Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

# Evaluation of the arguments presented in the appeal of the rejection of the plant protection product Plenum 50 WG made by the Norwegian Food Safety Authority

**Opinion of the Panel on Plant Protection Products of the Norwegian Scientific Committee for Food Safety**


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# Contributors

Persons working for VKM, either as appointed members of the Committee or as *ad hoc* experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

## Acknowledgements

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## Assessed by

The report has been evaluated and approved by the Panel on Plant Protection Products of VKM.

**Panel on Plant Protection Products:**

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# Background

The Norwegian Food Safety Authority has rejected an application for approval of Plenum 50 WG due to lack of documentation for one of the metabolites of pymetrozine. The rejection was partly based on a risk assessment performed by the Panel on Plant Protection Products of the Scientific Committee for Food Safety (VKM), published June 26th 2012 (VKM 2012). The Norwegian Food Safety Authority rejected the application due to lacking documentation concerning genotoxicity and general toxicity of one of the metabolites of pymetrozine, the CGA 300407 metabolite.

The applicant, Syngenta, has appealed the decision that was made by the Norwegian Food Safety Authority, arguing that the documentation for assessing the health risk of the metabolite is adequate. Furthermore, Syngenta claims that there is no indication that pymetrozine would cause developmental effects in humans. New documentation has not been submitted by Syngenta in connection with their appeal.

On this background the Norwegian Food Safety Authority, in a letter of January 18th 2013, requested VKM to evaluate the arguments put forward by Syngenta in the appeal. The working group on human toxicology of the VKM Panel on Plant Protection Products discussed the arguments in a meeting on 19th February 2013. A draft opinion made by the working group was examined by the Panel on Plant Protection Products, and the opinion was adopted by the panel on March 4th 2013.

# Terms of reference

The Norwegian Food Safety Authority asks VKM to evaluate whether the argumentation put forward by Syngenta changes the earlier opinion of VKM on pymetrozine and its metabolite CGA 300407.

# Assessment

## Metabolite toxicity

The metabolite in question, CGA 300407, has been shown to occur in plants exposed to pymetrozine. It is required to test the metabolite since users and consumers will be exposed to it directly. In addition, the metabolite has been shown to be formed endogenously in animals, and it is likely to occur in humans.

## Possible role of metabolite CGA 300407 in the development of cancer

Pymetrozine has been shown to induce increased incidences of liver tumors in mice and rats, as well as lung tumors in female mice. The mechanism of tumor induction is a central question in relation to health risk assessment of pesticides. The identification of a genotoxic potential of the metabolite CGA 300407 raises the question if the tumors may occur via a genotoxic mechanism. CGA 300407 has been shown to induce chromosomal aberrations in Chinese hamster cells and human lymphocytes, and response in an *in vivo* Comet assay in mouse forestomach.

Syngenta argues that the negative *in vivo* Comet assay for the active ingredient pymetrozine precludes a role for the metabolite CGA 300407 via a genotoxic mechanism in the liver. It is

however questionable if the Comet assay is an adequate test for genotoxicity in liver in this case, since an *in vitro* Comet assay for the metabolite in mouse hepatocytes was reported to be negative.

The metabolite has been shown to induce responses in an *in vivo* Comet assay in mouse forestomach, thus proving the principle of *in vivo* genotoxic property. However, the relatively weak response following fairly high concentration gavage exposure also suggests that the Comet assay is an insensitive endpoint for aldehydes.

The metabolite is also negative for *in vitro* UDS on rat hepatocytes, suggesting that this is not a preferred endpoint for *in vivo* studies.

A relevant question is what would be the best assay to determine whether endogenously formed CGA 300407 could be involved in the induction of tumors in liver and lung via a genotoxic mechanism. The *in vivo* transgenic rodent mutation assay is a fairly new assay where an OECD test guideline has recently been made available. This assay is regarded as an appropriate test to follow up positive results in *in vitro* tests for gene mutation and chromosome anomalities in mammalian cells.

Syngenta suggests that benzaldehyde should be used as a reference chemical for the metabolite CGA 300407, based on structural similarities. The view of the VKM Panel on Plant Protection Products is that there is not enough documentation on toxicological similarities between benzaldehyde and the metabolite to do such an extrapolation.

### Reproduction/teratology

In the previous risk assessment (VKM 2012), the VKM Panel on Plant Protection Products concluded that the induced morphological changes in the pup brain in a developmental neurotoxicity study by Pinto (unpublished), in the absence of maternal toxicity, should be regarded as an adverse effect that could be relevant for humans. The panel concluded that this effect should be considered when classifying pymetrozine for possible teratogenic effects.

Syngenta argues that "There is therefore no indication that pymetrozine would cause developmental effects in humans, and thus there is no need to classify pymetrozine for developmental effects". This argument is given without including and discussing this particular developmental neurotoxicity study.

Concerning a harmonised classification of pymetrozine for developmental toxicity, it is the Risk Assessment Committee in ECHA that concludes on the harmonised classification of plant protection products.

## Conclusion

The VKM Panel on Plant Protection Products cannot see that the applicant, Syngenta, has provided data that is sufficient to rule out the possibility that the metabolite CGA 300407 is involved in the induction of tumors in rat and mouse liver and mouse lung via a genotoxic mechanism.

The VKM panel points to testing of pymetrozine in the *in vivo* transgenic rodent mutation assay, as a way to get closer to an answer on the above question.

Concerning the use of data from benzaldehyde as reference values for the metabolite CGA 300407, as suggested by Syngenta, it is the view of the VKM panel that there is too little

documentation on toxicological similarities between benzaldehyde and the metabolite to do such an extrapolation.

In the risk assessment of Plenum 50 WG (VKM 2012), VKM concluded that the induced morphological changes in the pup brain observed in a developmental neurotoxicity study should be considered as an adverse effect that could be relevant for humans. VKM concluded that this effect should be considered when classifying pymetrozine for possible teratogenic effects. The VKM panel cannot see that the appeal from Syngenta contains any comments or arguments against this conclusion.

# References

Pinto PJ. Unpublished. Pymetrozine: Developmental neurotoxicity study in rats. A study performed in 2003, sponsored by Syngenta.

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