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Re-assessment of the plant protection product PROMAN – with the active ingredient metobromuron

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

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Assessed and approved

The opinion has been assessed and approved by Panel on Plant Protection Products of VKM. Members of the panel are:

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Competence of VKM experts

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

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Summary

Proman is a broad spectrum selective herbicide for potatoes grown outdoors, containing the active substance metobromuron. VKM's Panel on Plant Protection Products has previously discussed questions concerning Proman raised by The Norwegian Food Safety Authority, and stated its opinion in a report of 21. January 2015 (http://www.vkm.no/dav/3c64afe035.pdf).

Following this report, The Norwegian Food Safety Authority turned down the application to register Proman as a plant protection product in Norway. The applicant filed a complaint on this decision, and the VKM Panel has been asked to reassess its previous opinion in light of the information given by the applicant in the complaint.

The VKM Panel has discussed the arguments put forward in the complaint. The arguments did not change the Panel's main conclusions in the original assessment. Some changes in the wording of the conclusions were however done, in order to put more emphasis on areas of uncertainty.

These are the standing conclusions of VKM's Panel on Plant Protection Products:

On the relevance of the carcinogenic effects observed in the rat carcinogenicity study; fibrosarcomas in females and pheochromocytomas and Leydig cell tumours in males:

It is the opinion of VKM's Panel for Plant Protection Products that the relevance of the observed incidences of mammary gland tumours and Leydig cell tumours in the rat carcinogenicity study is strengthened by the fact that the increases in tumours associated with exposure to metobromuron are observed in hormone responsive tissues. The panel concludes that the carcinogenic effects observed in the rat carcinogenicity study could be relevant for tumour induction in humans.

Higher incidences of still dumbbell-shaped centres of thoracic vertebrae and non-ossification of the 13th rib observed in the rat developmental toxicity study and whether these are considered to be malformations.

VKM's Panel on Plant Protection Products has discussed the classification of the different types of incomplete ossifications and concluded that incomplete ossification of sternebrae and non-ossification of the 13th rib in rats should by itself be considered to be variations, and not adverse developmental effects. On the other hand, the Panel agrees with ECHA that the "thoracic vertebral centres still dumbbell-shaped" should be considered as malformations, due to limited data and understanding of the mechanism underlying the

observed slow reversal of these anomalies. Furthermore, it is the view of the Panel that the different types of retarded ossification induced by the exposure should be considered as a whole when assessing for developmental effects.

Establishment of the NOAEL for the developmental toxicity study in rats and the reference value (ARfD).

VKM's Panel on Plant Protection Products supports the proposal of an ADI value of 0.008 mg/kg bw/day based on a NOAEL of 0.8 mg/kg bw/day from the 2-year study in mouse, and AOEL of 0.016 mg/kg bw/day based on the NOAEL of 1.6 mg/kg bw/day from the 1-year feeding study in dog. The panel suggests an alternative ARfD value of 0.03 mg/kg bw based on a LOAEL of 10 mg/kg bw /day for the observations of incomplete ossification in the rat developmental study.

The anti-androgenic potential of metobromuron.

The rat carcinogenicity study indicates that metobromuron may interact with the endocrine system. The data from the Hershberger *in vivo* rat study, the *in vitro* studies, as well as the comparison with demonstrated effects and mechanisms for flutamide and linuron is suggestive of an anti-androgenic effect. Thus, it is the opinion of the VKM Panel on Plant Protection Products that an anti-androgenic effect of metobromuron cannot be excluded.

Sammendrag på norsk

Proman er et plantevernmiddel med virkestoffet metobromuron som det er søkt bruksgodkjenning for i Norge. Middelet et tenkt brukt som ugressmiddel ved dyrking av poteter utendørs. Proman ble vurdert av VKMs Faggruppe for plantevernmidler i januar 2015 (http://www.vkm.no/dav/3c64afe035.pdf).

På grunnlag av blant annet VKMs rapport ble søknaden om godkjenning av Proman avslått av Mattilsynet. Søkeren har klaget på denne avgjørelsen, og Faggruppen for plantevernmidler ble bedt om å gi en vurdering av argumentene i klagen, og om disse argumentene medfører endring i VKMs konklusjon i den opprinnelige vurderingen.

I den opprinnelige vurderingen var det faggruppens oppfatning at de kreftfremkallende effekter som er observert hos rotter eksponert for metobromuron kan være relevante for mennesker. Videre var det faggruppens oppfatning at de ulike typer av forsinket forbeining som følge av eksponering for metobromuron bør vurderes samlet når en ser på stoffets evne til å indusere misdannelser, noe som påvirker faggruppens oppfatning av fastsettelse av toksikologiske referanseverdier. Faggruppen mente videre at de svulst-typer som er funnet i kreftforsøk på rotter, sammen med et såkalt Hershberger forsøk, supplerende *in vitro* studier, og strukturlikhet med linuron, tilsier at en ikke kan utelukke at metobromuron kan ha en anti-androgen effekt.

VKMs Faggruppe for plantevernmidler har diskutert argumentene fremsatt i klagen i møte 14. desember 2015. Argumentene endrer ikke panelets hovedkonklusjoner i den opprinnelige vurderingen. Det er imidlertid gjort noen små endringer i ordlyden på konklusjonene, for å legge mer vekt på områder av usikkerhet som er påpekt i klagen.

Abbreviations

ADI	Acceptable Daily Intake
AOEL	Acceptable Operator Exposure Levels
ARfD	Acute Reference Dose
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
g a.s./ha	Gram active substance per hectare
In vivo	Experiment on living organisms
In vitro	"In glass" – experiment outside an organism – in test tube
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
RMS	Reporting Member State
TP	Testosterone propionate
UF	Uncertainty Factor
VKM	Norwegian Scientific Committee for Food Safety

Terms of reference as provided by the Norwegian Food Safety Authority

Proman is a new product containing the new active substance, metobromuron. The intended use is as a broad spectrum selective herbicide for potatoes grown outdoors.

VKM's Panel on Plant Protection Products has previously on request from The Norwegian Food Safety Authority stated its opinion in a report of 21. January 2015 (http://www.vkm.no/dav/3c64afe035.pdf).

Following this report, The Norwegian Food Safety Authority turned down the application to register Proman as a plant protection product in Norway. The applicant filed a complaint on this decision, and the VKM Panel is requested to reconsider its previous opinion in light of the information and arguments given by the applicant in the complaint.

1 Re-assessment of metobromuron

The previous assessment of Proman with the active ingredient metobromuron by VKM's Panel on Plant Protection Products was discussed in meetings at 24. October and 21. November 2014, and was based on documentation mainly supplied by the manufacturer and some publications from peer reviewed journals (http://www.vkm.no/dav/3c64afe035.pdf).

Following the decision by The Norwegian Food Safety Authority to turn down the application to register Proman as a plant protection product in Norway, the arguments put forward in a complaint from the applicant were discussed in VKMs Panel for Plant Protection Products in meetings at 19. October and 14. December 2015.

For the original VKM assessment, see http://www.vkm.no/dav/3c64afe035.pdf. For more information on the complaint documents referred to, please contact The Norwegian Food Safety Authority. Below are the conclusions from the original report followed by discussion of the arguments as put forward in the complaint letter.

1.1 The relevance of the carcinogenic effects observed in the rat carcinogenicity study; fibrosarcomas in females and pheochromocytomas and Leydig cell tumours in males.

1.1.1 VKM's original conclusion

It is the opinion of VKM's Panel for Plant Protection Products that the relevance of the observed incidence in mammary gland tumours and Leydig cell tumours in the rat carcinogenicity study is strengthened by the fact that the increases in tumours associated with exposure to metobromuron are all observed in hormone responsive tissues. The panel concludes that the carcinogenic effects observed in the rat carcinogenicity study are likely to be relevant for tumours that are influenced by the endocrine system, also in humans.

1.1.2 VKM's response to arguments in the complaint

The view of the applicant is summarized as follows on page 4 in the complaint document:

"The conclusion under this point should be amended both with regard to the decision of the Food Safety Authority [FSA) and the VKM report. The Leydig cell tumours and the conjecture of the fibrosarcoma and pheochromocytoma with endocrine activity should be omitted. Accordingly, the text must be changed to state an R40 classification in line with the EFSA proposal."

The response from VKM:

The European Food Safety Authority (EFSA) has concluded as follows on the carcinogenicity studies: "No oncogenic effect was observed in mice, but in rats an increased incidence of mammary gland fibrosarcomas were observed in females and increased incidence of pheochromocytomas in males were considered to be potentially relevant for humans and may indicate that classification as carcinogenic category 2, H351 "suspected of causing cancer" may apply" (http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3541.pdf).

In Norway, classification of pesticides is the duty of the Norwegian Food Safety Authorities, and will not be commented on by VKM. The role of VKM is to comment on how to interpret and assess the test results presented by the applicant.

The applicant points to that the EU authorities, in their proposal for carcinogen classification, have not considered the Leydig cell tumours, and that this is based on "standard procedure of using historical control data". As stated in the VKM report, it is the view of VKM that historical control data should be used with care, and not automatically be used to overrule the control data in the actual experiment. The incidence of Leydig cell tumours shows a steadily increasing dose response curve from 16% in the control to 36% at the highest dose. (Data from control and with increasing doses: 8/50 (16%), 11/50 (22%), 12/50 (24%), 16/50 (32%), 18/50 (36%) [P=0.01; Chi-square test for trend]) The historical control data is reported to range 16-52%, and as explained in the original report, VKM disagrees with the view of the applicant that this should imply that observed incidences below 52% should be considered as negative responses due to what the applicant refers to as "standard procedure of using historical control data". There may be cases where historical control data should be considered, but for the present Leydig cell tumour data, with clear dose response, it is the opinion of VKM that the study specific experimental control data are more relevant than the maximum value of a set of historical control data.

When it comes to the discussion of possible mechanisms involved in the tumour induction, the applicant find it unfounded that VKM points to the possibility that a hormonal response could underlie the tumour induction by metobromuron. VKM suggests this as a possibility based on the observation that all three tumour bearing organs are hormone responsive, but obviously, the exact mechanism underlying the tumour induction is not proven. VKM cannot see that this observation is very controversial.

In light of the arguments put forward by the applicant, and our recent re-evaluation, VKM is however prepared to accept that the last sentence in the conclusion has a too strong focus on mechanism, and could instead be replaced by the sentence: "The panel concludes that the tumour inducing ability of metobromuron observed in the rat carcinogenicity study could be relevant for tumour induction in humans." Thus, we find it pertinent to point to the possibility of an endocrine mechanism, but leave the mechanistic suggestion out of the conclusion on human relevance.

1.1.3 VKM's revised conclusion

It is the opinion of VKM's Panel for Plant Protection Products that the relevance of the observed incidences of mammary gland tumours and Leydig cell tumours in the rat carcinogenicity study is strengthened by the fact that the increases in tumours associated with exposure to metobromuron are observed in hormone responsive tissues. The panel concludes that the carcinogenic effects observed in the rat carcinogenicity study could be relevant for tumour induction in humans.

1.2 Higher incidences of still dumbbell-shaped centres of thoracic vertebrae and non-ossification of the 13th rib observed in the rat developmental toxicity study and whether these are considered to be malformations.

1.2.1 VKM's original conclusion

VKM's Panel on Plant Protection Products has discussed the classification of the different types of incomplete ossifications and concluded that incomplete ossification of sternebrae and non-ossification of the 13th rib in rats should by itself be considered to be variations, and not adverse developmental effects. On the other hand, the Panel agrees with ECHA that the "thoracic vertebral centres still dumbbell-shaped" should be considered as malformations, due to limited data and understanding of the mechanism underlying the observed slow reversal of these anomalies. Furthermore, it is the view of the Panel that the different types of retarded ossification induced by the exposure should be considered as a whole when assessing for developmental effects.

1.2.2 VKM's response to arguments in the complaint

The view of the applicant is summarized as follows on page 5 in the complaint document:

"The conclusions under this point should be amended both with regard to the decision of the FSA and the VKM report. The assessment of metobromuron and recognition of a NOAEL of 10 mg/kg without malformations in the rat teratology study should be in line with the conclusions of the EU review as it represents the overall EU/EEA opinion."

The response from VKM:

The applicant argues that the view of ECHA to consider "thoracic vertebral centres still dumbbell-shaped" as malformations was related to one specific substance, cycloxidim, where the studies for this substance had shown very slow reversal of these anomalies. Since the studies on metobromuron are older (from 1982), reversibility has not been studied, and on this basis the applicant argues that the conclusion by ECHA in the case of cycloxidim is not valid for metobromuron. VKM disagrees with the applicant's argument and find it reasonable

to refer to the view of ECHA in cases where data on the reversibility of the "thoracic vertebral centres still dumbbell-shaped" are missing.

The fact that cartilage staining and assessment of reversibility was not mandatory in study requirements in 1982, when tests for metobromuron were conducted, does not exempt metobromuron from the possibility of treatment-induced foetal effects. The applicant should have studied this further to demonstrate that the anomalies induced by metobromuron are different from those of cycloxidim. The finding of several different types of retarded ossification induced by the exposure adds to the uncertainty regarding the potential of metobromuron to induce developmental effects.

Thus, the conclusion of VKM on this point has not been changed.

1.3 Establishment of the NOAEL for the developmental toxicity study in rats and the reference value (ARfD).

1.3.1 VKM's original conclusion

VKM's Panel on Plant Protection Products supports the proposal of an ADI value of 0.008 mg/kg bw/day based on a NOAEL of 0.8 mg/kg bw/day from the 2-year study in mouse, and an AOEL of 0.016 mg/kg bw/day based on the NOAEL of 1.6 mg/kg bw/day from the 1-year feeding study in dog. The panel suggests on the other hand an ARfD of 0.03 mg/kg bw based on a LOAEL of 10 mg/kg bw /day with the observations of incomplete ossification in the rat developmental study.

1.3.2 VKM's response to arguments in the complaint

The applicant disagrees with VKM's suggestion to use LOAEL of 10 mg/kg bw /day as the basis for setting of ARfD.

This suggestion by VKM was based on the underlying view that the different developmental toxicity endpoints showing retarded ossification could be mechanistically and phenotypically linked, and could therefore be considered as a whole when setting toxicological reference values.

We do agree with the applicant that such a mechanistic link is not proven, and realize that some more emphasis could have been put on uncertainty related to this point. Thus, the wording of the conclusion has been revised.

The opinion of using LOAEL of 10 mg/kg bw /day, based on viewing the different endpoints showing retarded ossification as a whole, is however still the view of VKM.

VKM pointed to an apparent effect on the gripping reflex, also seen in litters of the lowest dosed animals (15 ppm; 1.1 mg/kg bw/day). This effect was observed in the F1a and F2a litters. In the F1b, F2b and F1c litters, no effect of exposure was observed.

The applicant judges the observations as incidental. We agree that there are inconsistencies between litters, suggesting either incidental effects or that the induced effect may be litter dependent. Because of the weak data of the gripping reflex experiments this was not included in the original conclusion.

1.3.3 VKM's revised conclusion

VKM's Panel on Plant Protection Products supports the proposal of an ADI value of 0.008 mg/kg bw/day based on a NOAEL of 0.8 mg/kg bw/day from the 2-year study in mouse, and AOEL of 0.016 mg/kg bw/day based on the NOAEL of 1.6 mg/kg bw/day from the 1-year feeding study in dog. The panel suggests an alternative ARfD value of 0.03 mg/kg bw based on a LOAEL of 10 mg/kg bw /day for the observations of incomplete ossification in the rat developmental study.

1.4 The anti-androgenic potential of metobromuron.

1.4.1 VKMs original conclusion

The rat carcinogenicity study indicates that metobromuron may possess endocrine disrupting potency. The data from the Hershberger *in vivo* rat study and the *in vitro* studies is suggestive of a weak anti-androgenic effect. Thus, it is the opinion of the VKM Panel on Plant Protection Products that an anti-androgenic effect of metobromuron cannot be excluded.

1.4.2 VKMs response to arguments in the complaint

VKM concluded in its report that it cannot be excluded that metobromuron possesses anti-androgenic properties. This conclusion is based on three lines of indications:

1. Tumours in hormone responsive tissues
2. Findings in *in vivo* and *in vitro* studies for hormonal effects
3. Structure and effect similarity with linuron

Point 1 has been discussed above.

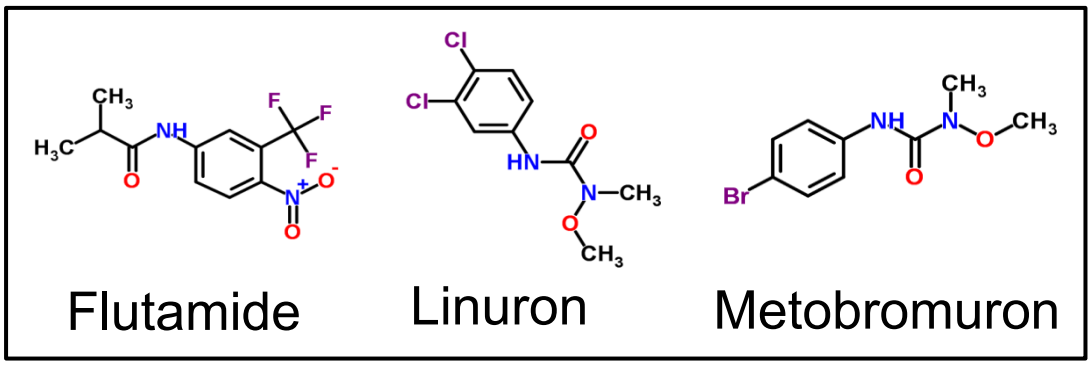
Point 2 is discussed in the original VKM report.

Regarding point 3, VKM is not aware of any available data showing direct comparison between linuron and metobromuron. As far as we can see, such data has not been given in the material provided in the complaint. In the document from ToxAdvice GmbH/Dr.W. Kobel,

data is indicated to exist for linuron, while for metobromuron, the listings "No indication", "No RED established" etc is given. It is however not explained whether this means that experimental data is available or lacking. Since no references or data are presented, it is assumed that no data is available. Thus, VKM cannot find arguments in the complaint material that warrants alteration in the VKM conclusion that "…an anti-androgenic effect of metobromuron cannot be excluded".

Flutamide is a classical substance with demonstrated anti-androgenic properties. The anti-androgenic properties of flutamide have been mechanistically linked to its potent ability to induce Leydig cell tumours. As referred to in the original VKM report on metobromuron, published data also show that linuron, a herbicide with structural similarity to metobromuron, induce endocrine disrupting effects as well as Leydig cell tumours. Several lines of evidence also suggest that the Leydig cell tumours induced by linuron occur via an anti-androgenic mechanism.

As shown in the figure below (From: chemspider.com), flutamide, linuron and metobromuron possess structural similarities.



Based on the above, it is the opinion of VKMs Panel on Plant Protection Products that this supports the view that metobromuron may have anti-androgenic properties, and that the Leydig cell tumours induced by metobromuron may occur via an anti-androgenic mechanism.

It should be noted that the conclusion does not say that an anti-androgenic mechanism is proven, but in light of all data taken together, VKM is of the opinion that such a property of metobromuron cannot be excluded. The conclusion is slightly altered to better include the uncertainty with regard to the possible anti-androgenic effects.

1.4.3 VKM revised conclusion

The rat carcinogenicity study indicates that metobromuron may interact with the endocrine system. The data from the Hershberger *in vivo* rat study, the *in vitro* studies, as well as the comparison with demonstrated effects and mechanisms for flutamide and linuron is suggestive of an anti-androgenic effect. Thus, it is the opinion of the VKM Panel on Plant Protection Products that an anti-androgenic effect of metobromuron cannot be excluded.