Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Terbuthylazine (ISO); N-tert-butyl-6-chloro-N'-ethyl-1,3,5-triazine-2,4-diamine

EC Number: 227-637-9
CAS Number: 5915-41-3

CLH-O-0000001412-86-66/F

Adopted

05 June 2015

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON TERBUTHYLAZINE (ISO); N-TERT-BUTYL-6-CHLORO-N'-ETHYL-1,3,5-TRIAZINE-2,4-DIAMINE
COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: **Terbuthylazine (ISO); N-tert-butyl-6-chloro-N'-ethyl-1,3,5-triazine-2,4-diamine**
CAS Number: **5915-41-3**
EC Number: **227-637-9**
Dossier submitter: **United Kingdom**

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2014	Italy	Federchimica/Agrofarma	Industry or trade association	1
Comment received				
The classification proposed by RMS (UK) for terbuthylazine is "carcinogenic category 2/ H351 / R40 / suspected of causing cancer". The reason for this classification proposal originates from an observed increased incidence of mammary adenocarcinomas in the Wistar rat strain. Similar increased incidences of mammary tumours were observed in the Sprague-Dawley rats administered terbuthylazine. However trough specific mechanistic studies with other compounds of chlorotriazines family it was concluded that these findings are the results of a well-established specific mode of action which is NOT RELEVANT TO HUMANS. Despite the companies interested believe the available dataset is sufficient to demonstrate that such classification proposal is not warranted for terbuthylazine, they have been generating additional experimental data in both rat strain to further demonstrate that the mode of action of terbuthylazine is not relevant for humans. This additional data, along with other supporting evidence, are made available by the companies for consideration during the ECHA classification process. Therefore Federchimica/Agrofarma ask to ECHA to evaluate and taken into consideration in a comprehensive way all the data now available that show that the mode of action of terbuthylazine is not relevant for humans and therefore classification "carcinogenic category 2/ H351 / R40 / suspected of causing cancer" is not appropriate.				
Dossier Submitter's Response				
Thank you for your comment. See our response to comment 7.				
RAC's response				
Noted. See response to comment number 7.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	2
Comment received				
Syngenta considers that the information provided in table 7a page 14 should not be taken				

into consideration for the classification of terbuthylazine for the reasons mentioned in the attached confidential document.

(ECHA note: The following confidential attachment was submitted with the comment above. [Attachment 1]. The attachment concerns the impurity levels.)

CONFIDENTIAL Statement SYNGENTA terbuthylazine classification

Dossier Submitter's Response

Thank you for your comments. We note the changes to the production process and the lower levels of impurities in the technical material. The proposed classification for terbuthylazine is based on available data on terbuthylazine itself and not on the presence of the impurities. Should classified impurities be present in the technical material at or above levels relevant for classification, they should be taken into account.

RAC's response

RAC supports the response of the DS.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		MemberState	3

Comment received

MS-FR agrees with the classification proposed for acute toxicity and STOT RE. MS-FR does not support the classification for carcinogenicity.
MS-FR agrees with the classification proposal regarding environmental hazard. We also agree with the proposed values for the acute and chronic M factors.

Dossier Submitter's Response

Thank you for your comments. Classification was based on residual concern for mammary gland tumours in Wistar rats due to the limited data available supporting the assertion chlorotriazines have a comparable effect on the hypothalamic-pituitary-ovary axis in Wistar rats as they have in Sprague-Dawley rats. During the public consultation, Industry have submitted additional studies that add weight to this assertion and which the UK consider should be taken into account by RAC during the decision making process. See full response to comment 7.

RAC's response

RAC agrees with the comments by FR and supports those of the DS.

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2014	Germany		MemberState	4

Comment received

The DE CA supports the proposal for harmonized classification and labeling of the UK CA for Terbuthylazine.

Dossier Submitter's Response

Thank you. However, further information is now available which supports the argument that the mammary tumours in Wistar rats occur via the same mode of action as those in Sprague-Dawley rats which have been dismissed as not relevant for humans.

RAC's response

RAC supports the comments by the DS. See response to comment number 7.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number

05.12.2014	Belgium		MemberState	5
Comment received				
The tumours reported are only observed in the Sprague-Dawley rats. The incidence of fibroadenoma, adenoma or carcinoma observed in the mammary glands are within the HCD and are not significantly increased. The carcinoma (14 vs 4 in the control) are significantly increased at the high dose (750ppm) but are still within the HCD (range 4/80-17/80) (Gfeller 1983a). The Leydig cell tumours are also reported and are increasing at 750ppm (12,5% vs 3,8% in the control) but are observed in the top dose exceeding the MTD (59% of the control for the BW). It is known that the mammary gland tumours in Sprague-Dawley rats occur at a high spontaneous rate. For the Leydig cell tumours, the incidence is occurring at dose exceeding the MTD and can be considered as unrelated to the intrinsic potential of the substance itself to cause tumours. Therefore, we consider that the classification Cat. 2 for carcinogenicity is not appropriate and we support a non-classification.				
Dossier Submitter's Response				
Thank you for your comment. Mammary tumours were observed in both Wistar and Sprague Dawley rats. The tumours in Sprague Dawley rats were dismissed due to the similarities between terbuthylazine and Atrazine. Residual concern remained for the Wistar rat tumours due to only limited data being available at that time showing chlorotriazines have a comparable effect on the hypothalamic-pituitary-ovary axis in Wistar rats as in Sprague-Dawley rats. During the consultation, industry submitted additional studies that add weight to this assertion and which the UK now consider should be taken into account by RAC during the decision making process.				
RAC's response				
RAC supports the comments from both BE and the DS.				

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2014	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	6
Comment received				
Please refer to the attached position statement made on behalf of both Syngenta and Oxon companies. The notifiers agree with the dossier submitter that it can be considered there were no treatment related carcinogenic effects in Leydig cells of rats of potential concern to human health and that the apparent increase in the benign Leydig cell tumours in male Sprague-Dawley rats can be dismissed as an artefact of the increased survival rate of animals in the high dose group as compared to the controls *(ECHA note: The following attachment was submitted with the comment above. [Attachment 2])* *Terbuthylazine - Position on Leydig Cell Tumours in Sprague Dawley-derived rats*				
Dossier Submitter's Response				
Thanks for agreeing with our conclusions with regards to Leydig cell tumours				
RAC's response				
RAC agrees with the conclusions proposed.				

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2014	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	7

Comment received

Please refer to the attached position statement made on behalf of both Syngenta and Oxon companies (notifiers). Two new studies have been conducted in 2014 for which OECD summaries are available. These OECD summaries are being submitted as public attachment (Handa, 2014 and Stump, 2014). The notifiers now consider that enough information is available to establish that the mode of action which has been demonstrated in the Sprague Dawley rat for chlorotriazines is also operative in the Wistar rat. As such, the notifiers consider that the Carc 2; H351 classification is not warranted for terbuthylazine. Both final study reports are available and can be submitted upon request.

(ECHA note: The following attachments were submitted with the above comment [Attachments 3, 4 and 5])

- *Stump DG, 2014. Terbuthylazine: A study of the effects of 4 days of exposure on the estrogen-induced luteinizing hormone (LH) surge in ovariectomized Sprague Dawley rats. (summary)*
- *Handa R, 2014. Terbuthylazine: An oral (gavage) study to assess the effects on the hormone-induced luteinizing hormone surge in ovariectomized female Wistar rats. (summary)*
- *Position on Mammary Tumours in Rats*

Dossier Submitter's Response

Thank you for these documents. The UK has reviewed the results of these non-standard studies and agrees that terbuthylazine has a similar effect on the LH surge as atrazine in both Sprague Dawley and Wistar rats. These studies support the decision of the UK to dismiss the mammary gland tumours in Sprague-Dawley rats and add weight to the argument that the tumours in Wistar rats occur by a mechanism not relevant to humans. Therefore, full consideration should be given to these new data.

RAC's response

RAC agrees that the new data from studies conducted with terbuthylazine and atrazine in both ovariectomized Sprague Dawley and Han Wistar rats, support a common mechanism of action involving the perturbation of the hypothalamic-pituitary-ovary axis. Terbuthylazine has a similar effect on the LH surge as atrazine in both Sprague Dawley and Wistar rats. The mode of action for chlorotriazine-induced mammary tumours in female Sprague Dawley rats can now be extrapolated to Han Wistar rats, and is based on their shared sensitivity to chlorotriazine-mediated suppression of the LH surge. Sufficient data exists to consider this mode of action to be not relevant to humans.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2014	United States		Individual	8

Comment received

These comments are presented on behalf of James W. Simpkins, Ph.D., Robert J. Handa, Ph.D., and myself. We are independent scientists who were asked by Syngenta to review the original study reports relevant to possible reproductive toxicity and carcinogenicity of terbuthylazine. Based upon our review we conclude that the identification of terbuthylazine as either a reproductive toxicant or a carcinogen is not consistent with the scientific data.

Chronic exposure of rats to terbuthylazine resulted in an increased incidence of mammary tumors at daily dose levels of 7.6 mg/kg bw in an Oxon study and 10.7 mg/kg bw in a Syngenta study. In this regard, terbuthylazine is similar to atrazine, another chlorotriazine herbicide that is structurally different by only 1 carbon in one of the side chains of the molecule (an isopropyl in place of a *tert*-butyl group). The effect of atrazine on mammary tumors in the rat is due to prolonged exposure to endogenous estrogen and prolactin as a

consequence of suppression of the luteinizing hormone (LH) surge and consequent anovulation (persistence of estrogen production by follicles) in aging animals. The suppression of the LH surge by atrazine consists of a decrease in the amplitude and the area under the time–concentration curve of the surge. Dr. HandaT has studied atrazine and terbuthylazine in our laboratories and have shown that at equimolar exposure levels, these two chlorotriazines have the same effect on the LH surge in estradiol and progesterone-primed ovariectomized rats. The mode of action of terbuthylazine and atrazine in producing mammary tumors is not relevant to women, because the preovulatory LH surge mechanism is different in humans and other primates compared to rodents. Rodent ovulation occurs in response to a brief LH surge during a critical 2-hour period on the afternoon of proestrus when gonadotropin-releasing hormone (GnRH) surges in response to increasing plasma estrogen levels. The role of the rodent GnRH in ovulation is deterministic. By contrast, ovulation in women occurs in the absence of a GnRH surge, in response to an estrogen-stimulated increase in GnRH/LH pulsatile release from the pituitary lasting for 2–3 days. The role of GnRH is permissive with respect to ovulation in women, allowing the pituitary gland to respond to circulating estrogen. In contrast in rodents, the GnRH surge is deterministic in the timing of the LH surge. Aging rats lose the ability to mount an LH surge, but aging women retain the ability to produce GnRH and pituitary gonadotropins. The ovary in the aging woman becomes unresponsive due to the lack of responsive follicles, and estrogen production falls, whereas aging rat ovaries continue to produce estrogen. Therefore, mammary tumor production in aging rats in response to the chlorotriazines occurs by a mode of action that is not relevant to humans.
Dossier Submitter's Response
Thank you for your comments. Your comments reflect those presented in the UK C&L dossier for terbuthylazine.
RAC's response
Noted and agreed.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		MemberState	9
Comment received				
Based on the weight of evidences included in the CLH report, FR does not support the classification. This proposal will be confirmed with the new study performed by the notifier and submitted to ECHA (depending on its acceptability and its relevance).				
Dossier Submitter's Response				
Thank you for your comment. See response to comment 3.				
RAC's response				
Noted. RAC supports the comments by FR and the DS.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	Belgium		MemberState	10
Comment received				
The DS concludes no effects were observed in the absence of marked toxicity that provides sufficient evidence to cause a strong suspicion of reduced fertility/ impaired development toxicity. However according to the guidance it is generally very difficult to prove a causal relationship between a parentally mediated mechanism and adverse effects in the offspring. In order to determine whether a reproductive toxic effect is independent or secondary to a parental effect, it would be most appropriate to correlate individual data for offspring and				

their parents. But this information is absent in the dossier. In the two generation study (Masters et al., 1992), 4 females failed to become pregnant following two matings due to absent corpora lutea at 300ppm. At the same dose , the pup weight is decreasing (F1 shows a decrease of 19% by day 21 with a slight delay in sexual maturation compared to control, the same is observed in the F2). In the One-generation study (Gainger, 1999), there is a dose-related decrease observed in the pup weight. The DS justified those effects as likely secondary, non-specific, consequence of maternal toxicity and therefore not relevant for the classification. We cannot support this statement because there is no consistent justification as no individual data are presented in the dossier. Besides, we disagree with some NOAELs values in the dossier. In the Fitzgerald study (1990), no maternal effects are observed at the lowest dose (1 mg/kg bw/day) and the NOAEL value is the mid dose (5 mg/kg bw/day). In the Gainger study (1990) the offspring NOAEL derived at 50 ppm that we consider as a LOAEL due to the decrease in the female body weight gain observed (10%).Can the DS justify his choice for the NOAEL? We also disagree with the interpretation of the results as a consequence of repeated dose toxicity. Indeed, in the two-generation study (Krishnappa, 1998), the pups born dead and the decrease of the viability index should be considered as developmental effect and not as a repeated dose effect. Consequently, the non-classification is weekly justified and cat.2 cannot be excluded.

Dossier Submitter's Response

Thank you for your comments.

We do not see the added value of doing individual data analysis as requested because data exists showing these types of effects occur when bodyweight is reduced. Furthermore, we consider the results of the repeat dose study suggest the effects on pup weight and viability observed are due to repeated dose toxicity in the young rather than a developmental effect.

Please note, the NOAELS were agreed by EFSA during the review of the active substance; they are included in the CLH document for information purposes only.

RAC's response

There is clear evidence from published studies where body weight loss in SD rats can be responsible for a number of changes to reproductive indices including reduced numbers of corpora lutea, elongation of puberty in adolescents and reductions in pup body weight. The RAC supports the DS in the first part.
As indicated by the notifier in a specific response to this point, for the F1 generation in the Krishnappa (1998) study, the statistically significant differences in pup survival noted in the high dose group at days 1 and 4 are primarily due to whole litter losses in 2 dams occurring shortly after birth. Also there is no consistency, seen in 1 of 2 studies in Wistar rats and not seen in Sprague-Dawley rats.

Date	Country	Organisation	Type of Organisation	Comment number
11.11.2014	United States		Individual	11

Comment received

These comments are presented on behalf of James W. Simpkins, Ph.D., Robert J. Handa, Ph.D., and myself. We are independent scientists who were asked by Syngenta to review the original study reports relevant to possible reproductive toxicity and carcinogenicity of terbuthylazine. Based upon our review we conclude that the identification of terbuthylazine as either a reproductive toxicant or a carcinogen is not consistent with the scientific data.

Rat studies do not show effects of terbuthylazine on fertility at exposure levels that are not toxic to the adult animals. Reproductive effects noted in the terbuthylazine studies are due to maternal toxicity and not to a direct effect of terbuthylazine on the reproductive system. In a 2-generation study by Masters and Bell (1992), a reduction in fertility of the first filial

generation at 300 ppm in the diet occurred as a result of reduced food and water consumption. There was a decrease in corpus luteum number in the parental and first generation females at this dose level that was quantitatively similar to a decrease in corpus luteum number associated with feed restriction and weight reduction in a study by Terry et al. (2005). A small delay in puberty (about 1 day) in first generation males and females in the terbuthylazine 2-generation study was also consistent with effects of body weight decrements in terbuthylazine-treated animals. In another 2-generation study performed by Oxon, decreased pup survival during lactation in both generations was observed at dietary dose levels of 100 and 200 ppm. This finding was not observed in a 1-generation study at the same laboratory with dietary dose levels up to 350 ppm. Moreover, the finding of a decrease in pup survival was an artifact of analysis on a per-pup basis rather than the preferred per-litter basis. Reanalysis of the data on a per-litter basis indicated that there was no effect of treatment on pup survival during lactation.
Dossier Submitter's Response
Thank you for comment. RAC may find this information useful in their discussion.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.11.2014	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	12
Comment received				
Please refer to the attached position statement made on behalf of both Syngenta and Oxon companies. The notifiers agree with the dossier submitter that it can be considered that the apparent reduced effects on fertility in Sprague-Dawley rats at the top dose level are not attributable to a direct effect of terbuthylazine on mating or fertility. These findings reflect the high level of background variation in mating performance in the animals and/or are secondary to the general systemic toxicity observed, specifically a significantly lower bodyweight gain that is seen in concurrent controls. *(ECHA note: The following attachment was submitted with the above comment [Attachment 6])* *Terbuthylazine - Position on Reproduction in Sprague Dawley Rats*				
Dossier Submitter's Response				
Thank you for agreeing with our classification proposal.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	Belgium		MemberState	13
Comment received				
We support the classification Acute tox 4 for oral route (H302) and the non-classification for the other routes.				
Dossier Submitter's Response				
Thank you for agreeing with our proposal.				
RAC's response				
Agreed.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	Belgium		MemberState	14
Comment received				
We consider that the classification Cat. 2 is not well justified. There is no clear explanation related to the decrease of the BW excepted the reduction of the food consumption, which is more or less in the same range as the reduction of the body weight. In the absence of no clear findings explaining the observed reduced bodyweight and no other effects relevant for classification (histopathological effects, organs toxicity), we consider that the data presented are quite poor to support Cat. 2.				
Dossier Submitter's Response				
Thank you for your comment. A significant reduction in bodyweight/bodyweight gain was observed below the relevant cut-off for classification in rats, rabbits and dogs. Bodyweight loss/reduction was the lead effect and was sufficiently severe to result in the top dose levels in the majority of studies being below the cut-off for classification. In one rat and one dog study, the severity of the effects also leads to early termination of the study. It is true that food consumption was also reduced in these studies and that unpalatability of the diet may be the cause of bodyweight reductions. However, this is unlikely to be the sole (or major) cause as bodyweight was also adversely reduced (as was food consumption) following oral gavage and dermal (occlusive) administration of terbuthylazine to rabbits, where palatability of the diet is not an issue. Although the underlying cause of these bodyweight effects is unclear, the severity of the effects (leading to termination of the study, etc) meant that they could not be ignored and therefore they were considered relevant for classification.				
RAC's response				
RAC agrees with the DS. The changes in several body weight parameters are consistent through a wide variety of studies incorporating sub-acute, chronic, neurotoxicity and reproductive toxicity data.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2014	France		MemberState	15
Comment received				
STOT RE 2 – H373: FR agrees with the conclusion that the decreases of food consumption, of body weight and of body weight gain are treatment related in all species. However, FR is questioning regarding the relevance of these effects for a classification.				
Dossier Submitter's Response				
See response to comment number 14.				
RAC's response				
Noted. The interpretation of STOT RE usually requires the identification of a specific effect on an organ or tissue. Terbuthylazine has many non-specific effects except for those on body weight parameters which are quite consistent.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number

05.12.2014	Belgium		MemberState	16
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species (acute : algae Microcystis Aeruginosa with calculated 96h ErC50 = 0.018 mg/l (nom)/Lemna gibba with 7d EC50 (frond no.) = 0.0128 mg a.s./l (nom), chronic : algae Desmodesmus Subspicatus with 72h NOErC= 0.0011 mg/l (nom)), the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic acute1, H400 and Aquatic Chronic 1, H410. Furthermore, the substance shows no potential to bioaccumulate (BCF<500). In view of the proposed classification and toxicity band for acute toxicity between 0.01mg/l and 0.1 mg/l, an M-factor for acute toxicity of 10 should be assigned and an M-factor for chronic toxicity of 10 (not rapidly degradable substance and NOEC between 0.001 mg/l and 0.01mg/l). In conclusion: we agree with the proposed environmental classification by the UK CA.				
Dossier Submitter's Response				
Thank you for your comments. We acknowledge Belgium's agreement with the proposed environmental classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2014	Finland		MemberState	17
Comment received				
The Finnish CA supports the proposed classification Aquatic Acute 1; H400 with M-factor of 10, Aquatic Chronic 1; H410 with M-factor of 10 for Terbuthylazine.				
Dossier Submitter's Response				
Thank you for your comments. We acknowledge Finland's support for the proposed environmental classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
01.12.2014	Germany		MemberState	18
Comment received				
p. 80 chapter 5.4 Aquatic toxicity, point 5.4.2.1 Short term toxicity to aquatic invertebrates: We would suggest addition of an acute aquatic invertebrate study conducted with Mysidopsis bahia (Ward, G. S., 1988, Report No. 87356-0210-2130) which was not considered in the report but is available for a national registration for central zone in Germany. The study result is LC50 = 0.092 mg a.s./L (nominal, 96 hours, static system). In this study, no analytical measurements have been conducted. However, from our point of view this does not invalidate the study, in fact, the result can be seen as "best case" when taking into account a DT50 of 72 hours in water. The LD50 value of this study supports the suggested classification and labelling and should be added for completeness, since this represents the most sensitive endpoint for acute toxicity to aquatic invertebrates.				
Dossier Submitter's Response				
We thank Germany for pointing out this additional acute aquatic invertebrate study conducted on *Mysidopsis bahia*. This study was not available to us in a pesticide dossier or database, and so we have not confirmed its validity. However, we note that probably the				

same study (identical Report No./ID) is referenced and is presumably considered reliable in the US EPA Reregistration Eligibility Decision (RED) for terbuthylazine (EPA 738-R-95-005, March 1995) as: Ward, G. (1988) Acute Toxicity of Technical Terbuthylazine to Mysid Shrimp (*Mysidopsis bahia*) Under Static Conditions: Laboratory Project ID 87356-2210-2130. Unpublished study prepared by Environmental Science and Engineering, Inc. 23 p.

This gives an acute EC50 (for 'pink shrimp') of 0.1097 mg/L, which is slightly higher than 0.092 mg/L (perhaps re-calculated by the EPA). The 0.092 mg/L endpoint is however also used in an Australian evaluation of terbuthylazine from 2001 (National Registration Authority for Agricultural and Veterinary Chemicals, ISSN1443-1335).

An acute mysid LC50 of 0.092 - 0.1097 mg a.s./L, is notably lower than the acute EC50s for *Daphnia* of 11.0 - >69.3 mg a.s./L reported in the CLH dossier, however it is not lower than the EC50s reported for a number of algal species and *Lemna* in the range 0.01 - 0.1 mg/L. Therefore the proposed Acute Category 1 classification for terbuthylazine and Acute M-factor of 10 will not change.

RAC's response

Noted. Thank you for the additional information, which however does not change the proposed classification.

ATTACHMENTS RECEIVED

1. CONFIDENTIAL Statement SYNGENTA terbuthylazine classification. Submitted by Syngenta Crop Protection AG on 5.12.2014. (Filename: CONFIDENTIAL Statement SYNGENTA terbuthylazine classification) *[Please refer to comment 2]*

2. Terbuthylazine - Position on Leydig Cell Tumours in Sprague Dawley-derived rats. Submitted by Syngenta Crop Protection AG on 28.11.2014. (Filename: Terbuthylazine - Position on Leydig Cell Tumours (Nov 2014)) *[Please refer to comment 6]*

3. Stump DG, 2014. Terbuthylazine: A study of the effects of 4 days of exposure on the estrogen-induced luteinizing hormone (LH) surge in ovariectomized Sprague Dawley rats. (summary). Submitted by Syngenta Crop Protection AG on 28.11.2014 (Filename: Terbuthylazine - SD Rat LH Surge OECD Summary (from Audited Draft)) *[Please refer to comment 7]*

4. Handa R, 2014. Terbuthylazine: An oral (gavage) study to assess the effects on the hormone-induced luteinizing hormone surge in ovariectomized female Wistar rats. (summary). Submitted by Syngenta Crop Protection AG on 28.11.2014 (Filename: Terbuthylazine - Han Wistar Rat LH Surge OECD Summary) *[Please refer to comment 7]*

5. Position on Mammary Tumours in Rats. Submitted by Syngenta Crop Protection AG on 28.11.2014 (Filename: Terbuthylazine - Position on Mammary Tumours (November 2014 Update Statement)) *[Please refer to comment 7]*

6. Terbuthylazine - Position on Reproduction in Sprague Dawley Rats. Submitted by Syngenta Crop Protection AG on 28.11.2014 (Filename: Terbuthylazine - Position on Effects on Reproduction (November 2014)) *[Please refer to comment 12]*