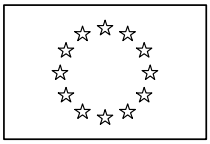

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COMMUNICATION FROM THE COMMISSION TO THE COUNCIL

The combination effects of chemicals

Chemical mixtures

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1. INTRODUCTION

In recent years there has been an increasing focus on the effects on human health and on the environment arising from exposure to many different chemicals. These effects are variously referred to as combination effects, mixture effects or cocktail effects. The European Parliament has consistently drawn attention to the need to take account, in the context of EU chemicals' legislation, of the combined effects of different chemicals on human health and the environment. On 22nd December 2009, the Council, based in part on concerns arising from the Danish toddler study (Box 1), adopted a set of conclusions on the "combination effects of chemicals"[1].

Box 1. Mixtures to which human populations are exposed

In 2009, The Danish authorities published the results of a study[2] in which the exposure of toddlers (2 year old children) to chemical mixtures in the form of multiple endocrine disruptors from several sources were examined. The study examined exposure through the food chain, through indoor air and dust, through clothes and shoes, through contact with toys, through the application of health care and hygiene products and through contact with articles such as changing mats and bath mats. On the basis of the predicted concentration of the various substances the study concluded that there was a need to reduce exposure to anti-androgen and oestrogen substances from food, indoor air and consumer products.

The Council in particular, invited the Commission, *"… to assess how and whether relevant existing Community legislation adequately addresses risks from exposure to multiple chemicals from different sources and pathways, and on this basis to consider appropriate modifications, guidelines and assessment methods, and report back to the Council by early 2012 at the latest."*

The purpose of the present Communication is to respond formally to the invitation from the Council and in particular to assess whether the current EU legislation which is built predominantly on the assessment of single substances and single sources, guarantees the high level of protection required by the Treaty. The challenge of dealing with chemical mixtures will also be taken-up in the context of preparing the future priorities for environmental policy. Actions taken to reduce exposure to potentially harmful chemical mixtures will also contribute to the achievement of the objectives in the Health for Growth programme[3]

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1 Council conclusions on combination effects of chemicals. 2988th Environment Council meeting Brussels, 22 December 2009.

2 Survey and Health Assessment of the exposure of 2 year olds to chemical substances in consumer products. Danish Ministry of the Environment, Environment Protection Agency, (2009)

3 Proposal for a Regulation of the European Parliament and of the Council on establishing a Health for Growth Prpgramme, the third multi-annual programme of EU action in the field of health for the period 2014-2020. COM(2011) 709 final.

The present document draws heavily upon the joint opinion of three scientific Committees[4] (hereinafter "the Scientific Committees") and also takes into account a major study "State of the Art Report on Mixture Toxicity" financed by the Commission[5] .

2. MIXTURES[6] IN THE CONTEXT OF EU CHEMICALS LEGISLATION

In the EU as in other parts of the world, chemicals' legislation is built on the foundation of assessments carried out on individual chemical substances. These assessments are frequently used as the basis for decisions related directly to the individual substances. However, in addition to the rules governing the assessment and management of individual substances, there is also an extensive body of EU legislation dealing with various types of mixtures.

2.1 Intentional Mixtures

In the case of intentional mixtures, the composition of the mixtures is well known and the assessments are based on the properties of the constituents supplemented, where appropriate, by tests carried out on the entire product. Examples of this type of legislation include rules for the classification, labelling and packaging of mixtures[7], rules for the authorisation of plant protection products[8], the rules governing the composition of cosmetics[9], rules governing the approval of medicinal products for human use[10] and rules governing the approval of veterinary medicinal products[11].

2.2 Mixtures originating from a single source.

Discharges to the environment during the production, transport, use or disposal of goods, often contain a mixture of chemical substances. Where the composition is known or the components can be identified by analytical methods, assessments can be made based on knowledge of the constituents. Where the composition is unknown an assessment would need to be based on tests carried out on the whole mixture. There are very few examples of EU legislation specifically requiring the assessment or testing of whole mixtures. However, the requirement set down in the Water Framework Directive[12] for water bodies to achieve good

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4 Toxicity and Assessment of Chemical Mixtures. Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENHIR) and Scientific Committee on Consumer Safety (SCCS). Joint Opinion adopted on 14th December 2011. http://ec.europa.eu/health/scientific_committees/environmental_risks/opinions/index_en.htm

5 Web site of DG ENV of the European Commission. http://ec.europa.eu/environment/chemicals/effects.htm

6 The terms "chemical mixtures", "chemical cocktails" and the "combination effects of chemicals" are often used interchangeably. For reasons of clarity, the term "chemical mixtures" will be used in the present document.

7 Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures. OJ L 353, 31.12.2008, p. 1.

8 Regulation EC No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market. OJ L 309, 24.11.2009, p. 1.

9 Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30th November 2009 on cosmetic products. OJ L 342, 22.12.2009, p. 59.

10 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. OJ L 311, 28.11.2001, p. 67

11 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. OJ L 311, 28.11.2001, p. 1

12 Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000, establishing a framework for Community action in the field of water policy. OJ L 327, 22.12.2000, p. 1.

ecological status as well as good chemical status entails a focus not only on the concentrations of individual chemicals but also on their effects in combination.

2.3 Mixture of Chemicals originating from multiple sources and through multiple pathways.

In relation to the assessment of multiple substances from multiple sources, which represents the main focus of the concern raised by the Council, there are only a limited number of examples in EU legislation. In the context of REACH[13] guidance has been developed concerning the assessment of multiple sources of exposure to a single substance and in specific cases to the assessment of several closely related and similarly acting substances (e.g. different salts of the same metal or a number of closely related derivatives of organic substances[14]. In the workplace, employers are required to carry out an assessment of hazardous chemicals including an obligation to assess the risks presented by all such chemical agents in combination[15] In relation to the establishment of maximum levels for pesticide residues in, or on, food and feed of plant and animal origin[16] the panel on Plant Protection Products of the European Food Safety Authority (EFSA), developed approaches for taking account of cumulative and synergistic effects when setting maximum residue levels (MRLs) for pesticides with similar modes of action[17]. EFSA is also developing methodology for pesticides with a dissimilar mode of action for occupational exposure[18]

2.4 Conclusion

In conclusion, where chemical mixtures are assessed and regulated under EU legislation this is predominantly in relation to chemical products of known composition. Some complex mixtures discharged/emitted to the environment from a single source (factory, facility, etc), are also subject to controls. There are a few examples of assessments and controls being carried out in relation to several substances originating from different sources and through different pathways but these are limited in their scope. Currently, within the framework of EU legislation, there is no mechanism for a systematic, comprehensive and integrated assessment of mixture effects taking into account different routes of exposure and different product types. Thus the recent study carried out in Denmark (see Box 1) highlighting the concerns associated with the exposure of toddlers to different endocrine disruptors could not, at present, trigger a comprehensive assessment within the context of EU legislation.

3. CAN EXPOSURE TO SMALL CONCENTRATIONS OF DIFFERENT SUBSTANCES HAVE NEGATIVE EFFECTS?

We have seen in section 2 that there exists a very extensive corpus of legislation designed to ensure that the concentrations of chemical substances to which human beings or animals and plants, are exposed are within safe limits. On condition that the legal requirements are

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13 Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18th December 2006 concerning the Registration, Authorisation and Restriction of Chemicals-REACH. OJ L 136, 29.5.2007, p. 1.

14 http://echa.europa.eu/documents/10162/13632/information_requirements_part_e_en.pdf

15 Council Directive 98/24/EC of 7th April 1998 on the protection of the health of workers from the risks related to chemical agents at work. OJ. L131, 5.5.1998, p11

16 Regulation (EC) No 396/2005. OJ. L70, 16.5.2005, p1

17 EFSA Journal 2008; 704: 1-85 http://www.efsa.europa.eu/en/efsajournal/doc/705.pdf and EFSA Journal 2009; 7: 1167. http://www.efsa.europa.eu/en/efsajournal/pub/1167.htm

18 http:www.efsa.europa.eu/en/supporting/pub/232e.htm

respected, this means that although we (also animals and plants) are exposed to small concentrations of many different chemicals none of these chemicals should be present above their individual safe limits. This being the case and in order to respond to concerns expressed by the Council, we need to examine whether or not a mixture of chemical substances, originating from different sources and through different pathways, in which each of the substances is present at very low concentrations , could have negative effects on human health or the environment.

The Scientific Committees indicated that, under certain conditions, chemicals present in a mixture will act jointly in a way that the overall level of toxicity is influenced. In particular, chemicals with common modes of action[19] may act jointly to produce combination effects that are larger than the effects of each of the mixture components applied singly. However, in the case of substances with different modes of action (independently acting[20].), the Scientific Committees concluded that there is no robust evidence available to indicate that exposure to a mixture of such chemicals is of health concern if the individual chemicals are present at or below their zero effect levels. As to whether the possibility of exposure to mixtures of chemical substances is a potential cause for concern (in relation to human health), the Scientific Committees concluded that " *if the intended level of protection is achieved for each individual substance, the level of concern for mixtures of dissimilarly acting substances should be assumed to be negligible*".

However, in relation to ecological effects, the situation is less clear and the Scientific Committees concluded that "*In summary, for ecological effects, the exposure to mixtures of dissimilarly acting substances at low, but potentially relevant concentrations should be considered as a possible concern, even if all substances are below the individual* **P**redicted **N**o **E**ffects **C**oncentrations *(PNECs). Consequently there is a need for improving the current knowledge and methodologies, and developing holistic approaches for the ecological risk assessment of chemicals under realistic conditions."*

4. THE SCIENTIFIC CHALLENGE

4.1. Identifying priorities

As indicated in the previous section, exposure to mixtures of chemicals even when these chemicals are present at low (real-world) concentrations may give rise to concerns. However, the number of potential combinations of the tens of thousands of substances currently in commerce is astronomical and the attention of the risk assessors should be focussed on those situations where the potential for negative impacts is highest. The Scientific Committees have provided clear indications concerning the criteria and methodologies that could be applied to identify chemical combinations/mixtures that are priorities for further assessment (see Box 2).

Box 2. Extract from detailed recommendations of the Scientific Committees in relation to setting priorities

[19] According to the Scientific Committees a Mode Of action is a plausible hypothesis about measurable key events by which a chemical exerts its biological effects. A common mode of action is defined by EFSA as "involving the same key events leading to an adverse health effect following interaction of the compound with its biological target[s]

[20] According to the Scientific Committees, Independent Action occurs where the modes of action and possibly, but not necessarily, the nature and sites of toxic effects differ between the chemicals in a mixture and one chemical does not influence the toxicity of another.

In view of the almost infinite number of possible combinations of chemicals to which humans and environmental species are exposed some form of initial filter to allow a focus on mixtures of potential concern is necessary. The following criteria are proposed for consideration:

1) Human and/or environmental exposure at significant levels.

2) Chemicals that are produced and/or marketed as multi-constituent substances or commercial mixtures with several components and/or active ingredients and/or substances of concern.

3) Potential serious adverse effects of one or more chemicals at the likely exposure levels.

4) Likelihood of frequent or large scale exposure of the human population or the environment.

5) Persistence of chemicals in the body and/or in the environment.

6) Known information of potential interaction at levels of human and environmental exposure.

7) Predictive information that chemicals act similarly.

8) Particular attention should be paid to mixtures for which one or more components are assumed to have no threshold for its effects.

4.2. The scientific assessment of chemical combinations/mixtures

When a particular chemical mixture is identified as a priority for further assessment the Scientific Committees has also provided detailed advice concerning the methods that are currently available for assessing/predicting the toxicity of such chemical mixtures (see Box 3).

Box 3. Extract from detailed recommendation from the Scientific Committees in relation to assessment

In view of the huge variety of human exposures to chemical mixtures, the default assumption in human risk assessment had been that the chemicals generally acted by dissimilar modes of action. In cases, however, where information is available to indicate a similar mode of action, a dose/concentration addition approach is appropriate. A dose/concentration addition approach, if applied to chemical mixture components with unknown modes of action, may result in an over-prediction of toxicity; using the independent action approach may however underestimate toxicity. Therefore, in the case of unknown modes of action, the dose/concentration addition approach is also preferable to ensure an adequate level of protection.

In ecotoxicology, any approach should be referred to specific endpoints and to defined taxonomic groups of organisms. […]A significant limitation of component-based approaches is that they are only applicable to mixtures of which the major components are known.

4.3. Knowledge/Data gaps

While providing extensive guidance regarding the identification of chemical mixtures of highest concern and the methodologies for assessing such mixtures, the Committees also drew

attention to the many data and knowledge gaps that impede a more systematic and effective application of these methodologies (see Box 4).

Box 4. Extract from detailed Recommendations from the Scientific Committees in relation to knowledge gaps

With regard to the assessment of chemical mixtures a major knowledge gap at the present time is the lack of knowledge on where, how often and to what extent humans and the environment are exposed to certain chemical mixtures and how exposure may change over time. There is a need to better understand human and environmental exposures, both through the use of monitoring and modeling.

For many chemicals, there is no good information on mode of action. Currently there is neither an agreed inventory of modes of action, nor a defined set of criteria on how to characterise or predict a mode of action for data-poor chemicals or how to group chemicals into assessment groups.

Interactions[21] of chemicals in mixtures are difficult to foresee, particularly for long-term effects. Research is needed to define criteria that predict potentiation or synergy.

In ecotoxicology, the problem is even more complex. A knowledge of all possible modes of action that may occur in the different types of organisms of a complex biological community is difficult (if not impossible) to be attained. On the other hand, it must be considered that ecologically relevant endpoints are generally broader and not so specific (e.g. toxicity on specific organs, etc.) as in human toxicology. A full review of the literature should be made to prepare a state-of-the-art on mixtures biodegradation modelling.

The Committees also indicated that "the REACH Regulation is generating the largest database on chemicals in history and that this information could be used to reduce some of the current uncertainties……."

4.4. Can the assessment of chemical mixtures be carried out in a more systematic way in the context of EU legislation?

On the basis of the opinion from the Scientific Committees it appears that having identified a particular chemical mixture as a priority for further assessment, the scientific methodology is available for carrying out such assessments although there are currently many knowledge/data gaps that might act as a barrier to actually applying these methods. The question therefore remains as to whether the current state of knowledge is sufficiently robust to support a more systematic assessment of chemical mixtures in the context of EU legislation. The Scientific Committees also provided clear recommendations with regard to this matter (see Box 5).

Box 5. Extract from the Recommendation of the Scientific Committee in relation to the possibility to undertake assessment of mixtures in a more systematic way in the context of EU legislation

[21] The Scientific Committees indicated that the term interaction describes the combined effect of two or more chemicals when it is stronger (synergistic, potentiating or supra-additive) or weaker (antagonistic, inhibitive, sub-additive) than would be expected on the basis of dose/concentration addition.

In many cases, knowledge is insufficient for a robust scientific analysis. If toxicologically significant interactions can be excluded, the components of a mixture are identified and known mode of action information is available, either a dose addition or independent action model should be applied. This set of information, in human toxicology, is, however, rarely available and, in most cases, very cost- and labour-intensive to generate.

In ecotoxicology, the mode of action should be known for all the relevant taxonomic groups of aquatic and terrestrial ecosystems. Thus, the availability of information is even more limited; in addition, modes of actions considered dissimilar at the individual level may affect the same population relevant endpoint, and therefore, the dose/concentration addition model may be more appropriate for predicting effects at the population level.

In order to prioritize chemical mixtures for possible assessment it is first necessary to consider whether there is significant human or environmental exposure to the mixture or its components. Unless there are indications of a significant interaction, a dose/concentration addition model could be used if the components of the mixture exert their biological effects via an identical or similar mode/mechanism of action. If the mixture components act dissimilarly, the independent action model would be applied. It further appears justifiable that a dose/concentration addition approach should be used as default approach in cases where neither mode of action nor dose-response information is available to ensure adequate conservatism in the assessment.

In addition to the recommendations referred to in Box 5, the Scientific Committees also provided a decision tree that could be applied when dealing with chemical mixtures (for further details see Scientific Committees' opinion).

5. CONCLUSIONS

5.1. In relation to the current situation

(1) Current EU legislation does not provide for a comprehensive and integrated assessment of cumulative effects of different chemicals taking into account different routes of exposure. In the case where a mixture of concern is identified and where such a mixture contains chemical substances regulated under different pieces of EU legislation, no mechanism currently exists for promoting an integrated and co-ordinated assessment across the different pieces of legislation.

(2) In the case of chemicals with independent modes of action, the establishment of "safe levels" based on the assessment of individual substances appears, in relation to human health, to provide a sufficient safeguard against possible negative effects from mixtures/combinations.

(3) However, where chemicals have similar modes of action there is a potential for cumulative effects when such chemicals are present together in a mixture (even when the concentration of each substance is below its "safe level") and then, the concentration/dose addition approach is preferred in order to assure an adequate level of protection.

(4) In relation to the effects on wild species and ecosystems, the situation is less clear and the possibility of combination/mixture effects should be considered both in the

case of independently acting chemicals as well as for chemicals with similar modes of action.

(5) Methodologies for the identification of chemical mixtures of potential concern as well as for the assessment of chemical mixtures are available. However, there are extensive knowledge and data gaps (mainly related to the mode of action and exposure data) that limit the extent to which mixtures can be properly assessed. Information being collected in the context of EU legislation, in particular the REACH Regulation, will contribute to reducing current uncertainties.

(6) Notwithstanding the knowledge and data gaps it is possible to assess mixture toxicity in a more systematic manner in the context of EU legislation. When information regarding the mode of action and dose/response is not available, or inconclusive, a default assumption of dose/concentration addition provides a higher level of protection but may also overestimate negative effects. This limitation and the additional costs it might imply shall be taken into account in the case where possible management measures are being considered

(7) While not specifically addressed in the opinion from the Scientific Committees, the assessment of chemical mixtures must be carried out in respect of the principle of reducing, refining and replacing testing on vertebrate animals.

5.2. In terms of operational follow-up

In the light of the above conclusions the Commission will:

(1) Establish an ad hoc working group of relevant services and associated Agencies and Authorities (EFSA, ECHA, EMEA and EEA) to strengthen co-ordination across the different pieces of legislation and to promote the integrated assessment of priority mixtures, taking into account the risks of human and environmental exposure. The ad-hoc working group will co-ordinate the work of bringing together the data and oversee the integrated assessment of priority mixtures. Any follow-up action would be taken in the frame of the legislation under which each substance is currently regulated.

(2) Develop, by June 2014, and taking account of the opinion of the Scientific Committees, technical guidelines to promote a consistent approach to the assessment of priority mixtures across the different pieces of EU legislation. Such guidelines shall not replace existing rules where such exist nor shall they impose additional obligations or burdens on economic operators. The development of these guidelines will be co-ordinated by the ad-hoc working group referred to in point (1) above.

(3) Support improved understanding of the chemical mixtures to which human populations and the natural environment are actually exposed by :

(a) reviewing, in consultation with the associated Agencies, the monitoring data which is currently collected under EU legislation or generated in the context of EU funded research projects[22];

[22] Taking into account the actions of the European Environment and Health Action Plan {SEC(2004)729} /* COM/2004 416 final

(b) promoting a more coherent approach to the generation, collection, storage and use of chemical monitoring data in relation to humans and the environment, through the creation of a platform for chemical monitoring data. This would help identify links between exposure and epidemiological data in order to explore potential biological effects and lead to improved health outcomes.

(4) Examine the opportunities for addressing some of the other knowledge gaps, in particular relating to (i) the mode of action of chemicals, (ii) grouping chemicals into categories or assessment groups; (iii) predicting interactions and (iv) identifying chemical substances that are the main drivers of mixture toxicity. These actions may in part be supported through Horizon 2020, the future EU framework programme for research and innovation.

(5) Promote consistent and science-based approaches to the risk assessment of chemical mixtures at a global level by participating in relevant international activities This will help protect health and the environment as well as promoting the competitiveness of European industry.

(6) Publish a report on the assessment of chemical mixtures by the end of June 2015, reviewing the progress and experience associated with the actions identified under points 1 to 5 above.

In carrying out the actions set out under points 1-5 above the Commission will collaborate with the Member States and other stakeholders. The modalities of this collaboration will need to be defined and will, wherever possible, make use of existing structures.