1. CLH Report

0-General			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

1-Identity of the substance			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

2-Proposed Harmonised Classification and Labelling			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
1	2.1 Table 6	**BASF**: We strongly disagree with the dossier submitters proposals for Repr. 1B H360FD. *See comments in the section 10-Evaluation of Health hazards*	

3-History of the previous classification and labelling			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

4-Justification that action is needed at community level			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
1	§ "Change in existing entry due to new data" p5	**BASF**: We strongly disagree with the dossier submitters proposals for Repr. 1B H360FD. *See comments in the section 10-Evaluation of Health hazards*	

5-Identified uses			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

6-Data sources			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

7-Physicochemical properties			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

8-Evaluation of Physical Hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

9-Toxicokinetics			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		BASF: No comments.	

10-Evaluation of Health hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
1	10.8.1 Table 10 p12 and 10.8.2 Summary	**BASF**: We do not agree with the NOAEL for fertility/sexual function based in shortened gestation length. *See comment (1) of annex 1 of CLH report*. We consider that the fertility NOAEL is 1600 ppm.	
2	10.8.3 p13	**BASF**: In the 2-generation study, no statistical relevant effects was observed on gestation length using Dunnett test which is the statistical method normally used in this kind of study now (like in the extended 1-G study). The very slight decrease observed in the extended 1-generation is not considered to be toxicologically relevant S*ee comment (1) of the annex 1.*	
3	10.8.3 p14 classification proposal.	**BASF**: The classification proposal for fertility is clearly disproportionate in relation with the observed effects: doubtful effects on dog prostate and gestation length. A position paper on classification was sent to the RMS during the AIR 3 evaluation of dimethomorph (BASF DocID 2017/1033551). Please consider this paper for the classification proposal.	

10-Evaluation of Health hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
4	10.8.4 table 12 p14-15	**BASF**: Developmental effects: AGD/AGI are statistically significant only at the high dose. For seminal vesicle and prostate, sight weight changes were not accompanied with histopathological finding and were observed concurrently with general toxicity (delayed growth). *See comments (2), (3) of annex 1 of CLH report.*	
5	10.8.5 p17	**BASF**: For effects in AGD/AGI, the preferred approach should be the use of litter as the experimental unit. Therefore, changes are only observed in the high dose. For this end point NOAEL should be set at 800 ppm based on litter-based data.	
6	10.8.5 p17	**BASF**: Dimethomorph shows slight anti-androgenic properties at high doses in vitro. A full ED assessment has been performed and is available *See comment (5) of annex 1*	

10-Evaluation of Health hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
7	10.8.7 p19	**BASF**: We fully disagree with the following statement in the CLH report "It is considered likely that the anti-androgenic mechanism will also induce other adverse effects not observed in standard studies. This includes effects on the brain by in utero exposure to anti-androgens such as phthalates (Miodovnik, 2014)." Very potent anti-androgen substances as Vinclozoline and Flutamide did not induce effects in the brain. Such a conclusion for dimethomorph is just a supposition.	
8	10.8.7 p 19 conclusion.	**BASF**: We strongly disagree with the classification proposal Repr. 1B for developmental effects.	Slight effects are observed in the high dose only on AGD/AGI and sexual maturation. Effects seen on organ weight (seminal vesicles and prostate were observed without histopathological correlate. No effects were observed in the developmental studies in rats and in rabbits. The slight effects observed in the extended 1-generation on sexual parameters in males could be explained by the slight anti-androgenic properties of dimethomorph. However other parameter like nipple retention, sperm parameters, hormonal levels, typical for anti-androgens were not observed. The slight delay in general pup development and the slight effects observed only in this study do not trigger a classification 1B, which in this case is clearly disproportionate. Please take into consideration BASF position paper on classification (BASF DocID 2017/1033551) which compare harmonized classification of 226 substances for which some of these effects were observed. **According to ECHA decisions, no substances were classified in Cat 1B for effects on anogenital distance or preputial separation only.**

10-Evaluation of Health hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
9	10.10.1 p 28	**BASF: STOT RE 2 was not proposed in the CLH report, we agree with that.** **In the RAR and during the praper meeting a STOT RE 2 was proposed, we strongly disagree with this proposal.**	For the 90-day study the severity grading was not reported. For the one-year study, the severity of prostatic interstitial fibrosis was slightly increased as was indicated by mean severity* of 1.5, 2.0, 2.0 and 2.5 at 0, 150, 450 and 1350 ppm, respectively. It should be noted that "**The light microscope appearance of the prostates all lay within the normal range for young laboratory dogs**. There was an apparent increase in the proportion of interstitial fibrosis (including smooth muscle) as the group dosages increased. However, some of this effect was probably due to a slightly different level of section and **in none of the animals was the degree of interstitial tissue of a pathological nature**." (Excerpt of the discussion in the results section of the report (Page 72)) We disagree with the classification proposal of the RMS and EFSA praper peer review. There is a significant reduction in prostate weight after 52 weeks and 13 weeks of treatment but no clear histopathological correlation could be observed. Based only on prostate weight, STOT RE cat. 2 is not warranted. Moreover, the thresholds for classification STOT RE 2 based on allometric extrapolation and adjustments for study duration for dogs are 100 and 25 mg/kg bw/d for a 90-day and 1-y study respectively. If the threshold is reached for the 90-d study, it is not the case for the 1-y study which is more relevant for classification.

11-Evaluation of Environmental hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

12-Evaluation of additional hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

13-Additional Labelling			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

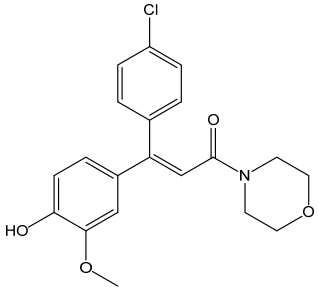
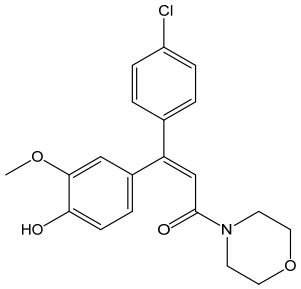
14-References			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

2. Annex I to the CLH Report

0-General			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

1-Physical Hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations

2-Toxicokinetics			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
1	Chapter 2.1.6, Study 6 p.18, Table 14	**BASF**: In the table presenting the data for the high dose group, the values given in the last line for "total" are wrong, these are the ones from the low dose group. The correct values are For tmax: male 85.79%, female 80.98% For 24 h: male 26.29%, 30.37% For 168 h: male 0.14%, female 0.10%.	
2	Chapter 2.1.7 Study 7 (new) pp.44 to 50, Figure 1	**BASF**: Figure 1 presents the metabolic pathway which is separated into several figures representing different metabolic steps. From p. 44 onwards through p.50, the last text line on these pages (below the figure) belongs to the figure on the succeeding pages as a title. These text lines should be moved to the next pages, respectively.	

2-Toxicokinetics			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
3	Chapter 2.1.7 Study 7 (new) p.52, Table 24	**BASF**: The structures for metabolites M550F007E and M550F007Z (both have molecular weight 373) are missing in the table. This was corrected in the final version of the RAR for Dimethomorph. We kindly ask to add the structures to the table: M550F007E:  M550F007Z: 	

2-Toxicokinetics			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
4	Chapter 2.1.8 In vitro metabolism study p. 83 Conclusion	*"It was however noted in the HPLC chromatograms that a large peak was present in the rat at 180 minutes which was not present in the dog or human hepatocyte samples."* **BASF**: We would like to point out, that (by superposing the chromatograms) it can be seen that this peak is also present in the chromatograms of dog and human hepatocytes at the same retention time, however in much smaller amounts. We therefore believe that this peak (metabolite) is not unique in rat, but also present in the other tested species. It was however not elucidated since this in vitro study was designed to investigate the occurrence of unique human specific metabolites (none such were found in this study). No elucidation of all main peaks occurring in the chromatograms was intended, all the more since for the rat a new in vivo study is available with extensive elucidation of all structures occurring in amounts above 1% dose. Thus, we believe that the elucidation of the nature of this peak from rat hepatocytes is not relevant within this study scope.	

3-Health hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
1	B.6.6.1.2 p94-95	**BASF**: We do not agree on the derived NOAEL for fertility and reproductive function. The slight decrease in gestation length at the high dose is not considered to be a treatment related effect. Therefore, the reproductive NOAEL of this study should be set at 144 mg/kg bw/d instead.	In the extended 1-generation study, the mean duration of gestation values varied between 22.0 and 22.3 days in control, 300 and 800 ppm test groups without any relation to dosing. The mean duration of gestation was statistically significantly decreased in comparison to the concurrent control group in the 1600 ppm test group ($p \leq 0.01$). The value (21.4 days) was marginally below the historical control range (21.5 to 22.3 days), while the concurrent control (22.3 days) was at the upper range of the historical control data. When compared to individual data, gestation duration is between 21 and 23 days (as it was also observed in the 2-generation study). Moreover, for the gestation length the intrinsic vagueness of the measurement has to be considered. Gestation length is measured from the detection of sperm after each mating to the day of parturition. For detection of sperm this means the female is placed in the cage of the male partner at 16:00 pm and the next check for sperm is taking place around 7.00-9.00 am of the following morning, thus, mating may have taken place within a time span of 17-19 hours. Similarly, animals are checked for parturition twice daily on weekdays and the day of parturition is given as 24h period from about 15:00 of one day until about 15:00 of the following day, again adding an uncertainty of about 12 hours. Considering the low accuracy of the measurement, the marginal difference of 0.1 day compared to the historical control range observed for the high dose can be considered as very minor. Based on the slight difference between high dose group and historical controls and taking into account that concurrent controls were in the upper range of the historical controls and, moreover, based on the fact that no effects were seen in the 2-generation study with the appropriate statistical method, this slight decrease in duration length can be considered as a chance finding. According to the study director, as this effect didn´t go along with any adverse effects on developmental status and well-being of the newborns, it is considered to be non-adverse and of no toxicological relevance.

3-Health hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
			Reduced gestation length cannot be linked to the overall toxicological profile of dimethomorph. Considering a potential MoA, reduced gestation length cannot be linked to anti-androgenic properties: very potent anti-androgens (e.g. Vinclozoline and Flutamide) did not show any effects on pregnancy duration. In the absence of other potential MoA, it can be confirmed that this effect is not relevant.
2	B.6.6.1.2 p119	**BASF**: Please note that the historical controls for anogenital distance (AGD) should not include the controls of the study itself. In this case historical controls data from 16 studies carried out between 2011 to 2015 in Wistar rats are 2.99-3.13 mm. Therefore, it is clear that AGD in the control group of this study is outside the historical control range data. Which can have an impact in the statistical significance of the effects seen at higher doses.	
3	B.6.6.1.2 p 142	**BASF**: Effects on seminal vesicles: please note the decrease in seminal weight observed in test groups 12 and 13 are observed without any histopathological finding and concurrently with significant decrease in terminal body weight. Therefore, we consider that this is not an adverse effect.	
4	B.6.6.1.2 p 144	**BASF**: We agree that effects on testes weight is considered to be unlikely treatment related. HCD on testes weight were provided to the RMS, please consider to add them in the CLH report in table 63.	Historical control data for testes weight[1] (mean and range) 3.632 (3.554-3.781) 1.049 (0.986-1.124 [1] Historical control data for testes weight in cohort 1b in three extended one-generation studies carried out in the same lab with the same strain between 01 Jan 2010 – 21 Jun 2018.

3-Health hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
5	3.10.3	**BASF**: Some studies demonstrate that dimethomorph could act on androgen receptors at high doses in vitro (antagonist). In the framework of the AIR3 process, renewal of dimethomorph a full ED assessment was performed according the the ECHA/EFSA ED guidance document and transmitted to the RMS, EFSA and ECHA. The results are reported in the RMS revised RAR. Please consider to add this assessment for completeness. BASF doc ID 2018/1202679	
6	3.12.1.11 p 213	**BASF**: Acceptability of the study. Please consider that RMS consider that "The study was set up as a chronic toxicity study using 20 animals/sex/dose. While neoplastic findings were also evaluated in this study considering the lower number of animals this evaluation is considered to be of lower reliability compared to the full carcinogenicity study in rats"	
7	3.12.1.11 p218 Table 121	**BASF**: Please consider to add the following sentence "The neoplastic findings in the testes of the chronic study are discussed together with the findings of the carcinogenicity study."	
8	3.12.1.11 p218 Conclusion	**BASF**: The NOAEL of the study is 11.9 mg/kg bw/d. Please correct	
9	3.12.1.12 p224 conclusion	The NOAEL of the study is 11.3 mg/kg bw/d. Please correct	

4-Environmental hazards			
No.	Column 1 Reference to assessment report	Column 2 Comment (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
1	CLH report, 11.6.3, p. 42	**BASF:** The CLH report states that the algal study by Jatzek (2001) on *Pseudokirchneriella subcapitata* according to OECD TG 201 is not reliable because actual mean measured concentrations were not presented in the RAR and a NOEC cannot be determined. It should be note that the algal study by Jatzek (2001) is considered acceptable by the RMS in the revised RAR from January 2019. Mean measured concentrations are reported and EC_{50} and NOEC values are re-calculated for growth rate and yield based on geometric mean measured concentrations (E_rC_{50} = 65.6 mg/L, $NOEC_r$ = 5.4 mg/L; E_yC_{50} = 26.5 mg/L, $NOEC_y$ = 5.4 mg/L). Furthermore, it is confirmed that the study meets all validity criteria according to the current version of OECD TG 201. For details please refer to the revised RAR Volume 3CA, B9, p. 167-170). Accordingly, the algal study by Jatzek (2001) is reliable and can be used for classification purposes. Please consider the additional information on the algal study by Jatzek (2001) provided in the revised RAR.	