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Risk assessment of the active plant protection product ingredient MCPA (4-chloro-2-methylphenoxyacetic acid). AOEL and ADI determination

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

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2015: 04
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Assessed and approved

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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

MCPA (4-chloro-2-methylphenoxyacetic acid) is the active ingredient in several registered herbicides. VKM concluded in 2006 that the effects observed in experiments with dogs were of little relevance to humans, and an AOEL value of 0.036 mg/kg bw/day was proposed, based on renal effects in a 90-day study in rats. The manufacturer is of the opinion that AOEL should be set to 0.11 mg/kg bw/day, and ADI to 0.05 mg/kg bw/day, based on the view that since a 90-day and 2-year study in rats were conducted in the same lab using the same rat strain, it is reasonable to eliminate effects which are not reproduced in both sets of data. The Norwegian Food Safety Authority has therefore requested VKM's Panel for Plant Protection Products for an opinion on the determination of NOAEL values based on the 90-day and 2-year studies in rats, and consider if it is acceptable to use the manufacturer's approach for an overall consideration of the submitted studies. The Panel has discussed the findings in the two rat studies and concluded that it is not considered acceptable that individual studies separated by several years, in this case studies performed in 1985 and 1988, are taken together and data not reproduced in both sets eliminated. The Panel is still of the opinion that both AOEL and ADI for MCPA should be set to 0.036 mg/kg bw/day based on a NOAEL of 3.6 mg/kg bw/day (50 ppm) from assessment of the renal effects in the 90-day study in rats. The manufacturer has also requested a reconsideration of the present values for dermal absorption which was set by the Norwegian Food Safety Authority during the administrative review of the product MCPA 750 Liquid in 2013. VKM's Panel on Plant Protection Products supports the conclusion of the Norwegian Food Safety Authority concerning the determination of values for dermal absorption of MCPA. This includes the consideration of remaining substance in skin after washing as part of the absorbed dose in the *in vitro* studies, and the use of the same experimental time period in the *in vitro* and *in vivo* experiments as a basis for the so-called "Triple-pack-approach" for determination of human dermal absorption.

Key words: VKM, risk assessment, Norwegian Scientific Committee for Food Safety, pesticide, MCPA

Sammendrag på norsk

MCPA (4-klor-2-metylfenoksyeddiksyre) er virkestoff i flere registrerte ugressmidler. VKM konkluderte i 2006 med at effektene som er observert i eksperimenter med hunder var av liten relevans for mennesker, og en AOEL verdi på 0,036 mg/kg kroppsvekt /dag ble foreslått, basert på nyre-effekter i et 90-dagers forsøk på rotter. Produsenten er av den oppfatning at AOEL bør settes til 0,11 mg/kg kroppsvekt /dag, og ADI til 0,05 mg/kg kroppsvekt /dag, basert på den oppfatning at siden et 90-dagers og et 2-års forsøk på rotter ble utført i samme laboratorium, er det rimelig å kunne se bort fra funn som ikke er gjort i begge forsøk. Mattilsynet har bedt VKMs Faggruppe for plantevernmidler om å vurdere fastsettelse av NOAEL-verdier basert på disse to rotteforsøkene, og vurdere om det er akseptabelt å bruke produsentens tilnærming til en samlet vurdering av forsøkene. Faggruppen har diskutert denne problemstillingen og konkluderer med at det ikke anses som akseptabelt at enkeltstudier som er utført med flere års mellomrom, i dette tilfellet studier utført i 1985 og 1988, slås sammen og at en ser bort fra funn som er gjort i bare ett av forsøkene. Faggruppen er fortsatt av den oppfatning at både AOEL og ADI for MCPA bør settes til 0,036 mg/kg kroppsvekt /dag, basert på en NOAEL på 3,6 mg/kg kroppsvekt /dag (50 ppm), basert på effekter på nyre 90-dagers forsøket på rotter. Produsenten har også bedt om en ny vurdering av gjeldende verdier for dermal absorpsjon som ble fastsatt av Mattilsynet ved en administrativ gjennomgang av middelet MCPA 750 Flytende i 2013. VKMs Faggruppe for plantevernmidler støtter konklusjonen fra Mattilsynet for fastsettelse av verdier for dermal absorpsjon av MCPA. Dette gjelder måten gjenværende testsubstans i hud etter vasking brukes i beregning av absorbsjon i *in vitro* studier, og at det anvendes data fra det samme eksperimentelle tidsrom i *in vitro* og *in vivo* forsøkene som grunnlag for bruk av «Triple-pack»-metoden for fastsettelse av dermal absorpsjon hos mennesker.

Abbreviations

ADI	Acceptable Daily Intake
AOEL	Acceptable Operator Exposure Levels
EU	European Union
In vivo	Experiment on living organisms
In vitro	“In glass” – experiment outside an organism – in test tube
LOAEL	Lowest Observed Adverse Effect Level
MCPA	4-chloro-2-methylphenoxyacetic acid
mg/kg bw/day	milligram per kilogram bodyweight per day
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
ppm	Parts Per Million
US EPA	United States Environmental Protection Agency
VKM	Norwegian Scientific Committee for Food Safety

Background as provided by the Norwegian Food Safety Authority

The predecessor of VKM's Panel for Plant Protection Products, "Rådet for plantevernmidler", performed an assessment of the active herbicide ingredient MCPA in 2000, where AOEL was set to 0.02 mg/kg bw/day based on 1-year dietary experiments using dogs. In 2006, VKM was asked by the Norwegian Food Safety Authority to re-assess the basis for the setting of AOEL for MCPA and consider whether the dog was a relevant model for studies of the toxicity of phenoxy acids. VKM concluded that the effects observed in experiments with dogs were of little relevance to humans, and that a new AOEL therefore should be determined. AOEL was now proposed set to 0.04 mg/kg bw/day, based on renal effects in a 90-day study in rats.

The manufacturer of MCPA has now asked for a re-assessment of the reference values for MCPA.

Terms of reference as provided by the Norwegian Food Safety Authority

The manufacturer is of the opinion that AOEL should be set to 0.11 mg/kg bw/day, and ADI to 0.05 mg/kg bw/day (Nufarm Group, 2013). The manufacturer also wants a reconsideration of the values for dermal absorption. During the administrative review of the product MCPA 750 Liquid in 2013, the Norwegian Food Safety Authority established new values for dermal absorption on the basis of existing studies, since this has not previously been considered by the Food Safety Authority or the Norwegian Scientific Committee for Food Safety (Mattilsynet, 2004). The manufacturer disagrees on these values for dermal absorption (Nufarm Group, 2013).

Based on this, the Norwegian Food Safety Authority has asked VKM to perform the following assessment of MCPA:

Determination of AOEL and ADI

Determination of values for dermal absorption

Assessment

1 Introduction

“Rådet for plantevernmidler” suggested in 2000 that AOEL for MCPA should be set to 0.02 mg/kg bw/day based on 1-year dietary experiment using dogs. In 2006, VKM concluded that the effects observed in experiments with dogs were of little relevance to humans, and a new AOEL value was proposed, 0.04 mg/kg bw/day, based on renal effects in a 90-day study in rats. The manufacturer is now of the opinion that AOEL should be set to 0.11 mg/kg bw/day, and ADI to 0.05 mg/kg bw/day (Nufarm Group, 2013). The manufacturer also requests a reconsideration of the present values for dermal absorption which was set by the Norwegian Food Safety Authority during the administrative review of the product MCPA 750 Liquid in 2013. The manufacturer disagrees on these values for dermal absorption (Nufarm Group, 2013).

Based on this, the Food Safety Authority has asked VKM to perform an assessment of the AOEL and ADI values, as well as the determination of values for dermal absorption (Mattilsynet, 2014).

2 Hazard identification and characterisation

2.1 Determination of AOEL and ADI

The manufacturer has requested a new assessment of reference values for MCPA, and argues for an AOEL value of 0.11 mg/kg bw/day and an ADI value of 0.05 mg/kg bw/day.

The manufacturer is of the opinion that since the 90-day and 2-year study in rats were conducted in the same lab in the same time period using the same rat strain, it is reasonable to eliminate observed effects which are not reproduced in both sets of data when assessing the relevance of the observed effects (MCPA Task Force, 2009; MCPA Task Force III, 2005).

The manufacturer believes that this approach was not used the last time the reference values for MCPA were determined, and requests a new assessment (Nufarm Group, 2013).

The Norwegian Food Safety Authority has therefore requested VKM for an opinion on the determination of NOAEL values based on the 90-day and 2-year studies in rats, as well as to consider if it is acceptable to use the manufacturer's approach for an overall consideration of the submitted studies (Mattilsynet, 2014).

2.1.1 Effects in the 90-day study in rats

The main discussion relates to whether the increase in absolute kidney weight in male rats at the dose of 10.9 mg/kg bw/day (150 ppm) is sufficient to allow for NOAEL to be set at 3.6 mg/kg bw/day (50 ppm). VKM set NOAEL to 50 ppm (3.6 mg/kg bw/day in males) when this study was assessed in 2006. The manufacturer argues that there is no statistically significant increase in relative kidney weight in males, and that no increase in kidney weight and histopathological changes was observed for 5.0 mg/kg bw/day (80 ppm), neither at 52 nor at 104 weeks in the 2-year study in rats. Thus, it is the opinion of the manufacturer that a NOAEL above 80 ppm is more correct, that the increase in kidney weight in the 90-day study results from functional hypertrophy, and that this is an adaptive rather than an adverse effect. Based on this, the manufacturer considers that 10.9 mg/kg bw/day (150 ppm) should be used as NOAEL for the study.

In a meta-study by Craig and co-workers (Craig et al., 2014) at US EPA with data extracted from reports published in the National Toxicology Program (NTP), the US EPA's database of Provisional Peer-Reviewed Toxicity Values and EPA's Integrated Risk Information System, a statistically significant relationship between absolute, but not relative, kidney weight and renal histopathological findings in chemically treated rats was observed. They concluded that the evaluation of absolute kidney weight is a useful method for identifying potential renal toxicants. This implies that increase in absolute kidney weight observed in male rats after exposure to MCPA may be indicative of renal toxicity without the need for confirmation with concomitant increase in relative kidney weight.

Another finding at 150 ppm in the 90-day study is a statistically significant decrease in cholesterol level in female rats. The manufacturer argues that this is an isolated finding and that it must be regarded as arbitrary, since female rats at 450 ppm had higher cholesterol levels than animals in the control group, and that this is also the case for female rats at 150 ppm when sampling halfway through the study (after 42 days) (MCPA Task Force, 2009; MCPA Task Force III, 2005).

In addition, the manufacturer argues that a similar change in cholesterol levels was not observed in the 2-year study. Thus, the manufacturer concludes that the NOAEL should be set at 150 ppm for the 90-day study in rats, equivalent to 10.9 mg/kg bw/day, resulting in a AOEL of 0.11 mg/kg bw/day.

2.1.2 Effects in the 2-year study in rats

The main discussion concerning effects in the 2-year study in rats is about the observed decrease in triglycerides in males and females at 80 ppm, and whether the statistically significant increase in kidney weight in females at 80 ppm is sufficient for NOAEL to be set at 20 ppm. In the last comprehensive assessment of MCPA by the Norwegian Food Safety Authority (Mattilsynet, 2004), NOAEL for males was set to 80 ppm. More uncertainty was associated with the findings in females, but a NOAEL of 20 ppm was set. The manufacturer

argues that the decrease in triglycerides was only observed in individuals, that the values were generally within the range of historical control data, and that the lack of dose-response draws doubts about whether this is treatment related (Nufarm Group, 2013).

Regarding the statistically significant increase in absolute kidney weight in females, the manufacturer argues that no statistically significant increase was observed in the highest dose group (lack of dose-response). The manufacturer also argues that since a statistically significant increase in kidney weight was not observed in males, it should be questioned whether the increase in females at 80 ppm is treatment related, also since male rats have been found more vulnerable to renal effects of MCPA than female rats.

At week 52 there was an increase in chronic nephropathy in male rats in the highest dose group, but this was not observed in female rats. It is the opinion of the manufacturer that this is further evidence to support that the increase in kidney weight at 80 ppm in females is a coincidence. Thus, the manufacturer considers that NOAEL should be set to 80 ppm for the 2-year study in rats, corresponding to 5.2 mg/kg bw/day, resulting in an ADI of 0.05 mg/kg bw/day, and has promoted this view to the Rapporteur Member State (RMS) for reassessment of MCPA in the EU (Italy). Based on this, ADI in EU was changed from 0.01 mg/kg bw/day to 0.05 mg/kg bw/day in 2008, while the discussion of AOEL is still being considered by EU.

From all information submitted by the manufacturer and that provided by van Ravenzwaay et al. (2005) and Bellet et al. (1999), it must be concluded that MCPA has adverse effects on the kidneys. When the 90-day study and the 2-year study are taken together, it is observed that the major increase in kidney weight in males occurs at low exposure concentrations, below 10.9 mg/kg bw/day (150 ppm) and perhaps as low as 1.25 mg/kg bw/day (20 ppm, 2-year study – 52 week observation), although not statistically significant at 1.25 or 5.0 mg/kg bw/day (20 or 80 ppm). However, due to possible differences in experimental and animal conditions, the VKM panel does not find it acceptable that individual studies separated by several years, performed in 1985 and 1988, can be taken together in detail and considered as one. The adverse effect levels should therefore be assessed from observations in male rats of the 90-day study, giving a LOAEL of 10.9 mg/kg bw/day (150 ppm) and a NOAEL of 3.6 mg/kg bw/day (50 ppm). Consequently, using the safety factor of 100 the AOEL and ADI will be 0.036 mg/kg bw/day.

2.1.3 Conclusion

Based on the arguments described above, it is the opinion of VKMs panel on Plant Protection Products that both AOEL and ADI should be set to 0.036 mg/kg bw/day both derived from a NOAEL of 3.6 mg/kg bw/day (50 ppm) for renal effects in the 90-days study in rats.

2.2 Dermal absorption

Values for dermal absorption were determined by the Norwegian Food Safety Authority in 2013. The manufacturer does not agree on these values (Nufarm Group, 2013) and VKM has been requested to determine values for dermal absorption of MCPA based on the available test results (Mattilsynet, 2014).

2.2.1 Dermal absorption *in vitro*, rat and human skin

Information is provided from one study on *in vitro* dermal absorption (MCPA DMA 750 g/L formulation: *In vitro* absorption through human and rat epidermis) (Mattilsynet, 2004), and should be evaluated on the basis of OECD Guideline No. 428 (OECD, 2004).

Instead of using "split-thickness" skin membranes, epidermis from rat and human were used. This is unusual, and no reason for this is stated. Concentrations tested in the study were: concentrated preparation (750 g MCPA/L) and 1/83 dilution corresponding to maximum applied concentration of 9 g/L.

Exposure lasted 24 hours (Group A) or 8 hours (Group B), and the concentration of MCPA in the receptor liquid for Group A was measured at 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours after application of the test compound. After 24 hours, the test compound was washed away and the skin membrane was analysed for residual test compound. Group B was only measured after 8 hours (Mattilsynet, 2004).

The manufacturer and Reporting Member State (RMS, EU) has not included the remaining amount of MCPA in the epidermis as absorbed, but have defined absorbed MCPA as only what is measured in the receptor liquid. In the OECD Guideline 428 (OECD, 2004) and "Guidance Notes on Dermal Absorption" (No. 156) (OECD, 2011), it is however recommended to include test compound remaining in the skin after washing as absorbed substance. Thus, the EU values for dermal absorption are lower than what has been proposed by the Norwegian Food Safety Authority who followed the OECD Guideline and considered MCPA remaining in the skin as part of the absorbed substance.

It is debatable which time points should be used. OECD guideline 428 states that the exposure time may vary, but that a sampling time of 24 hours is normally required. When using a "triple-pack approach", the exposure time should however be similar for the *in vitro* and *in vivo* studies (se 2.2.2 below). Thus, on this basis it is the most appropriate to use values from 8 hour exposure from both Group A and B.

For human skin, this resulted in an *in vitro* dermal absorption of about 8% for the concentrated solution and 13 % for the diluted one. For rat skin, the corresponding *in vitro* dermal absorption was 16 % and 54 %, resulting in factors of difference between rat and human skin absorption of about 2 and 4 for concentrated and diluted solutions, respectively.

2.2.2 Dermal absorption *in vivo* in rat

The *in vivo* study of dermal absorption in rats was conducted on the basis of OECD Draft Guideline No. 427, Skin Absorption: *In Vivo* Method (2000), but should be assessed according to OECD Guideline 428 (OECD, 2004).

The concentrations tested are the same as in the *in vitro* studies. Active substance was radiolabeled and 4 male rats per group were exposed for either 4 or 10 hours and sacrificed after 4, 10, 24 or 96 hours. At each time interval, samples were extracted and analyzed for residual radioactivity (stools, blood cells, plasma, carcass and skin; from both the exposed area and surrounding skin).

At the high dose, absorption through the skin increased during the first 10 hours, i.e. immediately after end of exposure, to a maximum of 22.09%. At time point 96 hours the material absorbed was 12.87% of actual dose. This reduced amount is by the provider take as proof of almost complete absorption of applied dose already immediately after exposure.

However, the results of this high dose experiment seem to be inconsistent as one would not expect reduced absorbed amount with time. The highest value found at 10 hours is therefore used for assessment of dermal absorption.

At the low dose, about 7% penetrated through the skin within the first 10 hours. After 96 hours 9.40% of the dose had penetrated the skin. The study does not contain data showing detailed absorption over time. Thus, it is not known if the maximum absorption was reached before 96 hours. It is, however, stated in the manufacturer's report that most of the absorption occurring post-dosing occurred within 24 to 96 hours. Thus, it may seem reasonable to assume that the maximum absorption is 9.40%.

The Norwegian Food Safety Authority has estimated dermal absorption in the *in vivo* study taking into account the MCPA remaining in the skin:

Absorbed MCPA = MCPA absorbed + MCPA in surrounding skin + MCPA in skin at the application site

For concentrate:

22.09 + 6.43 + 5.68 = 34.2%

For diluted sample:

9.40 + 0.33 + 6.19 = 15.92%

2.2.3 «Triple-pack approach»

A "triple-pack approach" adjusts the dermal absorption measured in rats in vivo with the ratio between dermal uptake in vitro in human and rat skin, respectively. The Norwegian

Food Safety Authority has concluded that for MCPA also the remainder of substance in the skin *in vitro* should be included in the “triple pack approach” for calculating dermal absorption. The values for absorption *in vitro* at 8 hours in rat and human skin have been used to adjust the measured values for dermal absorption in rats *in vivo* at 10 hours. The estimated values for human dermal absorption obtained in this way was 17% and 4% for concentrated and diluted MCPA solutions, respectively.

According to the OECD guidelines and the "Guidance Notes On Dermal Absorption" No. 156 (OECD, 2011), the amount of test compound remaining in skin after washing should in most cases be included in what is considered as absorbed.

The manufacturer has argued that only what remains of the substance in the skin in the *in vivo* study should be considered as absorbed, and not the skin remainder in the *in vitro* studies. This is because at the high dose he claims that most of the dose is absorbed early post exposure and no or little of what remains in the skin after that period is absorbed. He seeks support in “Guidance notes” (no. 156) (OECD, 2011) for his view, that this remainder should not be included in the absorbed dose when at least a portion of the residue in the skin is unlikely to be absorbed.

The manufacturer accepts to use *in vitro* data when calculating ratios for absorbance through skin of rats and humans (Nufarm Group, 2013), and also to include remainder in the skin as absorbable in *in vivo* experiments for dermal absorption at both the high and the low dose. It is the opinion of the manufacturer that in vitro studies are only representative for the barrier function of the skin, but does not provide a realistic picture of the *in vivo* uptake of the substance. This could be taken as an argument to only consider results from *in vivo* studies, but this would then prevent the use of a "triple-pack approach."

Absorption of chemicals through skin is dependent on many factors, for example, but not limited to, solubility of chemical in fat/water, amount of water in the skin, physical condition of the skin, thickness of the skin, blood perfusion, metabolic capacity and amount of fat in subcutis. Further, there are many uncertainties in methods used for assessing absorption through skin. Therefore, one should consider *in vitro* methods with care. Split thickness skin consists of various parts of the dermis in addition to the epidermis depending on the setting of the knife used for cutting of the skin slice. In the dermis there are different types of cells compared with the epidermis, in addition to blood vessels, hair roots, sweat glands and sebaceous glands. With regard to this, the split thickness skin model constitutes a more complex and more *in vivo*-like model than the epidermis, however, it is still an *in vitro* model without connection to the body’s blood system. As a consequence of this, for different substances different ratios between absorption of concentrated versus diluted test substance may be found. Thus, each chemical substance must be evaluated on an individual basis without too much stress put on the ratios observed for other substances.

Regarding the “triple-pack approach” the same method should be used for all parts of the assessment for each chemical. This implies that if amount of chemical left within the skin in the *in vivo* part of the approach is accepted as absorbed or absorbable, then the amount of

chemical left within the epidermis should be accepted as absorbed or absorbable. Thus, it is the opinion of the VKM panel that the previous conclusions of the Norwegian Food Safety Authority of a human dermal penetration factor for the working day of 17 % for the concentrate (750 g/L) and 4 % for field strength (1:83 dilution) are still valid.

2.2.4 Conclusion

Based on the above described considerations, VKMs Panel on Plant Protection Products supports the conclusion of the Norwegian Food Safety Authority concerning the determination of values for dermal absorption of MCPA. This includes the consideration of remaining substance in skin after washing as part of “absorbed” substance. The following values for dermal absorption are suggested: 17 % for the concentrated solution (750 g/L) and 4 % for the field strength solution (9 g/L).

3 Conclusions

VKM's Panel on Plant Protection Products has discussed the specific questions in the Terms of reference and has the following conclusions:

Determination of AOEL and ADI

It is the opinion of VKM's panel on Plant Protection Products that both AOEL and ADI for MCPA should be set to 0.036 mg/kg bw/day using a NOAEL of 3.6 mg/kg bw/day (50 ppm) based on renal effects in the 90-day study in rats.

Determination of values for dermal absorption

VKM's Panel on Plant Protection Products supports the conclusion of the Norwegian Food Safety Authority concerning the determination of values for dermal absorption of MCPA. This includes the consideration of remaining substance in skin after washing as part of "absorbed" substance. The following values for dermal absorption are suggested: 17 % for the concentrated solution (750 g/L) and 4 % for the field strength solution (9 g/L).

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