



Statement on the applicability of the 2008 VKM report "Combined toxic effects of multiple chemical exposures" after consideration of more recently published reports on risk assessment of combined exposures

Opinion of the Steering Scientific Committee of the Norwegian Scientific Committee for Food Safety

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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.

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Introduction

The theoretical principles for the various types of combined toxic effects of multiple chemical exposures and the description of models for handling cases where such effects are likely to occur are still applicable as described in the VKM report from 2008. The conclusions presented in this report are still valid, but for some points precisions have been made.

Background

The report "Combined toxic effects of multiple chemical exposures" was produced by The Norwegian Scientific Committee for Food Safety (VKM) in 2008 at a request of the Norwegian Food Safety Authority (Mattilsynet). VKM was asked to evaluate how combined toxic effects of multiple chemical exposures related to human and animal health and substances in animal feed were addressed in their risk assessments. In order to do so, three recent international reports should be considered when answering the request. The most relevant principles of risk assessments of combined toxic effects of multiple chemical exposures described in these reports, and in available scientific literature published later than 2003, were included in the report. The terms of reference did not include evaluation of how toxic effects of chemicals in mixtures were addressed in environmental risk assessments and this was therefore not considered specifically in the report.

Since the VKM report was published in 2008 there has been an increasing focus on effects of multiple chemical exposures on both human and animal health and on the environment. The publicity in various types of media on effects referred to as cocktail effects, combination effects, multiple stressors etc. reflects a growing public concern and a corresponding demand for identification and regulation of mixtures of chemicals that may pose a risk to public health or to the environment.

Terms of reference

Both national and international bodies have drawn attention to the effects of multiple exposures to chemicals and several scientifically based reports have been published in recent years and questions have been raised whether the 2008 VKM report is still applicable. The Scientific Steering Committee of the Norwegian Scientific Committee for Food Safety therefore decided to make a statement on the applicability of the 2008 VKM report "Combined toxic effects of multiple chemical exposures" in relation to more recent knowledge on risk assessment of combined exposures. The statement should address:

- the conclusions in the VKM report in relation to the recent report published by EU Commission DG Health & Consumers (SCER/SCHENIHR/SCCS, 2012)
- the conclusions in the VKM report in relation to scientific literature published after 2008

Assessment

The VKM report published in 2008 presents an overview of the basic knowledge and methodological concepts of combined toxic effects of multiple chemical exposures at the time of its publication. When related to scientific literature on combined toxic effects of multiple chemical exposures published after 2008, the descriptions of methods and the guidelines given in the VKM report are still applicable. Furthermore, recent publications do not reveal scientific evidence or concepts in conflict with the conclusions given in the VKM report. However, some later reports and scientific papers get closer into and add new insight into

several of the areas included in the report. This is briefly discussed in the following statement. For further details the reader referred to VKM report: Combined toxic effects of multiple chemical exposures, VKM 2008 (<http://www.vkm.no/dav/15ec300082.pdf>)....

1 Evaluation

1.1 Combined effects of multiple chemical exposures at doses below the respective effect threshold of each substance (in VKM 2008, conclusions in bullet points 1 – 4)

Concerns are expressed on whether mixtures of chemical substances, in which each of the substances is present at low doses, may have negative health effects. In this context, low doses are referred to as doses close to the NOAEL, effect threshold or point of departure (POD) for the individual substances. As presented in the VKM report, distinction should be made between mixtures of components that share a similar mode of action and mixtures in which the substances act by different modes of action.

If substances act by a similar mode of action (similar mechanism), dose addition is assumed and adverse effects of the mixture may be expected, even if the individual substances are present at doses below their respective no-observed-adverse-effect-levels (NOAELs). In addition to the assumption of similar mode of action, the dose-addition approach is also based on evaluation of the shape and slope of the individual dose-response curves for substances within groups of chemicals. Along with this, increasing interest has been shown to endocrine disrupting chemicals. If groups of chemicals bind to the same receptor, that is acts by a similar mode of action, dose addition should be used in risk assessments. However, as pointed out in the report by the European Commission (EC) Scientific Committees, grouping of chemicals may be difficult and no generally agreed criteria for grouping of substances exist (SCHER, SCCS, SCENIHR, 2012).

If substances act by different mode of action (dissimilar/independent mechanism), effect/response addition is assumed and adverse effects are considered unlikely if the individual substances does not affect the toxicity of each other and that each substance is present at a doses below their respective zero effect level. It has been discussed that experimentally derived NOAELs do not necessarily represent the true zero effect levels, and therefore it cannot be excluded that exposure at the NOAELs might contribute to effects. For multiple exposures to substances that act independently this is regarded unlikely at relevant human exposures as these are usually orders of magnitude below the NOAELs.

If no information on mode of action is available, use of the dose addition method may overestimate, whereas the independent action approach may underestimate the combined effects. In cases of unknown toxic mechanisms the use of dose addition is therefore considered sufficiently protective.

Interactions (synergy, antagonism and potentiation) of chemicals in mixtures are reported in some experiments, but such effects are difficult to predict and their likelihood need to be considered on a case-by-case basis. A recent review reported that in most of the studies where synergy was demonstrated, the doses of the individual substances exceeded their respective point of departure (POD) or Reference point (RfP) for establishment of health based guidance values (Boobies *et al.*, 2011). Furthermore, in a number of these studies the synergy

was dose-dependent and observed only at the higher doses in the study. In the small number of studies (6 of 90 reported) where low-dose synergy was demonstrated and could be quantitatively estimated, the toxicity did not exceed the levels predicted by additive models by more than a factor of 4. This supports the conclusion drawn by EFSA that significant toxic interactions are "- much less likely to occur at doses below the effect levels for individual component compounds than at higher doses" (EFSA, 2008). However, more studies are required to determine interaction of chemicals in mixture at real world exposures.

1.2 Proposed methods and models for risk assessment of multiple exposures to chemicals/chemical mixtures (in VKM 2008, conclusion in bullet point 6)

VKM includes the possible combined effects of multiple chemical exposures in their risk assessments where this is relevant and there are available data. A proposed procedure for risk assessments of chemicals in mixtures is presented in the report from 2008. More recently, the EC Scientific Committees have published an opinion in which a recommended decision tree for the risk assessment of chemical mixtures was presented (SCHER, SCCS, SCENIHR, 2012). There is also increasing interest in using tiered approaches in the risk assessment of combined effects of multiple chemical exposures, and a framework for this was presented by the WHO Framework for the Risk Assessment of Combined Exposure to Multiple Chemicals (WHO 2009, Meek *et al.*, 2011). These suggestions are mainly based on the same principles as the procedure proposed in VKM, 2008. However, both exposure and hazard assessments are difficult to perform with the very limited data available. In order to predict the toxic effect of a chemical mixture, the individual components of the mixture have to be identified. Furthermore, their mode of action and their dose-response curves have to be known or at least be appropriately assumed. As concluded in the report by the EC Scientific Committees, such information is rarely available (SCHER, SCCS, SCENIHR, 2012).

1.3 Risk assessments of combined effects of exposure to multiple pesticides in VKM (in VKM 2008, conclusion in bullet point 7)

Within the VKM, environmental risk assessment of toxic chemicals is in practice restricted to pesticides. The Scientific Panel on Plant Protection Products performs risk assessment of pesticides as a basis for approval of plant protection products (PPPs) on the Norwegian market. In these assessments combined effects of all ingredients present in the PPPs are addressed by the requirement that effect studies on various aquatic and terrestrial, non-target organisms must be done on both the individual active ingredient(s) and the composite PPPs. Thus, combined effects of pesticides are assessed in those cases when a PPP contains more than one active ingredient. However, the effect of multiple exposures to pesticides and other toxic components that may occur in the environment is currently not covered in the risk assessment of the individual PPP.

1.4 Differences in methods in human and environmental risk assessment (in VKM 2008, conclusion in bullet point 10)

The request from the Norwegian Food Safety Authority was to consider combined toxic effects of multiple chemical exposures related to human and animal health and components in animal feed. Thus, the basic concepts used in evaluation of effects referred in the VKM report were not intended to fully cover combined effects on the environment. The combined toxic effects are mainly described as dose addition, response addition or interactions, and are applicable to the responses of individual organisms. In ecotoxicology, however, the objective is also to assess the risk for higher hierarchical levels such as populations and communities and it is suggested that in such cases multiple exposures to substances that act independently should be considered a possible concern even if all substances are below their individual predicted no effect concentrations (PNECs). Since substances that act independently at the individual level may similarly affect end points at the population level, it has been suggested that the dose-addition approach may be more appropriate at the population level (SCHER, SCCS, SCENIHR, 2012). Test procedures and considerations other than those described in the VKM report may therefore be needed in environmental risk assessments.

2 International activities on risk assessments of effects of multiple chemical exposures

VKM follows closely what is going on regarding chemical mixtures/multiple chemical exposures within EFSA, the Scientific Committees of the European Commission and World Health Organization. Examples of current activities on chemical mixtures at EFSA are (EFSA, 46th Advisory Forum Meeting, December 2012):

- Finalisation of a scientific report reviewing international frameworks for human risk assessment of mixtures ("Combined exposure to multiple chemicals").
- An *ad hoc* Working Group chaired by DG Environment and with representatives from the European Agencies (EFSA, EMA, ECHA, EEA) and the Commission (JCR, DG-SANCO) has recently been established (2012). The aim is among other things to develop guidelines and identify mixtures of priority across different areas relevant for human, animal and environmental risk assessments.
- Procurement (December 2012 – December 2014): To get a systematic review/Meta-Analysis on metabolic interactions/synergistic effects of mixtures for 100 chemicals of relevance to EFSA.

Conclusion

- When compared to scientific literature on combined toxic effects of multiple chemical exposures published after 2008, the theoretical principles for the descriptions of methods and the guidelines given in the VKM report are still applicable. Furthermore, recent publications do not reveal scientific evidence or concepts in conflict with the conclusions given in the VKM report.
- The dose addition approach is based on assumption of a similar mode of action within groups of chemicals. However, no generally agreed criteria for grouping of substances exist. If substances act by different modes of action, adverse effects are considered unlikely if individual substances are present at doses below their respective zero effect

level. It has been discussed that experimentally derived NOAELs do not necessarily represent the true zero effect levels, and it cannot be excluded that exposure at the NOAELs might contribute to effects. If no information on mode of action is available, the use of dose addition is considered sufficiently protective. Interactions seem to be less likely to occur at doses below the effect levels for the individual components than at higher doses, but more experimental studies are required to determine interaction at realistic exposures.

- The proposed procedure for risk assessments of chemicals in mixtures presented in the report from 2008 is still applicable and may be used where this is relevant and there are available data.
- The Scientific Panel on Plant Protection Products performs risk assessment of pesticides as a basis for approval of plant protection products (PPPs) on the Norwegian market. In these assessments combined effects of all ingredients present in the PPPs are addressed.
- In environmental risk assessments, where end points for higher hierarchical levels such as populations and communities of organisms are used, test procedures and considerations other than those described in the VKM report may be needed.

References

SCHER, SCCS, SCENIHR, Opinion on the Toxicity and Assessment of Chemical Mixtures, 2012. Toxicity and Assessment of Chemical Mixtures (2012).
http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scher_consultation_06_en.htm

EU Commission Communication from the Commission to the Council: The combination effects of chemicals – Chemical mixtures, COM (2012) 252 final.

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2012:0252:FIN:EN:PDF>

WHO/IPCS – Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework (2009).

<http://www.who.int/ipcs/methods/harmonization/areas/aggregate/en/index.html>

M.E. (Bette) Meek et al.. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework (2011).

<http://www.ncbi.nlm.nih.gov/pubmed?term=Meek%20202011%20WHO%2FIPCS>

<http://www.sciencedirect.com/science/article/pii/S0273230011000638>

Danish Ministry of the Environment (Miljøstyrelsen) Expert workshop on combination effects of chemicals, 28-30 January 2009, Hornbæk, Denmark (Kortenkamp and Haas, 2009).

http://www.mst.dk/English/Chemicals/endocrine_disruptors/report_from_expert_workshop_on_combination_effects/

DTU Fødevareinstituttet - Kemiske cocktails kan forstyrre hormonerne (2009).

<http://www.food.dtu.dk/Default.aspx?ID=21525&PID=215804&NewsID=1954>

EFSA – Chemical Mixtures – Update on Activities. Presentation at the 46th Advisory Forum meeting, Cyprus 05-06 December, 2012.

EFSA - Scientific Opinion of the PPR Panel on Risk Assessment for a Selected Group of Pesticides from the Triazole Group to Test Possible Methodologies to Assess Cumulative Effects from Exposure through Food from these Pesticides on Human Health (2009).

<http://www.efsa.europa.eu/en/scdocs/doc/1167.pdf>

EFSA - Opinion of the Scientific Panel on Plant Protection products (PPR) and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005 (2008).

<http://www.efsa.europa.eu/en/scdocs/doc/705.pdf>

VKM - Combined toxic effects of multiple chemical exposures (2008).

http://vkm.no/eway/default.aspx?pid=277&trg=Content_6498&Main_6177=6498:0:31,2366&Content_6498=6187:1656702::0:6295:8:::0:0

Alan Boobies et al.. Critical analysis of literature on low-dose synergy for use in screening chemical mixtures risk assessment (review 2011).

<http://preview.ncbi.nlm.nih.gov/pubmed/21309635>

Denis A Sarigannis and Ute Hansen. Considering the cumulative risk of mixtures of chemicals – A challenge for policy makers (review, 2012).

<http://www.ncbi.nlm.nih.gov/pubmed?term=Denis%20A%20Sarigannis%20and%20Ute%20Hansen%202012>

Swedish Chemical Agency: Hazard and Risk Assessment of Chemical Mixtures under REACH (2010). www.kemi.se/Documents/Publikationer/Trycksaker/PM/PM3_10.pdf