if survival falls below 50% after week 94 in the highest dose groups, then the study is not unduly compromised” (emphasis added). But survival at 24 months was 20%, 24%, 32%, 38% in the control, low, mid and high dose group, respectively, which shows that the OECD validity criteria are not met. The UK criterion mentioned in the RAR is also not fulfilled, because survival fell below 50% in week 92-93 for the control group and in week 87-88 for the lowest dose group.

Obviously, RMS took the applicant’s claim at face value. In the dossier (Document M-CA, Section 5, p. 54) the applicant claimed, “Although survival was lower than 50% under the experimental conditions employed, the study is not considered to be unduly compromised. Low survival is a common issue in long-term studies with Sprague-Dawley rats. Survival fell below 50% only after week 94 in the highest dose groups, i.e. during the last weeks on study.”

The applicant failed to report the unacceptably decreased survival in the control and lowest dose groups (see above) stating (emphasis added): “A **slightly** higher mortality rate was observed in control groups when compared to treated groups.” The applicant concluded: “Overall, the study is thus considered to be valid and acceptable for assessment of carcinogenicity.”

RMS Spain did not follow up on this, but referred to a “fat rat syndrome”¹² as the reason for the decreased survival rate, ignoring the recommendation given on page 4 of OECD Guidelines 451 and 453: “If animals from this strain and source are known to present problems in achieving the normally accepted criteria of survival for long-term studies” (see Guidance Document No. 116) (emphasis added).

¹² This term refers to the shorter life-span of the Sprague-Dawley rats becoming obese at late age as compared, e.g. to Wistar rats. However, many regulatory studies with Sprague-Dawley rats compliant with the required 24 month study duration. Therefore, reference to a “fat rat syndrome” is not acceptable.

The increase in liver adenoma observed in the mouse carcinogenicity study was dismissed by comparing the results with those of a single additional study (60 animals per sex) performed in the same laboratory at approximately the same time and in the same strain of mice. However, because this was only one study, it is impossible to conclude whether the outlier was the tumour incidence of this additional study or that of the control animals in the phosmet study. According to Guidance 116 (OECD 2012, p. 135) “the concurrent control group is always the most important consideration in the testing for increased tumour rates”. Therefore, the dismissal of the observed increase in liver adenoma in phosmet-treated mice is not acceptable.

3.6.2. CONCLUSION

For rat studies it is crucial to have a duration of at least 24 months, with sufficient survival to ensure that test substance-related development of tumours can be assessed properly, throughout a sufficiently long period of the animals’ lifetime. RMS ignored that this requirement was violated, accepted an invalid rat study, and concluded that no evidence exists for neoplastic effects of phosmet. This is particularly worrisome, because in addition to accepting an invalid negative study in rats, the RMS dismissed the observed increase in liver adenoma in the mouse study based on unacceptable HCD. Also, it should be noted that in the rat study, non-neoplastic changes in the liver (fatty liver) were observed more frequently in the high dose group of both male and female rats.

3.7. PIRIMICARB

RMS: **United Kingdom**; Year of RAR: **2017**; Proposed category: **2**

The proposal to classify pirimicarb as a category 2 carcinogen was based on one rat and two mouse carcinogenicity studies. Three further rat studies and one additional mouse study conducted before 1975 were considered of limited value. All these additional studies suffered from high mortality due to respiratory disease. RMS used the 2014 opinion of ECHA’s Risk Assessment Committee, which applied category 2, “based on the increased incidence of lung adenomas in female C57 black mice and the absence of mechanistic data that could dismiss the relevance of these lung adenomas for humans” (RAR Volume 1, p. 35).

3.7.1. ASSESSMENT

Tumour findings in the rat study need to be taken seriously

In the 1992 study using Alpk:ApfSD rats, increased incidences of astrocytoma were observed in both sexes and of thymomas in females.

In the “Neoplastic findings” section of the RAR, “increased incidences of .. astrocytoma” were dismissed, because they “occurred .. without statistical significance” (Volume 3 B.6, p.97). However the data presented in the same document (Table B.6.92, p. 98) contradict this claim. In the legend it is pointed out that the tumours depicted in this table were “selected based on statistically significant trend”. The statistical analysis was performed using the log rank test of Peto and Pike. The astrocytoma incidences are shown below, and, using the Cochran–Armitage trend test for our own calculations, significance could be shown for the overall data set.

Astrocytoma incidences (animals with tumours/total number of animals)

** borderline statistically significant (p=0.0580, one-sided Cochran–Armitage trend test, own calculation)*

SEX	AT STUDY TERMINATION				ALL ANIMALS (INCLUDING EARLY DEATHS)			
Dose (ppm)	0	75	250	750	0	75	250	750
Males	0/22	2/18	0/25	1/24	0/64	3/64	2/64	3/64
Females	0/37	0/32	0/33	0/36	0/64	1/64	0/64	2/64
Males and females combined	0/59	2/50	0/58	1/60	0/128	4/128	2/128	5/128*

It should be noted that the incidence in male rats might have been higher, if the mortality had been lower. Guidance 116 (OECD 2012, p. 80) states: “For a negative result to be acceptable in a rat carcinogenicity bioassay, survival in the study should ideally be no less than 50% in all groups at 24 months.” In the case of this study, survival for male rats at 104 weeks was 42%, 35%, 48%, and 46%, for the control, low, mid, and high dose group, respectively, making the study of questionable validity for risk assessment. The RMS denied an association between pirimicarb and the observed astrocytoma, because the “incidence in male and female rats was at the upper limit of the historical control range” (RAR Volume 3 B.6, p.99). Besides more general flaws (reference to the HCD range, which is discouraged by OECD Guidance 116, and using HCD accumulated over 10 years instead of the recommended 5 years), taking into consideration the lower than acceptable survival of males in the current study, HCD should not have been used at all.

Furthermore, dose-dependent increases in the incidence of uterine stromal cell sarcomas and uterine stromal cell polyps were dismissed, using the same flawed HCD as described in the preceding paragraph.

The increased incidence in thymomas was considered not treatment-related, because this tumour was seen only in females, was supposedly without statistical significance, and lacked a dose-response relationship. In the study conclusion, thymomas were not even mentioned. This tumour was observed at study termination at an incidence of 0/36, 1/32, 0/33, and 3/34 (animals with tumours/total number of animals) for the control, low, mid, and high dose group, respectively. Using the Cochran–Armitage trend test (one-sided, own calculations) an error probability of 0.034 was determined, showing statistical significance. Taking into account the late occurrence of this tumour and therefore the relatively low number of animals available for assessment, it can be argued that a dose-response relationship exists even though no thymomas were observed in the mid-dose group. Considering the late occurrence of this tumour type and the reduced survival rate in males (below 50% at study termination),

the claim that this tumour was observed only in one sex is questionable. In summary, none of the arguments used to dismiss the observation of an increased incidence in thymomas withstands a thorough examination.

Turning OECD Guidance 116 upside down

For the study using Swiss-derived mice, the RMS concluded: “In this study there is evidence of a carcinogenic potential for pirimicarb but with the limitations in the historical control data and reduced survival this data alone is not sufficient to conclude on carcinogenicity” (emphasis added, RAR Volume 3 B.6, p.107). Arguing that the reduced survival (mainly in high-dose females) in the current study is an obstacle to concluding on the carcinogenic potential of pirimicarb turns the considerations in OECD guidance 116 upside down. For pirimicarb increased tumour incidences were observed in spite of reduced survival which can be expected to be even more pronounced when survival is not affected. With good reason, the OECD states that survival below 50% after an 18 months’ duration in a mouse study is considered an obstacle “for negative results to be acceptable” (emphasis added, OECD 2012, p. 80). Also, it is not clear what is meant with “the limitations in the historical control data”. Data from six other studies actually confirm the findings of the present study. In contrast to the abuse of HCD in the RARs for other pesticides, the time span of the HCD (compiled from studies between 1977 and 1983, while the study itself was conducted from 1977-1979) is almost compliant with the restrictions stipulated by OECD (2012). The RAR mentions an increased incidence of pulmonary adenomas, liver tumours, mammary gland adenocarcinomas, and papillary cystadenomas of the ovary (Volume 3 B.6, pp. 104-107), findings supported by HCD. Nevertheless, the RMS described the increase in multiple tumour types as only “equivocal evidence of a carcinogenic potential”.

The RMS considered the increase in liver tumours as “limited evidence of carcinogenic potential”, because of lack of “a clear dose response” although in some instances even the range of HCD was exceeded. It should be noticed that dose spacing was not even in this study, with a dose increase by a factor of 2 from the low to the mid dose and by a factor of 4 from the mid to the high dose which can obscure the dose-response relationship (see table below). It seems that this was ignored by RMS (as well as ECHA’s Risk Assessment Committee). Furthermore, a monotonic dose-response should not be assumed to be a prerequisite for judging the carcinogenic effect as real, because inter-individual biological variability can play a role. Using the Cochran-Armitage trend test (own calculations) revealed significant increases in malignant liver tumours for both males and females (see table below).

Mammary gland tumours

The RMS considered the increased incidence of mammary gland adenocarcinoma as limited evidence, because the top dose exceeded the maximum tolerated dose (MTD, 10% decrease in body weight gain, see OECD 2012, p.53). However, it should be kept in mind that the “MTD is often used in the assessment of a chronic toxicity or a carcinogenicity study to decide whether the top dose tested was adequate to give confidence in a negative result” – i.e. a finding that there is no carcinogenic effect (emphasis added, OECD 2012,

p.53). Here, the RMS discusses positive findings (i.e. that there is a carcinogenic effect) as related to exceeding the MTD. But the main concern of a reduced body weight gain is that it could mask carcinogenic effects, because a negative correlation between body weight gain and tumour incidence has repeatedly been described.

In addition, using the data presented in the RAR and following a common approach, we combined the incidences of adenoma and adenocarcinoma tumours and assessed them with the exclusion of the high dose group that exceeded the MTD. As shown in the table below, even then, the increase was still statistically significant.

Finally, concerning this study using Swiss mice, the RMS acknowledged an increase in pulmonary adenomas for the top dose in males and the top and the mid dose in females (see table below). This is of particular interest, because an increased incidence in pulmonary adenomas was also seen in the second mouse study using C57BL/10JfCD-1 Alpk mice. Importantly, the MTD was not exceeded in this second mouse study (top dose: 700 ppm). An increased incidence of pulmonary adenoma was seen in both males and females. The study was of shorter duration (80 weeks as compared to 94 weeks in the study using Swiss mice), thus progression to malignancy with longer study duration could be possible. In summary, lung tumours associated with the administration of pirimicarb were seen in both mouse studies.

Tumour incidences in Swiss-derived mice (animals with tumours/total number of animals)*

SEX	MALES				FEMALES			
Dose (ppm)	0	200	400	1600	0	200	400	1600
Liver, malignant, nodule-type B	10/117	13/59	8/59	17/58 ^a	2/117	3/54	3/55	5/54 ^b
Mammary gland adenoma	-	-	-	-	0/114	0/57	2/57	0/57
Mammary gland adenocarcinoma	-	-	-	-	0/114	1/57	1/57	4/57
Mammary gland tumours combined	-	-	-	-	0/114	1/57	3/57 ^c	4/57
Papillary cystadenoma	-	-	-	-	0/110	1/58	3/55	3/56 ^d
Pulmonary adenoma	17/119	8/60	9/59	17/58 ^e	13/118	9/59	11/59	18/59 ^f
Pulmonary carcinoma	1/119	0/59	0/59	1/58	1/118	0/59	1/59	0/59

* two untreated control groups were used in this study which were combined here for the Cochran-Armitage trend test (one-sided)

^a significant $p < 0.001$

^b significant $p = 0.0298$

^c significant (excluding the high dose group) $p = 0.0188$

^d significant $p = 0.0340$

^e significant $p = 0.0039$

^f significant $p < 0.001$

3.7.2. CONCLUSION

According to the available data, RMS falsely classified pirimicarb as a category 2 carcinogen instead of classifying it as category 1B.

Malignant tumours were seen in the rat study and in one of the two mouse studies. In

addition, a significant increase in a benign tumour (pulmonary adenoma), which was also seen in the first mouse study, was demonstrated for males and females in the second mouse study. The tumours detected in the rat study were dismissed by the RMS with an invalid reference to HCD, as well as an alleged lack of statistical significance, which proved to be untrue. The malignant tumours seen in one of the two mouse studies were dismissed, because allegedly they were restricted to the top dose, which exceeded the MTD limit as defined by OECD guidance 116. However, we have shown that an increase in mammary tumours was statistically significant, even when the top dose was excluded.

According to the applicable legislation, a compound qualifies as a category 1B carcinogen, if an increased incidence was seen “of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species” (Regulation (EC) 1272/2008, p. 105). These criteria are fulfilled for pirimicarb.

3.8. THIACTOPRID

RMS: **United Kingdom**; Year of RAR: **2017**; Proposed category: **2**

The proposal to classify thiacloprid as a category 2 carcinogen was based on one rat and two mouse carcinogenicity studies. In addition, a number of mechanistic studies submitted by the applicant were taken into consideration

3.8.1. ASSESSMENT

According to the RAR, statistically significant increases in tumours were seen in the study using Wistar rats, as well as in the study using B6C3F1 mice. These increases related to uterine adenocarcinoma in female rats, to thyroid follicular cell adenoma in male rats, and to benign ovarian luteoma in female mice. Concerning the uterine adenocarcinomas in rats, the applicant claimed that a “long-term perturbation of sex steroid hormones .. may have been implicated in the tumour induction” (Volume 1, p. 30), but the RMS concluded: “However, there is no evidence to support this claim and so the uterine tumours in rats are regarded as being of relevance to humans” (Volume 1, p. 30)¹³. Likewise the RMS concluded for the benign tumours in the thyroid in rats and the ovary in mice that human relevance cannot be excluded.

For details – summarised in the tables below – RMS referred to the assessment performed by ECHA’s Risk Assessment Committee (RAC).

¹³ Under certain conditions a hormonal mode of action (as claimed here by the applicant) may imply a dose–response relationship for eliciting tumours, which can lead to the conclusion that the tumours seen are not relevant for humans, if they occur only at high doses which humans are not exposed to.

Tumour incidences in rats according to RAC, 2015 (animals with tumours/total number of animals)

p-values below incidences indicate statistical significance in Cochran-Armitage trend test (one-sided)

* significant in pairwise comparison

§ finding supported by historical control data

TUMOUR TYPE	DOSE (PPM) SEX	0	25	50	500	1000#
Thyroid follicular cell adenoma	Male	0/50	0/50	1/50	5/50*	8/49*,§ P<0.001
Uterine malignant adenocarcinoma	Female	6/50	3/50	3/50	14/50	18/50§ P<0.001
Uterine benign adenoma	Female	0/50	0/50	1/50	1/50	2/50 P=0.0548
Uterine malignant adenosquamous carcinoma	Female	0/50	0/50	0/50	1/50	2/50 P=0.0314

Tumour incidences in female B6C3F1 mice according to CLH Report, 2019 (animals with tumours/total number of animals)

* statistically significant using Cochran-Armitage trend test (one-sided) p=0.0090

§ finding supported by historical control data

TUMOUR TYPE	0	30	1250	2500
Benign ovarian luteoma	0/47	1/48	5/49	5/47*,§
Malignant luteoma	0/47	0/48	0/49	1/47

Contrary to the statement in the CLH Report (2009) that the increase in the ovarian luteoma was not statistically significant, there was a clear statistical significance for this tumour type (even if the two-sided test were used). In addition, progression to malignancy was shown for one female of the high-dose group.

ECHA and EFSA agreed that a category 1B classification could be considered, but although a definite mode of action was not fully demonstrated, a hormonal imbalance was accepted as plausible. RAC concluded that thiacloprid was not genotoxic. Because of this and based on the accepted hormonal mode of action, thiacloprid was classified as a category 2 carcinogen.

3.8.2. CONCLUSION

Thiacloprid should be classified as a category 1B carcinogen instead of category 2. This conclusion is based on statistically significant increases of tumour incidences seen in both the rat and the mouse study and the lack of a mode of action that could justify any claim that the tumours seen are irrelevant for humans. In contrast, ECHA and EFSA, while describing the mode of action considerations provided by the applicant as hypothetical, in the end accepted them as “proof” of lack of carcinogenicity and allocated a category 2 classification.

4. GENERAL CONCLUSION

The claim that glyphosate does not pose a carcinogenic hazard was based on a flawed and distorted use by the authorities of their own and other relevant guidelines and guidance documents (Clausing et al. 2018). This observation motivated this report, with the aim of investigating whether such a flawed application of guidelines and guidance documents occurred more often. For this purpose the RARs and related documents of eight pesticides were reviewed, for which the draft RARs were published after 2015. Seven of them were classified as carcinogenic category 2 according to EU directive 1272/2008 and one was classified as non-carcinogenic.

Two pesticides (diuron and chlorotalonil), while currently being classified as category 2 carcinogens in the EU pesticide database*, were proposed to be classified as category 1B carcinogens. As we agreed with this classification, we did not include the details of the results from the RARs for these two pesticides in this report. The results for the other eight pesticides are summarised in the table below.

*See <http://bit.ly/2Bi5RcX>

Summary of the conclusions drawn from reviewing the RARs.

PESTICIDE	CATEGORY IN RAR*	AGREED	INSUFFICIENT DETAIL	DISAGREED
Captan	2		X	
Chlorotalonil	1B	X		
Chlorpropham	2		X	
Dimoxystrobin	2		X	
Diuron	1B	X		
Folpet	2			X
Forchlorfenuron	2	X		
Phosmet	not carcinogenic			X
Pirimicarb	2			X
Thiacloprid	2			X

*See Appendix I

For four out of ten compounds, our conclusion was different from that of the respective RMS. Based on the available data, the strict application of EU and OECD guidelines and guidance documents resulted in a category 1B carcinogenicity classification for folpet, pirimicarb and thiacloprid. Data provided by the applicant for phosmet were insufficient to draw a conclusion on carcinogenicity. However, instead of requiring adequate data, RMS ignored this important data gap and concluded that phosmet is not carcinogenic.

For another three pesticides, the details provided in the RARs were insufficient to make a judgment about the authorities' classification. This is a strong indication that ideally, the public should have full access to the study reports (cf. Case T 329/17 of the European Court of Justice¹⁴), or that otherwise, much more detail needs to be provided in the RARs, resulting in a strong improvement of their quality.

Only for three RARs did we draw a similar conclusion as the RMS.

Flawed use of HCD played a key role in “downgrading” carcinogenicity classifications by the authorities.

The following recommendations result from the current analysis:

1. There is an urgent need to improve the use of applicable Guidelines and Guidance documents by the authorities. Neglect of, and/or flawed application of, these Guidelines/Guidance documents resulted in an insufficient assessment of the carcinogenic hazard for four out of ten compounds. This is not acceptable.
2. The classifications of folpet, pirimicarb and thiacloprid need to be upgraded to category 1B unless, based on a state-of-the-art weight of evidence evaluation, evidence to the contrary is transparently demonstrated so that the precautionary principle does not apply.
3. The market approval for phosmet must be withheld until appropriate data, compliant with applicable legislation and guidance documents, are provided by the applicant and are subjected to a satisfactory review by the authorities.
4. Public access to the full study reports needs to be granted or, as long as this access is not available, the level of detail of the RARs needs to be significantly increased. With regard to pesticides analysed in this report, this issue relates to captan, chlorpropham, and dimoxystrobin, for which it was impossible to properly scrutinize the authorities' assessment.

¹⁴ https://justicepesticides.org/en/juridic_case/hautala-and-others-v-efsa/

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6. ACRONYMS

BfR	Bundesinstitut für Risikobewertung ([German] Federal Institute for Risk Assessment)
CLH	Harmonised Classification and Labelling
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EU	European Union
HCD	Historical Control Data
IARC	International Agency for Research on Cancer
MTD	Maximum Tolerated Dose
OECD	Organisation for Economic Co-operation and Development
RAC	Risk Assessment Committee (of ECHA)
RAR	Renewal Assessment Report
RMS	Rapporteur Member State
UK	United Kingdom

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APPENDIX:

CARCINOGENICITY CATEGORIES EXPLAINED

According to Regulation (EC) No 1272/2008, three categories apply:

Category 1A:

Known to have carcinogenic potential for humans, classification is largely based on human evidence

Category 1B:

Presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.

The classification in Category 1A and 1B is based on strength of evidence together with additional considerations.

Such evidence may be derived from

- human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
- animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

CATEGORY 2:

Suspected human carcinogens

The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

The **Pesticide Action Network Germany (PAN Germany)** is a nongovernmental organisation informing about the negative consequences of pesticide use and promoting environment-friendly and socially fair alternatives. PAN Germany is part of the PAN International network. Our work comprises critical analyses of pesticides and their use, policy advice practical advice for farmers and consumers. <https://pan-germany.org/>

The **Health and Environment Alliance (HEAL)** is the leading not-for-profit organisation addressing how the environment affects human health in the European Union (EU) and beyond. HEAL works to shape laws and policies that promote planetary and human health and protect those most affected by pollution, and raise awareness on the benefits of environmental action for health.

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