Pesticides Research Nr. 80 2003
Bekæmpelsesmiddelforskning fra Miljøstyrelsen

Report on the Health Effects of Selected Pesticide Coformulants

Lea Stine Tobiassen, Elsa Nielsen, Pia Nørhede
and Ole Ladefoged
Danish Veterinary and Food Administration, Institute of Food Safety and Nutrition

Danish Environmental Protection Agency
Danish Ministry of the Environment

The Danish Environmental Protection Agency will, when opportunity offers, publish reports and contributions relating to environmental research and development projects financed via the Danish EPA.

Please note that publication does not signify that the contents of the reports necessarily reflect the views of the Danish EPA.

The reports are, however, published because the Danish EPA finds that the studies represent a valuable contribution to the debate on environmental policy in Denmark.

Contents

The appendices 1-18 are published only at the homepage of the Danish Environmental Protection Agency, http://www.mst.dk.

Preface

The report has been prepared by the Institute of Food Safety and Nutrition, Danish Veterinary and Food Administration, as a contract work under the pesticides research programme that is administrated by the Danish Environmental Protection Agency (Danish EPA).

The work has been followed by a Steering Committee who has contributed to the work with professional expertise, proposals and criticism:

Jørn Kirkegaard, Danish EPA
Annika Boye Andersen, Danish EPA
Sven Edelfors, Pharmacological Institute, University of Copenhagen
Gunnar Damgaard Nielsen, Danish National Institute for Occupational Health
Ole Ladefoged, Institute of Food Safety and Nutrition, Danish Veterinary and Food Administration
Elsa Nielsen, Institute of Food Safety and Nutrition, Danish Veterinary and Food Administration
Pia Nørhede (formerly Berthelsen), Institute of Food Safety and Nutrition, Danish Veterinary and Food Administration (until 1 December 2001) and Lea Stine Tobiassen, Institute of Food Safety and Nutrition, Danish Veterinary and Food Administration (from 1 January 2002).

The report was prepared by Lea Stine Tobiassen, Elsa Nielsen, Pia Nørhede, and Ole Ladefoged, Institute of Food Safety and Nutrition, Danish Veterinary and Food Administration.

The report reflects the views and opinions of the authors as well as of the members of the Steering Committee although consensus has not been reach on every aspect discussed in the report. It should also be noted that the report does not necessarily represent the views and opinions of the involved institutions.

Sammenfatning

Hjælpestoffer bruges udstrakt i formuleringen af pesticider, hvorved de udgør en potentiel sundhedsrisiko for mennesker gennem disses udsættelse for pesticider. I 1999 udtrykte Bichelkomitéen bekymring over, at hjælpestoffer ofte kan være mere akut giftige end aktivstofferne i plantebeskyttelsesmidler. Komiteen anbefalede, at godkendelsesproceduren for plantebeskyttelsesmidler blev udvidet til at omfatte datakrav for hjælpestoffer. Bichelkomitéen anbefalede desuden et forbud mod brug af kræftfremkaldende hjælpestoffer.

Dette projekt har til formål at vurdere udvalgte hjælpestoffers toksikologiske egenskaber. Disse vurderinger vil kunne indgå i grundlaget for en beslutning om, det er nødvendigt at revidere den eksisterende lovgivning. De toksikologiske egenskaber for 18 pesticidhjælpestoffer er vurderet på baggrund af den tilgængelige litteratur. Stofferne er fortrinsvis udvalgt på baggrund af de mængder, de markedsføres i, men derudover var der også flere udelukkelseskriterier.

Den database, der således er blevet samlet, viser en lav datatilgængelighed. Data udgøres overvejende af dyreforsøgsdata, hvorimod humane data er få og ofte af tvivlsom kvalitet og/eller relevans. De fundne data vedrører primært akut toksicitet og irritative effekter, og der er kun få data om sensibilisering, effekter ved gentagen eksponering, reproduktionsskadende effekter samt kræftfremkaldende effekt. En detaljeret farevurdering af disse hjælpestoffer vanskeliggøres derfor som følge af det manglende datagrundlag for en lang række effekter.

De toksikologiske vurderinger for de udvalgte hjælpestoffer viser at stofferne har en række sundhedsmæssige effekter. Mange af hjælpestofferne er irriterende for huden, øjnene og luftvejene. Nogle af hjælpestofferne har alvorlige sundhedsmæssige effekter som neurologiske påvirkninger, narkotisk effekt, sensibilisering, hæmolytisk effekt, og nyreskadende effekter. Et hjælpestof har muligvis en reproduktionsskadende effekt ved indånding af meget høje koncentrationer. Der er data vedrørende kræftfremkaldende effekt for 10 af de udvalgte hjælpestoffer, men ingen af disse stoffer har et kræftfremkaldende potentiale.

Projektets omfang er for begrænset til, at det kan danne grundlag for generelle konklusioner om sundhedsmæssige effekter eller om datatilgængeligheden for hjælpestoffer. Derudover betyder stofudvælgelsen, at stofferne muligvis ikke er repræsentative. Det er uvist, i hvor høj grad de fundne oplysninger kan ekstrapoleres til det store antal hjælpestoffer, der bruges. Imidlertid peger resultaterne på, at hjælpestoffer ikke er toksikologisk inerte, men at de tværtimod i visse tilfælde har endog alvorlige sundhedsmæssige egenskaber. Omfanget at dette problem kan dog ikke vurderes på grund af den begrænsede mængde toksikologiske data, der er tilgængelige for hjælpestofferne.
Det skal bemærkes, at der for de udvalgte hjælpestoffer ikke kan foretages en egentlig risikovurdering inden for dette projekts rammer, da projektet kun har omfattet en farevurdering, men ikke eksponeringsvurdering. Der kan således ikke udelukkende på baggrund af resultaterne i dette projekt drages en

konklusion, hvorvidt eksponering for disse udvalgte hjælpestoffer i plantebeskyttelsesmidler udgør en sundhedsmæssig risiko for mennesker ved anvendelse af disse midler.

På baggrund af resultaterne opnået i dette projekt kan det anbefales, at myndighederne tager yderligere tiltag hen imod en beskyttelse af menneskers sundhed som følge af udsættelse for hjælpestofferne ved brug af pesticider. Dette kan gøres for eksempel ved at stille krav om, at enten pesticidhjælpestoffernes eller pesticidernes toksikologiske egenskaber undersøges, således at der kan foretages en detaljeret farevurdering for alle relevante effektområder. En anden mulighed er en yderligere regulering af anvendelsen af visse hjælpestoffer i pesticider, det vil sige et forbud mod anvendelse af de hjælpestoffer for hvilke, der er identificeret særligt alvorlige sundhedsmæssige egenskaber.

Summary

Coformulants are widely used in the formulation of pesticides and thus constitute a potential health risk to humans through exposure to pesticides. In 1999, the Bichel Committee expressed concern that coformulants in some cases were more acutely toxic than the active substances in plant protection products and recommended that the approval system for plant protection products should also include data requirements on coformulants. The committee also recommended considering a ban of carcinogenic coformulants.

This project aims at compiling the available data and assessing the toxicological effects of selected coformulants in order to create at basis for decision making with respect to the possible need to revise the existing legislation. The effects of eighteen pesticide coformulants are assessed for adverse health effects on the basis of available literature. The substances for this project have been selected primarily on the basis of their tonnage on the market, but a number of exclusion criteria were also taken into account in the prioritisation.

The results of this project demonstrate that the data availability for the 18 selected coformulants is limited. Toxicological data are available for 16 of the selected coformulants; for 2 of these coformulants, relevant data are only available for acute toxicity and irritation. For the remaining 2 coformulants, no relevant data are available at all. The database for the individual substances consisted primarily of animal data, as human data were scarce and often of questionable quality and/or relevance. The data found related predominantly to acute toxicity and irritative effects, and only few data were located on sensitisation, repeated dose toxicity, toxicity to reproduction, and carcinogenicity. Furthermore, for many of the coformulants, various end-points have not been examined thoroughly although data are available. In conclusion, the hazard assessments of most of the selected coformulants may be hampered by the data gaps identified.

The hazard assessments of the selected coformulants showed a number of toxicological effects of the substances. Many of the substances were irritative to the skin, eyes and respiratory tract. Serious effects were reported on some of the coformulants including neurological effects, CNS depression, sensitisation, haemolytic effects, and nephrotoxicity. One coformulant is probably a developmental toxicant following exposure at very high concentrations. For none of the selected coformulants, a carcinogenic potential has been identified; however, data are only available for 10 of the selected coformulants for this end-point.

The scope of the project is too limited to make general conclusions on toxicity and data availability on coformulants. Also, the criteria for the prioritisation of the coformulants in this projects give rise to some bias regarding the representativity of the results obtained and thus, it is not known whether the conclusions made based on the 18 selected substances can be extended to the large number of coformulants used. However, the data indicate that

coformulants are not toxicologically inert, but in some cases even have serious adverse health effects.
It should be noted that a proper risk assessment cannot be performed for the selected coformulants as no exposure assessments have been carried out in this project, which only has focused on hazard assessment. Thus, no conclusions can be made exclusive based on the results obtained in this project whether exposures to these coformulants in pesticides may constitute a risk for humans of experiencing adverse health effects during the use of these pesticides.

On the basis of the results obtained in this project, it is recommended that the authorities take further measures to ensure that humans are protected from experiencing adverse health effects following exposure to coformulants used in pesticide formulation. A revision of the current approval scheme in order to include data requirements on all relevant toxicological end-points for either the coformulants or the pesticide coformulations could be considered in order to enable a detailed hazard assessment of every end-point of relevance to human health. Another measure could be a further regulation on the use of coformulants in pesticide formulations, i.e., to prohibit the use of coformulants for which serious health effects are identified.

1 Introduction

1.1 Aim of the project

The purpose of the project is to compile and evaluate the available toxicological information on selected coformulants in pesticide formulations in order to assess their adverse health effects. This report is aimed at creating a basis for discussion on whether a revision of the approval scheme for pesticides, as proposed by the Bichel-Committee in their report, is needed (Bichel Committee 1999b).

1.2 Background

Concern in the Danish Parliament on the increasing pesticide pollution, especially of the ground water, resulted in 1998 in the appointment by the Minister of the Environment and Energy of a committee of independent scientists from research, agriculture, green organisations, consumer organisations, food and agrochemical industry, trade unions and relevant ministries. The task of the committee was to analyse the consequences of different scenarios for partial or total phasing out of pesticides in the agricultural industry in relation to the present socio-economic factors related to production and use of pesticides.

This main committee, "the Bichel-Committee", and its four sub-committees on agriculture; on production, economics and employment; on health and environment; and on legislation, respectively, presented the result of their work in 1999 in four sub-committee reports and a main report. The main report evaluated the consequences, with respect to manufacturing, economy, legislation, health, employment and environment, of the production achieved by the agricultural industries to date. The sub-committees performed cost-benefit assessments of different scenarios for the total and partial phasing-out of pesticides (Bichel Committee 1999a). Based on the report from the subcommittee on health and the environment, the Bichel-Committee expressed concern that coformulants in some cases were more acutely toxic than the active ingredients (e.g., organic solvents) and that some of them were included in the Danish EPA List of undesirable substances (Miljøstyrelsen 1998). The Bichel-Committee recommended that the approval system should be extended so that the requirements on coformulants would approach the requirements set on the active ingredients of pesticides. The committee also recommended that consideration be given to ban all carcinogenic coformulants (MST 1999a).

1.3 Definitions

An *existing industrial chemical* is a chemical substance or preparation (containing more than one chemical substance) used for general purposes in industry and households, which was present on the market in the EU in

September 1981, when the EINECS-list[1] was formed. These chemicals are not subject to a specific approval procedure, as e.g. for pesticides. Industrial chemicals marketed later than September 1981 are subject to a notification procedure and are referred to as new substances. Many coformulants are existing industrial chemicals.

A *pesticide* is a plant protection product or a biocide. It is composed of one or more active ingredients and a number of coformulants.

A *plant protection product* is a pesticide used for pest control (herbicide, insecticide or fungicide) in agriculture, gardening or in forestry.

A *biocide* is a pesticide used for fungus, bacteria or insect control in non-agricultural use. Examples of biocides are rat-controlling products, mosquito-repellents, disinfection products and wood-protection products.

The *active ingredient* is the biologically active chemical in a pesticide, which has the actual controlling effect.

A *coformulant*, also called *"inert" or auxiliary substance* is a chemical substance, which is added to the active ingredient(s) in a pesticide to obtain better technical affinity of the product to the intended use of the pesticide. Coformulants include carrier substances, solvents, surfactants, dispersing agents, adhesives, absorption-promoting agents, antioxidants, bactericides, dyes, fillers, and perfume.

1.4 Scope

Coformulants include a large number of different chemicals that have various technical and physico/chemical properties in relation to their function in the pesticide formulation. In Denmark, 488 different substances are used as coformulants (Miljøstyrelsen 2003). These chemicals can be expected to have various toxicological profiles, some of them harmless (e.g., water) and some with serious toxicological properties (e.g., the organic solvent isophorone, which is a suspected carcinogen). Coformulants represent 69 % by weight of the pesticides sold in Denmark (1997-figure), corresponding to about 10000 tonnes (MST 1999b).

Therefore, even a minor toxicological concern could become significant in relation to the high amounts of coformulants used in pesticides. A detailed risk assessment would require specific exposure data in order to relate hazard and exposure. However, it is very difficult to obtain data on exposure. The widespread use and handling of pesticides mean that exposure to pesticides and thereby to coformulants may be high in some situations. Furthermore, a large number of coformulants are also marketed as industrial chemicals and thus may contribute to human exposure.

[1] EINECS: European Index of Existing Chemical Substances: list of 100 116 chemical substances on the market in the European Union in september 1981, based on notifications from the chemical industry.

1.5 Existing regulation

1.5.1 Approval procedure

1.5.1.1 Active ingredients

In Denmark, pesticides are regulated by the Statutory Order from the Ministry of the Environment on Pesticides (Miljø- og Energiministeriet 1998) under the Chemical Substance Act. This statutory order is based on the EU directive 91/414/EC on plant protection products (EEC 1991). According to this legislation, all pesticides marketed in Denmark must be approved by the Danish Environmental Protection Agency before their marketing and use in Denmark. The information required to fulfil a request for approval of a pesticide includes the composition of the product. On the active ingredient, a range of analytical methods; data on physico-chemical, toxicological, ecotoxicological properties; and data on environmental fate are mandatory. The toxicological requirements for the active ingredient include studies on acute toxicity, skin and eye irritation, skin sensitisation, short-term and long-term toxicity as well as specific end-points including, toxicity to reproduction, mutagenicity and carcinogenicity. Also metabolism studies on the active ingredient are required. For some of the end-points, studies in two different animal species must be conducted. The studies must comply with specific guidelines (OECD or EU-guidelines) and for toxicological end-points, be performed according to the rules of Good Laboratory Practice. The data requirements on the active ingredient are described in Annex 5.1 and 5.3 to the statutory order on pesticides. (Miljø- og Energiministeriet 1998).

1.5.1.2 Coformulants

The data requirements of the approval scheme also include some toxicological end-points for the pesticide formulations, namely acute toxicity, and skin and eye irritation. The applicant must therefore also provide test results on the specific pesticides for these end-points. Some indications on the acute toxicity and irritative potential of the coformulants used can be derived from this information. However, no information on long-term effects of the coformulants can be derived from these mandatory studies. Coformulants are not themselves at present subject to approval, as there are no specific demands by the authorities for toxicological documentation specifically related to the chemical substances added to the active ingredient in order to produce pesticide formulations. However, the precise composition of the pesticides must be known, so that all component substances can be identified. On this basis, the Danish EPA always requires data sheets containing brief information on physico-chemical and toxicological properties of the coformulants to the extent to which they have been studied (Miljø- og Energiministeriet 1998). A coformulant with a known serious long-term effect present in a pesticide above a certain percentage will trigger classification of the pesticide. Such a classification of the pesticide will entail exposure and risk assessment of the pesticide product with respect to its intended use. On this basis, the Danish EPA can refuse or withdraw approval of a pesticide because of adverse effects of a coformulant, even if the active ingredient is without alarming effects.

1.5.2 Classification and labelling

1.5.2.1 Substances

The rules on classification and labelling of chemical substances are laid down in directive 67/548/EEC (EEC 1967), which is implemented in Denmark by the statutory order from the Ministry of the Environment on classification,

packaging, marketing and sales of chemicals (Miljøministeriet 2002a) and in the statutory order from the Ministry of the Environment on the list of dangerous substances (Miljøministeriet 2002b). Classification of a substance consists of a categorisation in classes of danger and so-called risk phrases (R-phrases) describing the intrinsic physico-chemical, toxicological and ecotoxicological hazards of a chemical, and is performed end-point by end-point. It is performed according to specified criteria based on human as well as animal data, the latter referring to EU guidelines (Annex V to directive 67/548/EEC) and, for pesticides, also other internationally accepted guidelines (Annexes II and III to directive 91/414). Based on recommendations from an EU-group of experts, approximately 7000 chemical substances have until now been classified by the EU-Commission (Annex I to EU-directive 67/548/EEC).

1.5.2.2 Preparations

Preparations are classified according to the directives 88/379/EEC and 1999/45/EC (EEC 1988, EC 1999). Preparations are classified either on the basis of tests performed on the pesticide itself, following the same criteria for classification as for the substances, or by a calculation method taking into account the toxicity and the percentage of each ingredient in the preparation.

1.5.2.3 Classification of pesticides

According to the provisions of the legislation on pesticides, active ingredients and pesticide products are to be classified according to the rules of the classification directives 67/548/EEC (EEC 1967) and 88/379/EEC (EEC 1988). The national authorities classify the active ingredient and the pesticide product on basis of the information available. Thus, the classification of the active ingredient reflects the physico-chemical hazards, and the dangers to human health and to the environment covered by the data requirements. With respect to the pesticide product, classification for health effects will always reflect the toxicological effects of the coformulants with respect to acute toxicity and local irritation, which are the end-points where data are required for the pesticide product. Classification of the pesticide product will reflect long-term and specific effects caused by coformulants if the coformulants are adopted on the list of dangerous substances (Miljøministeriet 2002b).

1.5.2.4 Future regulation

No EU rules have applied hitherto for the classification with respect to specific effects or long-term effects of pesticide formulations. In Denmark, the Danish EPA has practised to classify pesticides for all end-points as non-pesticide preparations, i.e. on the basis of available toxicological information on the ingredients in the pesticide. From July 2004, this practise will be implemented with the new preparations directive 1999/45/EC (EC 1999) in the whole of the EU. The classification of the pesticide product will take into account the known toxicological properties of the coformulants and thus indirectly indicate toxicological effects of the coformulants, if they are expressed in the pesticide classification. However, the classification rules being based on available documentation, the classification of a pesticide containing coformulants where no data are available for a specific end-point will be incomplete.

1.5.3 Safety data sheets

A general requirement exists for every pesticide containing dangerous substances that a safety data sheet must be available at the workplace. The safety data sheet contains information on composition, health and

environmental effects of the pesticide, and first aid measures. However, no testing requirements are laid down in the safety data sheet regulation, which means that they are produced on the basis of available toxicological information.

1.6 Lack of data

The EU Commission has shown that data availability on High Production Volume Chemicals (over 1000 tonnes per manufacturer/importer per year in the EU) in the IUCLID database[2] was low, e.g., 14% having the minimum information for risk assessment and 21 % having no test data at all on human or environmental toxicity (Allanou et al. 1999). The Danish EPA has investigated the availability of data publicly available in RTECS[3]. The survey revealed an even lower data availability, as acute toxicity data were available for 13.4 % of the around 100000 industrial substances on the EU market (excluding New Notified substances and Pesticide substances), mutagenicity data for 3.9 %, data for toxicity to reproduction for 2.5 %, and data for carcinogenicity for 1.8 % of the substances (Miljøstyrelsen 2001).

1.7 Related projects

1.7.1 Pilot project on coformulants in herbicides

A pilot project from 1991 under the pesticide research programme was conducted on data availability and toxicity data screen of approved herbicides (Miljøstyrelsen 1992). Based on data from the PROBAS[4], the study showed that 8571 tonnes herbicides were used in 1990, of which 37 % (3176 tonnes) were coformulants. Of the 105 coformulants identified, 36 substances were present in more than 3 herbicides. Confidentiality rules established for the reporting from chemical companies to the Danish Product Register mean that the identity of substances used in 3 products or less may not be made publicly available. Data on these coformulants were scarce, with only a few references in RTECS[2], HSDB[5], the list of dangerous substances, the KRAN-lists[6] and/or IARC[7]-cancer classification list. For 7 out of 9 substances used in over 100 tonnes, no data were found. The few substances where some documentation was found were listed as toxic, neurotoxicants, reproductive toxicants, allergens, and/or carcinogens. The project concluded that there was limited toxicological information available for the main part of coformulants in herbicides. The available documentation indicated that the coformulants were not toxicologically insignificant. Some of them even had serious toxicological effects (Miljøstyrelsen 1992). The above pilot project calls for an investigation of the toxicology of coformulants, not only in herbicides, but also in all types

[2] IUCLID database. International Uniform Information Database on High Production Volume Chemicals - reported by the European Industry in the frame of the EU Existing Chemicals Risk Assessment Programme.

[3] Registry of Toxicity of Existing Chemical Substances: Database on toxicological references on chemicals. Contains information on ca. 160.000 substances.

[4] PROBAS: Database on chemical products notified to the Danish Product Register

[5] HSDB:Hazardous Substance Data Base

[6] KRAN- lists: 4 lists from the Danish National Occupational Institute identifying carcinogens (K), reprotoxicants (R), sensitiseres (A) and neurotoxicants (N).

[7] IARC: International Agency for Reasearch on Cancer. WHO research organ.

of pesticides. This information is called for as a basis for evaluating the need to adjust the existing approval system.

1.7.2 Nordic project on coformulants in plant protection products

A Nordic project "Auxiliary substances in plant protection products - their impact on health and environment" was launched in 2000. This project aims at establishing an overview on pesticide coformulants used in the Nordic countries, and create a negative list on substances with known toxicological and ecotoxicological properties and a list of substances to be further investigated for adverse health and environmental effects. The Nordic project will include summaries for health and environmental effects for 22 coformulants and is expected to be finalised in June 2003 (Nordic Council of Ministers 2003, in press). The Danish EPA is represented in the steering committee of the Nordic project, ensuring correlation between the Nordic and the Danish project and that there is no duplication of work in these projects.

2 Methodology

2.1 Prioritisation of substances for the project

The Danish EPA established the following criteria, prioritised in the following succession, for the selection of substances to be included in this project:

1. On the Danish market in over 10 tons/year (based on information from the Danish Product Registry).

2. Used in a high number of products on the Danish market (based on information from the Danish Product Registry).

3. The substance is not a priori toxicologically inert.

4. The substance is of special interest to the Danish EPA (e.g., adopted on LOUS[8], a substitute for the suspected endocrine disrupters nonylphenols, or evaluated in the similar Nordic project).

5. The substance is not on EU's Risk Assessment priority lists (EU regulation 93/393/EEC[9]) or classified on EU's list of dangerous substances for effects on reproduction or for mutagenic, carcinogenic effects.

6. Different functions of coformulants are represented (solvents, dispersing agents, fillers, carrier substances, surfactants, adhesives, bactericides, dyes).

The result was the selection of the 18 substances listed in Table 1. The Table compiles identity and physico-chemical properties of the substances, and groups the coformulants according to chemical classes.

[8] LOUS: List of undesirable substances from the Danish EPA included chemical substances prioritised because of their adverse effects and high tonnage on the market (MST 1998).

[9] Council Regulation 793/93/EEC of 23 March 1993 on the evaluation and control of the risks of existing substances.

Table 1: Physico-chemical properties for the 18 selected coformulants. Fysisk-kemiske data for de 18 udvalgte hjælpestoffer.

Chemical group	Chemical name	Acronym	CAS No.	MW	Molecular formula	Description	Vapour pressure (mmHg at 20ºC)	Solubility in water (at 20ºC)	Part. coeff. octanol/water (Log $P_{o/w}$)
Inorganic	Manganese (II) sulphate/ Mangane(II) sulphide		7785-87-7 18820-29-6	151.00 87.00	$MnSO_4$ MnS	Monohydrate: pale red crystals Pink/green powder or crystals	- -	520 g/l at 5ºC Insoluble	n.av. n.av.
Inorganic	Diammonium sulphate		7783-20-2	132.14	$H_8N_2O_4S$	Colourless orthorhombic crystals or white granules with no odour	-	754-770 g/l	-5.1
Organic - ether	Dimethyl ether	DME	115-10-6	46.07	C_2H_6O	Colourless flammable gas, slight ethereal odour	3982	328 g/l	- 0.18
Organic - amine	Hexamethylenetetramine		100-97-0	140.19	$C_6H_{12}N_4$	Colourless hygroscopic crystals or white crystalline powder with no or mild ammonia odour	0.004 (25ºC)	449 g/l (12ºC)	-2.13, -2.84 (calculated)
Organic - ester	1-Methyl-1,2-ethanediyl dioleate		105-62-4	605.0	$C_{39}H_{72}O_4$	Liquid	-	-	n.av.
Organic - ester	Isopropyl myristate		110-27-0	270.5	$C_{17}H_{34}O_2$	Colourless liquid with low viscosity	9.35×10^{-5} (25ºC)	Practically insoluble	>6 (calculated)
Organic - sulfonate	Sodium ligninsulfonate		8061-51-6	250-100000	-	Brown non-hygroscopic powder	-	Colloidal solutions in water	n.av.
Organic - sulfonate	Calciumdodecylbenzene - Sulfonate	CaDBS	26264-06-2	691.14	$(C_{18}H_{29}SO_3^-)_2 \bullet Ca^{++}$	Yellow/brown liquid or white granular solid	-	Miscible	-
Organic - glycol	Ethylene glycol		107-21-1	62.07	$C_2H_6O_2$	Clear colourless slightly viscous hygroscopic liquid with sweet taste	0.06	Miscible	–1.93 to –1.36
Organic - glycol	Propylene glycol	PG	57-55-6	76.0	$C_3H_8O_2$	Colourless viscous hygroscopic liquid	0.07	100 g/l	– 0.92

Chemical group	Chemical name	Acronym	CAS No.	MW	Molecular formula	Description	Vapour pressure (mmHg at 20ºC)	Solubility in water (at 20ºC)	Part. coeff. octanol/water (Log $P_{o/w}$)
Organic - glycol ether	2-Butoxyethanol	EGBE	111-76-2	118.2	$C_6H_{14}O_2$	Colourless liquid with a faint, mild ethereal odour	0.76	Miscible	0.81
Organic - glycol ether	1-Methoxy-2-propanol	2PG1ME	107-98-2	90.1	$C_4H_{10}O_2$	Colourless liquid with sweet ether-like odour	9	Completely soluble	-0.49 to –0.43
Organic - glycol ether	Diethylene glycol mono-*n*-butyl ether	DEGBE	112-34-5	162.23	$C_8H_{18}O_3$	Colourless liquid with bitter taste and weak odour	0.02	Miscible	0.3; 0.56; 0.82; 4.69
Organic - glycol ether	Dipropylene glycol monometyl ether	DPGME	34590-94-8	148.20	$C_7H_{16}O_3$	Colourless liquid with ether odour	0.278	Miscible	-0.64
Organic - glycol ether	Polyethyleneglycol-dodecylether	polyEGDE	9002-92-0	> 362	$(C_2H_4O)_n$-$C_{12}H_{26}O$	Colourless/yellow liquid with pleasant odour, or solid (depending on chain length)	-	n=4: >100 g/l	-
Organic - ketone	Cyclohexanone		108-94-1	98.14	$C_6H_{10}O$	Colourless/yellow oily liquid with peppermint/acetone odour	3.38	80 g/l	0.81
Organic - ketone	1-Methyl-2-pyrrolidone	NMP	872-50-4	99.13	C_5H_9NO	Colourless hygroscopic liquid with mild amine odour	0.29	Miscible	– 0.46 to 0.42
Organic - ketone	4-Hydroxy-4-methyl-2 pentanone	HMP	123-42-2	116.0	$C_6H_{12}O_2$	Colourless liquid with sweetish odour	0.97	Miscible	- 0.098

CAS No: Chemical Abstract Service Number
MW: Molecular weight
Part. coeff.: Partition coefficient
n.av.: Not available

2.2 Literature search

For the hazard assessments of the coformulants selected in this report, data have been collected from national and international criteria documents and monographs, from original scientific literature, and from the International Uniform Chemical Information Database (IUCLID) on High Production Volume Chemicals reported by European Industry in the frame of the EU Existing Chemicals risk Assessment programme. The standard references consulted in the literature search for the selected coformulants are given below:

ACGIH (1991). TLV's Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 1991-1992. Cincinnati, OH.

Arbete och Hälsa. Nordiska Expertgruppen för Gränsvärdesdokumentation. Arbetarskyddsverket.

Alarie Y (1981). Dose-response analysis in animal studies: prediction of human responses. Environ Health Perspect **42**, 9-13.

Amoore JE and Hautala E (1983). Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol **3**, 272-290.

At (1996). Grænseværdier for stoffer og materialer. Arbejdstilsynets At-anvisning Nr. 3.1.0.2, December 1996.[10]

ATSDR. Toxicological Profiles. U.S. Department of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Berlin A, Draper M, Krug E, Roi R and van der Venne MTh. The Toxicology of Chemicals. 1. Carcinogenicity. Summary Reviews of the Scientific Evidence, Luxembourg, Commission of the European Communities.

BUA. Beatergremium für umweltrelevante Alstoffe (BUA), Geschellschaft Deutscher Chemiker.

Chemfinder. Http://www.chemfinder.com

HSDB. Hazardous Substances Data Base.

IARC. IARC Monographs on the Evaluation of the Carcinogenic Risk to Humans, Lyon.

IRIS. Integrated Risk Information System. Database quest. US-EPA.

[10] Revised version in 2002: At (2002). Grænseværdier for stoffer og materialer. Arbejdstilsynets At-anvisning Nr. 3.1.0.2, Oktober 2002 was used in the individual hazard assessments.

IUCLID (2000). International Uniform Chemical Information Database. European Commission, ECB, JRC, Ispra.

Merck Index (1996). 12th. Ed., Rahway, New Jersey, Merck & Co., Inc.

Miljøministeriets bekendtgørelse af listen over farlige stoffer. (Statutory Order from the Ministry of the Environment on the List of Dangerous Chemical Substances).[11]

MM (1988). Bekendtgørelse om vandkvalitet og tilsyn med vandforsyningsanlæg. Miljøministeriets bekendtgørelse nr. 515 af 29. august 1988. (Statutory Order from the Ministry of the Environment no 515 of 29 August 1988 on water quality and control of water supply facilities).[12]

MST (1996). B-værdier. Orientering fra Miljøstyrelsen nr 15, 1996.[13]

MST (1990). Begrænsning af luftforurening fra virksomheder. Vejledning fra Miljøstyrelsen nr 6 1990.

RTECS. Registry of Toxic Effects of Chemical Substances database.

Ruth JH (1986). Odor thresholds and irritation levels of several chemical substances: a review. Am Ind Hyg Assoc J **47**, A142-A151.

Sullivan FM, Watkins WJ and van der Venne MTh (1993). The Toxicology of Chemicals. 2. Reproductive Toxicity. Vol. 1, Summary Reviews of the Scientific Evidence, Luxembourg, Commission of the European Communities.

Toxline plus 1999-2000/01.

WHO (1998). Guidelines for drinking-water quality. Second edition. World Health Organization, Geneva.

WHO (1987). Air Quality Guidelines for Europe. WHO Regional Publications, European Series No. 23, Copenhagen.

WHO. Environmental Health Criteria. World Health Organisation, International Programme on Chemical Safety, Geneva.

[11] Current version (2002): Miljøministeriets bekendtgørelse nr 439 af 3. juni 2002 af listen over farlige stoffer. (Statutory Order from the Ministry of the Environment no. 439 of 3 June 2002 on the List of Dangerous Chemical Substances) was used in the individual hazard assessments.

[12] Current version (2001): Bekendtgørelse om vandkvalitet og tilsyn med vandforsyningsanlæg. Bekendtgørelse nr. 871 af 21. september 2001.

[13] Revised version (2002). B-værdivejledningen. Vejledning fra Miljøstyrelsen Nr. 2 2002.(Guidance document no 2, 2002 from the Danish EPA on air contribution values) was used in the individual hazard assessments.

2.3 Principles for the hazard assessment

The scientific basis for the hazard assessment (hazard identification and hazard characterisation) of chemical substances as e.g., the coformulants consists of data elucidating the toxicological effects in humans and in experimental animals. Ideally, a complete database including information on toxicokinetics, acute toxicity, irritation, sensitisation, repeated dose toxicity, mutagenicity and genotoxicity, carcinogenicity, and toxicity to reproduction should be available for the hazard assessment of a coformulant.

Direct information about health effects in humans may be obtained from well-planned and documented epidemiological studies. Some types of effects as e.g., neurotoxicological effects, which are assessed by examining intellectual and psychological end-points can only be revealed from human studies as no adequate experimental models are currently available. In addition to epidemiological studies, information on effects in humans may be obtained from case reports (e.g., poisonings), clinical examinations, studies on volunteers, and experiences from the working environment.

For most chemical substances including coformulants, however, adequate human data are not available for a hazard assessment. Therefore, toxicological studies in experimental animals play an important role in hazard assessments. In the hazard assessment, the quality and relevance of the available studies on experimental animals are evaluated. Studies performed according to international guidelines as e.g., the OECD guidelines and the EU guidelines on studies of chemical substances in experimental animals (Annex V to Council Directive 67/548/EEC) are preferred because of their high scientific standard and comparability of the results. However, such studies are generally not available for most of the chemical substances in use.

Exposure to a chemical substance can result in a broad spectrum of effects varying from mild effects as e.g., irritation to fatal poisonings. The type and severity of the effects observed is most often correlated with the exposure concentration.
The first step in the hazard assessment is the hazard identification, i.e., an identification of the toxicological effects, which a substance has an inherent capacity to cause. The next step is the hazard characterisation, i.e., an estimation of the relationship between dose or exposure concentration to a substance, and the incidence and severity of an effect. Regarding the severity of a given effect, it is evaluated whether the effect can be considered as being adverse or not. According to WHO[14], an effect is considered as being adverse when there is a "change in morphology, physiology, growth, development, or life span of an organism, which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences". The hazard assessment also includes an evaluation of the 'no observed adverse effect level' (NOAEL) and 'the lowest observed adverse effect level' (LOAEL) for the various effects observed.

[14] WHO (1994). Assessing Human Health Risks of Chemicals: Derivation of Fuidance Values for Health-based Exposure Limits. Environmental Health Criteria 170, International Programme on Chemical Safety, World Health Organization, Geneva.

According to WHO[14], the NOAEL is the "greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target organism under defined conditions of exposure. Alterations of morphology, functional capacity, growth, development or life span of the target may be detected which are judged not to be adverse". Similarly, the LOAEL is the "lowest concentration or amount of a substance, found by experiment or observation, which causes an adverse alteration of morphology, functional capacity, growth, development or life span of the target organism distinguishable from normal (control organisms of the same species and strain under the same defined conditions of exposure".

When all the relevant toxicological data have been evaluated, the hazard(s) considered most important, "the critical effect(s)", is identified, i.e., the effect(s), which is judged to be most crucial following exposure to the substance in question.
The critical effect(s) can be considered to be of two types: those effects considered to have a threshold and those effects for which there is considered to be some risk at any level of exposure (non-threshold, e.g. genotoxic carcinogens). For those effects considered to have a threshold, a NOAEL (or LOAEL) is identified for the critical effect.

3 Results

In this project, 18 coformulants have been selected for a detailed hazard assessment; these hazard assessments are compiled in Appendices 1 to 18.

The toxicological effects and the data availability for the 18 coformulants are compiled in Table 2 (section 3.1), short summaries are presented in section 3.2, and the critical effects and existing regulation are summarised in Table 3 (section 3.3).

The selection procedure of the coformulants is described in section 2.1 and the principles for the hazard assessment is described in section 2.3.

3.1 Toxicological effects and data availability

The toxicological effects described in the public available literature and the data availability for the 18 coformulants are compiled in Table 2 and based on the hazard assessments.

For every of the following end-points, acute toxicity, irritation, sensitisation, repeated dose toxicity, toxicity to reproduction, mutagenicity and genotoxicity, and carcinogenicity, the available animal and human data regarding oral, inhalation, and dermal exposure are summarily described. Whenever possible, effect levels and LOAEL(C)s or NOAEL(C)s are included.

An overview on the data availability is included in the Table in the following way: Available data are summarised for each substance under each end-point. If no data are available for a specific end-point, the notation "No data" is listed. If data regarding a specific end-point are available for only one species and one exposure route, no specific mention on missing data for other species or other exposure routes for this specific end-point is made, i.e., no mention of e.g., human data means that no human data are available for this specific end-point.

Data for oral and dermal exposures are listed in the unit mg/kg b.w. or mg/kg b.w./day, while inhalation exposure data are listed in mg/m^3.

The following abbreviations are used in the Table:
anim: animal; **app**: approximately; **AST**: aspartate amino transferase; **av**: available; **aq**: aqueous; **bw**: body weight; **CNS**: central nervous system; **conc**: concentration; **d**: day(s); **decr**: decreased; **derm**: dermal; **dev**: developmental toxicity; **eff**: effect(s); **gi**: gastrointestinal; **gp**: guinea pig; **gpmt**: guinea pig maximisation test; **hist**: histological; **hr**: hour(s); **hum**: human; **incr**: increased; **inh**: inhalation; **irr**: irritation; **LAS**: linear alkylbenzene sulphonate; **LC_{50}:** lethal concentration for 50% of the animals in the study; **LD_{50}:** lethal dose for 50% of the animals in the study; **LO(A)EL(C)**: lowest observed (adverse) effect level (concentration); **mamm**: mammalian; **mat**: maternal toxicity; **min**: minimal; **Mn**: manganese; **mod**: moderate; **mth**: month(s); **neg**: negative; N**O(A)EL(C)**: no observed (adverse) effect level (concentration); **pos**:

positive; **rab**: rabbit; **resp**: respiratory; **sev**: severe; **sol**: solution, **wk**: week(s); **yr**: year(s).

Table 2: Compilation of toxicological effects and data availability of selected coformulants by end-point.
(Oversigt over udvalgte hjælpestoffers toksikologiske effekter og datatilgængelighed opstillet per effekttype).

Chemical name	Acronym	Acute effects	Irritation	Sensitisation	Repeated dose toxicity	Toxicity to reproduction	Mutagenicity	Carcinogenicity
Manganese (II) sulphate / Manganese (II) sulphide		Rat oral: LD_{50} 275-1082	Anim inh: 0.7-69 Mn (as dust)	No data	Hum inh: neurological eff LOAEC 0.14-1.59 Mn (as total dust) Monkeys inh: neurological eff Rats inh: lung inflammation Rats, mouse oral: nephropathy, thyroid and gi hyperplasia 200-731	Hum inh: decr sperm count and quality Mice oral: sperm abnormalities LOAEL 23 Rats oral: dev LOAEL 33	*In vitro*: Ames test neg/pos Mamm cells pos *In vivo*: Micronucleus pos Chromosome aberration pos Sex linked recessive mutation neg	Rat, mouse oral (2 yr): Adenomas in pituitary, thyroid, pancreas; carcinomas in pancreas
Diammonium sulphate		Hum inh: decr pulmonary function LOAEC 1 Rat inh: LC_{50} >1200 Rat oral: LD_{50} 2840-4250 Mouse oral: LD_{50} 610-640	Hum inh: resp tract/eye LOAEC 0.5 Rab: no skin/eye	No data	Hum inh (3 d, 2 hrs/d): pulmonary function NOEC 0.1 Rat inh (4-8 mth): pulmonary eff 0.5-1 Gp inh (20 d): pulmonary eff 1	No data	*In vitro*: neg	No data
Dimethyl ether	DME	Hum inh: CNS depression, 157000 Rat inh: LC_{50} 313000	No data	No data	Rat inh: liver (increased AST) NOEC 380	Rat inh: dev NOAEC 76000; mat (CNS) NOAEC 2400	*In vitro*: neg *In vivo*: neg	Rat inh (2 yr): neg up to 48000
Hexamethylene tetramine		Hum oral: bladder inflammation Rat oral: LD_{50} 9200	Hum: skin/eye Rab, gp: mild skin 2% sol Rab, gp: eye 0.1% in product, no eye 0.2% in saline	Hum inh: asthma Hum: pos skin 2% sol, neg skin 0.1% in product Gp: one gpmt pos	Hum oral: nausea, diarrhoea Rat, mouse, cat oral (13-104 wk): NOAEL1500, 2500 and 1250, respectively	Hum: no abnormalities in 200 newborns exposed during first trimester Rat dams oral: dev NOAEL 2000 Rat oral (20 wk): bw decr pups 2000 (dams + offspring) Dog oral: stillborn pups	*In vitro*: pos, neg *In vivo*: neg	Rat, mouse oral (up to 2 yr): neg 2500 Rat, mouse derm (up to 2 yr): neg 30% sol

Chemical name	Acronym	Acute effects	Irritation	Sensiti-sation	Repeated dose toxicity	Toxicity to reproduction	Mutagenicity	Carcinogenicity
				30% sol, one neg 0.2% sol		31, NOAEL 15, abnormalities in few pups 94		
1-Methyl-1,2-ethanediyl dioleate		No data	Hum inh: heated vapours	No data	No data	No data	No data	No data
Isopropyl myristate		Rat inh: lethargy (aerosol 16-20%) Rat oral: LD_{50} > 13700 Rat derm: LD_{50} > 5000	Hum skin: no-min (most studies), LOAEC 10% (one study Rab, mouse skin (3-28 d): mod-sev Rab: no skin/eye (Draize) Monkey inh (13 wk): resp tract 0.95-6.7	Hum skin: no (most studies), few pos case reports Gp: neg 0.1% sol	Gp inh (4-13 wk): incr lung weights from 10 Monkeys inh (13 wk): macrophage accumulation 0.95-6.7 Rat oral (up to 16 wk): NOAEL 2000	Mouse skin (1/wk, 18 mth): no gross abnormalities (1% sol)	*In vitro*: neg	Mouse derm (lifetime): neg undiluted, enhanced carcinogenicity of benzo(a)pyrene
Sodium ligninsulphonate		Rat inh: LC_{50} > 480 Rat oral: LD_{50} >40000 Mouse oral: LD_{50} 6000	Anim: eye, skin, upper resp tract	No data	Gp oral (6 wk): ulceration colon 1700 Rat oral (16 wk): hist changes liver/kidney, incr weight liver/kidney/spleen 10000, NOAEL 2500	No data No oestrogenic effect *in vitro*	No data	No data
Calciumdodecyl-benzene-sulphonate	CaDBS	Rat, mouse oral: LD_{50} about 4000	No data (Possibly skin, eye, resp tract by analogy to LAS)	No data	No data	No data	No data	No data
Ethylene glycol	EG	Hum oral: min lethal dose 1600 Rat inh: LC_{50} (1 hr) 10900 Rat, rab, mouse, gp, dog oral: LD_{50} >2000-15400 Rab derm: LD_{50}	Hum: low skin, low eye, resp Rab: eye, no skin	Hum: few case reports	Hum inh: resp irr LOAEC 17 Rat oral: kidney NOAEL 200	Rat, mouse oral: reproductive eff NOAEL 1000 (rat), 840 (mouse) Mouse inh: dev NOAEC 1000 Anim oral: dev NOAEL 1000 (rat), 150 (mouse), 2000 (rab)	*In vitro*: neg *In vivo*: neg	Anim oral (2 yr): neg up to 2000 (rat), up to 12000 (mouse)

Chemical name	Acronym	Acute effects	Irritation	Sensiti-sation	Repeated dose toxicity	Toxicity to reproduction	Mutagenicity	Carcinogenicity
		10600				Mouse derm: dev NOAEL 3550		
Propylene glycol	PG	Hum inh, oral: CNS depression, acidosis (high conc/doses) Rodents oral: LD_{50} 18000-30000 Rab derm: 20800	Hum: slight skin Rat inh: nose bleeding from 160; goblet cell enlargement from 1000 Rab: mild skin, eye	Hum: few case reports	Hum inh: no eff up to 94 Hum oral (13 mth): CNS depression 114 Rat: (90 d): haematological eff (not dose-related) Dog/cat oral (2 yr /2-17wk): haematological eff 5000/1100	Rat inh (18 mth): no eff fertility up to 354 Mice oral (14 wk): no eff fertility up to 10000 Rodents oral: no dev up to 1600	*In vitro*: neg *In vivo*: neg	Rat oral (2yr): neg Mouse derm (120 wk): neg
2-Butoxyethanol	EGBE	Hum oral: haemolysis high doses Rat inh: LC_{50} (4 hr) 2200-2400 Rat, rab, mouse, gp oral: LD_{50} 320-3100 Rab, gp, rat derm: LD_{50} 400-4800	Hum: eye, skin, resp NOAEC >100 Rab: mod-sev skin, sev eye	Hum: neg Gp: neg	Hum inh: haemolysis NOEC >3 Rat, mouse inh: haemolysis LOAEC 152 (rat, female mouse), NOAEC 152 (male mouse) Rat, mouse oral: haemolysis LOAEL 69/82 (rat), NOAEL 357 (mouse)	Rat, mouse, rab: not toxic to reproductive organs (male, female) Rab, mouse, rab: no reproductive eff Rat, mouse, rab: no dev	*In vitro*: neg *In vivo*: neg	Rat inh (2 yr): neg male, some evidence female up to 615 Mouse inh (2 yr): some evidence up to 1225
1-Methoxy-2-propanol	2PG1ME	Hum inh: CNS depression LOAEC 1125 Rat, gp inh: LC_{50} app 54600 Anim oral: LD_{50} 5000-10800 Rab derm: LD_{50} 13000 Anim: CNS depression	Hum inh: nose/eye (15 minutes), throat (45 minutes) LOAEC 938 Rat inh (4 hr): resp tract LOAEC 37500 Rab: no-min skin/eye	Gp: neg	Rat, mouse, rab, gp inh (up to 6 mth): CNS depression, eff liver 5450-21800 Rat, mouse inh (2 yr): eff liver 11250 NOAEC 3750 Dog oral: CNS depression from 920	Rat inh (10 d): no eff testes up to 2250 Mouse oral (25 d): no eff testes up to 2500 Dog oral (14 wk): macrophages in testes and epididymides LOAEL 462 Rat inh: delayed ossification sternebrae pups, and mat 11250 Rab inh: no eff up to 11250	*In vitro*: neg	Rat, mouse inh (2 yr): no eff up to 11250

Chemical name	Acronym	Acute effects	Irritation	Sensiti-sation	Repeated dose toxicity	Toxicity to reproduction	Mutagenicity	Carcinogenicity
						Rat oral: delayed ossification skull pups 739 Mouse oral: dev 3300 Rab oral: no eff 924		
Diethylene glycol mono-*n*-butyl ether	DEGBE	Rat inh: LC_{50} 73000 Rat, rab, mouse, gp oral: LD_{50} 2000-9600 Rat, rab derm: LD_{50} >2000	Hum: skin, eye, resp Rab, gp: low skin, mod eye	Hum: few case reports Gp: neg	Rat inh: systemic/local eff NOAEC 95 Rat oral: haematological eff LOAEL 50 Rat derm: systemic eff NOAEL 2000, local eff NOAEL 100-200	Rat oral/derm: reproductive eff NOAEL 1000 (oral), NOAEL 2000 (derm) Rat, mouse oral/derm: dev NOAEL 633 (rat, oral), 2050 (mouse, oral), 1000 (rab derm)	*In vitro*: neg *In vivo*: neg	No data
Dipropylene glycol monomethyl ether	DPGME	Rat inh: narcosis 3080 Anim oral: LD_{50} 5000-7500 Rab derm: LD_{50} 9400->19000	Hum: eye 20% sol, resp 456, no skin Rab: eye, no skin	Hum: neg	Rat inh (6-8 mth): CNS depression LOAEC 1848 Anim inh (6-8 mth): slight liver eff LOAEC 1848 Rat, rab inh (90 d): NOAEC 1232 Rat derm (28 d): NOAEL 1000 Rab derm (90 d): NOAEL 4700	Rat, rab inh (90 d): no eff testes up to 1232 Rat, rab inh: no dev up to 1756	*In vitro*: neg	No data
Polyethyleneglycol-dodecylether	PolyEGDE	Rat oral: LD_{50} 4150/8600	Hum: mod skin Rab: mild-mod skin 75-500 (different chain lengths), mod eye Rat: mucous membranes	No data	No data	No data	*In vitro*: neg *In vivo*: neg	No data
Cyclohexanone		Rat inh: LC_{50} 6200-32500 Rat oral: LD_{50} 1296-3460 Rab derm: LD_{50} 794-3160	Hum: eye, nose, throat from 306; skin from 162 Anim: skin, eye	Hum: one case report Mouse, gp: neg	Hum (14 yr): CNS symptoms LOAEC 162 Rat, rab inh/oral: CNS symptoms	Rat inh: male fertility reduced at 5712, NOAEC 2040 Rat, mouse inh: slight dev at 5712, mat at 5712	*In vitro*: overall neg *In vivo*: neg	Rat, mouse oral: incr incidence of some tumours, relevance questionable

Chemical name	Acronym	Acute effects	Irritation	Sensiti-sation	Repeated dose toxicity	Toxicity to reproduction	Mutagenicity	Carcinogenicity
		Hum, anim: CNS depression						
1-Methyl-2-pyrrolidone	NMP	Rat inh: LC_{50} 3100-8800 Rat oral: LD_{50} 3600-7900 Rat derm: LD_{50} 2500-10000	Hum: sev eye 3 (vapour), skin irr Rab: eye	Hum: neg Gp: neg	Rat inh (2 yr): NOAEC 400 (vapour)	Rat inh/oral: testis damage NOAEC 1000, NOAEL 1033 Rat inh/oral: reproductive eff NOAEC 480, NOAEL 160 Anim inh/oral/derm: dev NOAEC 350 (rat) 1000 (rab); NOAEL (oral) 330 (rat), 175 (rab); NOAEL (derm) 500 (rat), 1000 (rab); neurobehavioural teratology LOAEC 620	*In vitro*: neg *In vivo*: neg	Rat inh (2 yr): neg up to 400
4-Hydroxy-4-methyl-2-pentanone	HMP	Rat inh: LC_{Lo} 4830 Rat oral: LD_{50} 2520-4000 Rab derm: LD_{50} 13750	Hum inh: eye, nose throat at 483, skin defatting Rab: mild eye skin	No data	Rat inh (6 wk): CNS depression, eff liver, kidney (male)	No data	*In vitro*: neg	No data

anim: animal; **app**: approximately; **AST**: aspartate amino transferase; **av**: available; **aq**: aqueous; **bw**: body weight; **CNS**: central nervous system; **conc**: concentration; **d**: day(s); **decr**: decreased; **derm**: dermal; **dev**: developmental toxicity; **eff**: effect(s); **gi**: gastrointestinal; **gp**: guinea pig; **gpmt**: guinea pig maximisation test; **hist**: histological; **hr**: hour(s); **hum**: human; **incr**: increased; **inh**: inhalation; **irr**: irritation; **LAS**: linear alkylbenzene sulphonate; **LC_{50}:** lethal concentration for 50% of the animals in the study; **LD_{50}:** lethal dose for 50% of the animals in the study; **LO(A)EL(C)**: lowest observed (adverse) effect level (concentration); **mamm**: mammalian; **mat**: maternal toxicity; **min**: minimal; **Mn**: manganese; **mod**: moderate; **mth**: month(s); **neg**: negative; N**O(A)EL(C)**: no observed (adverse) effect level (concentration); **pos**: positive; **rab**: rabbit; **resp**: respiratory; **sev**: severe; **sol**: solution, **wk**: week(s); **yr**: year(s).

Data for oral and dermal exposures are listed in the unit mg/kg b.w. or mg/kg b.w./day, while inhalation exposure data are listed in mg/m^3.

3.2 Short reports

The hazard assessments for each of the 18 coformulants selected for this project are compiled in Appendices 1 to 18 to this report. This section contains a short summary on every substance, summarising the data found as well as the evaluation of the individual substances.

3.2.1 Manganese sulphate and manganese sulphide (Appendix 1)

3.2.1.1 Toxicokinetics

In humans, absorption of ingested inorganic manganese is about 3-5% and pulmonary absorption can be significant, both increasing with the solubility of the compound.
Animal studies indicate that manganese can be distributed directly to the brain from the nasal cavity via the olfactory pathway and thus bypassing the blood-brain barrier. Mice and rats chronically fed manganese sulphate had elevated tissue levels of manganese with liver and kidney levels being higher than brain levels. Excretion of manganese occurs primarily in faeces, the half-life being 13-37 days in humans.

3.2.1.2 Single dose toxicity

No human data were found. Oral LD_{50}-values in rats ranged from 275 to 1082 mg Mn/kg b.w.

3.2.1.3 Irritation and sensitisation

Inhalation of high concentrations of manganese dust (dioxide, tetroxide) can cause inflammation of the lung in humans and in animals.

3.2.1.4 Repeated dose toxicity

Occupational exposure to manganese dusts (mainly manganese dioxide) over longer periods (years) can lead to neurological effects (manganism), characterised by weakness, muscle rigidity, tremor, apathy and speech disturbances. Symptoms can start following 1-3 months of exposure. In most cases, the symptoms are irreversible. The levels of exposure causing manganism are in the range of 0.027-0.215 mg Mn/m^3 as respirable dust or 0.14-1.59 mg Mn/m^3 as total dust.
Monkeys exposed to manganese by inhalation exhibited neurological symptoms resembling manganism in humans, but neurological symptoms are seldom seen in rodents exposed to manganese.
Repeated manganese exposure of workers by inhalation at high concentrations may cause elevated serum prolactin and cortisol levels and a lowered blood pressure.
Effects in the forestomach, the kidneys and in the thyroid gland were seen in some strains of rats and/or mice exposed orally to high doses manganese sulphate (in the range of 200-730 mg Mn/kg b.w.) for 2 years.

3.2.1.5 Reproductive toxicity

Male workers suffering from manganism following exposure to high concentrations of manganese dust have shown decreased libido and decreased sperm quality and sperm count.
In animals, manganese sulphate has caused sperm head abnormalities and an increased percentage of abnormal sperm in male mice treated orally with doses from 23 mg Mn/kg b.w./day for 21 days; severe degenerative changes in testes of rabbits following a single dose (intratracheal instillation) of 158 mg/Mn/kg b.w as manganese dioxide; and degenerative changes in the testes

of rats and mice following intraperitoneal injection of manganese sulphate and in rabbits following intravenous injection of manganese chloride. Other studies in rats and mice (oral administration of manganese sulphate to rats at doses up to 232 mg/kg b.w./day for 2 years or up to 618 mg/kg b.w./day for 13 weeks; and to mice at doses up to 731 mg/kg b.w./day for 2 years or up to 1950 mg/kg b.w./day for 13 weeks) showed no histopathological effects in the testes. Administration by gavage of 33 mg Mn/kg b.w./day throughout gestation caused increased post-implantation loss in rats, but not in rabbits. No effects were seen on female reproduction in rats from dietary or drinking water treatment with manganese chloride at doses up to 620 mg/kg b.w./day or manganese tetroxide up to 1050 mg Mn/kg b.w./day throughout gestation.

School children exposed to increased levels of manganese in the drinking water and food showed poorer performance in school and in neurobehavioural tests as compared to children exposed to lower levels. However, other metals may have influenced these developmental effects. Studies in mice and rats treated orally with manganese tetroxide at doses from about 1050 mg Mn/kg b.w./day indicate that the reproductive function of offspring can be delayed; the reproductive effect was worsened by diets low in iron.
Structural abnormalities and delays were reported in pups of rats treated by gavage with 33 mg Mn/kg b.w./day, but not at 22 mg Mn/kg b.w./day. In most of the available studies, no biochemical or behavioural signs of neurotoxicity were evident in pups exposed *in utero* to manganese.

3.2.1.6 Mutagenicity and genotoxicity

Manganese sulphate was negative in one Ames test, but positive in another Ames test (one strain) as well as in other *in vitro* tests with and without metabolic activation. The substance caused an increased incidence of micronuclei and chromosomal aberrations in the bone marrow of mice treated orally, but was negative in a sex-linked recessive lethal mutation test in germ cells of fruit flies.

3.2.1.7 Carcinogenicity

A small increase in pancreatic adenomas and carcinomas was seen in male rats treated for 2 years with up to 331 mg Mn kg b.w./day as manganese sulphate. In a study with manganese sulphate in mice and rats over 2 years, a significantly increased incidence of thyroid gland follicular cell hyperplasia and a marginally increased incidence of thyroid gland follicular cell adenomas were seen in mice treated orally with 731 mg Mn/kg b.w./day, while no effects were seen at 228 mg Mn/kg b.w./day, or in rats at doses up to 232 mg Mn/kg b.w./day. In another chronic oral mice study with manganese sulphate, small increases in pituitary adenomas were observed in females at 905 mg Mn/kg b.w./day, but not in males at 722 mg Mn/kg b.w./day.

3.2.1.8 Evaluation

The critical effect of manganese following inhalation is neurotoxicity, occurring at concentrations of manganese in respirable dust in the range of 0.02-0.215 mg Mn/m^3 and in total dust in the range of 0.14-1.59 mg Mn/m^3. Manganese has also a potential to cause reproductive and developmental effects as evidenced by reproductive effects seen in workers suffering from manganism and by reproductive and development effects observed in rodents. However, most of the reproductive and developmental effects seen in rodent studies occurred after exposure via gavage or injection of the substance, administration routes which both lead to a high systemic concentration of

manganese and are of minor relevance regarding exposure of workers and the general population. In most studies, no biochemical or behavioural signs of neurotoxicity were evident in pups exposed *in utero* to manganese. Manganese sulphate showed positive results in several *in vitro* and *in vivo* tests. Small increases in thyroid gland follicular cell adenomas, pituitary adenomas, and pancreatic adenomas and carcinomas were observed in rodents exposed orally to relatively high doses of manganese sulphate for 2 years.

3.2.2 Diammonium sulphate (Appendix 2)

3.2.2.1 Toxicokinetics

When hamsters inhaled 0.2 mg/m^3 diammonium sulphate (particles), a substantial proportion was found in the nose; the clearance from the lungs was determined to be about 20 minutes. Oral toxicity data indicate absorption of diammonium sulphate from the gastrointestinal tract.

3.2.2.2 Single dose toxicity

Changes in pulmonary function (decreased flow rates, potentiation of the bronchoconstrictor action of carbachol) occurred in healthy and asthmatic workers exposed by inhalation to 1 mg/m^3 diammonium sulphate aerosols for 4 hours in combination with ozone, sulphur dioxide, or the bronchoconstrictor carbachol, while no changes were seen up to 0.5 mg/m^3.
For rats, the reported LC_{50}-value is above 1200 mg/m^3 following inhalation of diammonium sulphate for 8 hours.
One case of oral poisoning with diammonium sulphate leading to death was reported. Oral LD_{50}-values were reported to range between 2840 and 4250 mg/kg b.w. for rats and between 610 and 640 mg/kg b.w. for mice.

3.2.2.3 Irritation and Sensitisation

Volunteers exposed to 0.5 mg/m^3 reported irritation of the upper respiratory tract and of the eyes.
Diammonium sulphate was not irritating to skin or eye of rabbits.
No studies on the sensitisation potential of diammonium sulphate were found.

3.2.2.4 Repeated dose toxicity

No consistent changes in pulmonary function or in symptoms resulted from exposure of workers to 0.1 mg/m^3 for 2 hours/day for 2-3 days.
In animals, pulmonary function was affected following inhalation exposure of rats for 4 months to 0.5 mg/m^3 diammonium sulphate (mass median aerodynamic diameter of 0.44 μm). In rats exposed to 0.5 mg/m^3 diammonium sulphate for 8 months (but not for 4 months), there was an increase in alveolar fibrosis; the effect was reversible after three months of recovery. At 1 mg/m^3 (20 days), there was an increase in alveolar collagen content in rats and in guinea pigs. A significant increase in alveolar cord length was observed in rats exposed to 0.5 mg/m^3 for 4 months (but not after 8 months) and in rats and guinea pigs exposed to 1 mg/m^3 for 20 days. The number of non-ciliated epithelial cells in the bronchioles was increased in rats at 0.5 mg/m^3 for 4 or 8 months (but not after recovery). Hypertrophy and hyperplasia of non-ciliated epithelial cells in the alveoli and bronchioles was observed in guinea pigs (but not rats) exposed to 1 mg/m^3 for 20 days.
Immunological studies of peripheral lymphocytes or spleen cells of rats exposed to 0.5 mg/m^3 diammonium sulphate for 4 months revealed no depressive effects on the immune system.

3.2.2.5 Reproductive toxicity

No data were found for humans or for animals.

3.2.2.6 Mutagenicity and genotoxicity

Diammonium sulphate was negative in a number of *in vitro* tests, while no *in vivo* tests are available. Diammonium sulphate increased the mutagenicity of the known mutagen ethylmethanesulphonate in a chromosomal aberration study in V79 hamster cells.

3.2.2.7 Carcinogenicity

In a carcinogenicity study in Syrian hamsters treated intratracheally by intubation with 5 mg benzo(a)pyrene once a week for 15 weeks, simultaneously exposure by inhalation to 0.2 mg/m^3 diammonium sulphate 6 hours/day for 5 days/week did not have any effect on benzo(a)pyrene carcinogenicity.

3.2.2.8 Evaluation

The critical effects of diammonium sulphate are the local effects observed in the lungs, e.g., small changes in pulmonary function (humans and animals), and transient increased alveolar fibrosis, alveolar cord length, and hypertrophy and hyperplasia of non-ciliated epithelial cells in the alveoli and bronchioles of rats and guinea pigs. These effects occurred at concentrations around 0.5-1 mg/m^3 diammonium sulphate (mass median aerodynamic diameter of about 0.5 μm).

3.2.3 Dimethyl ether (DME) (Appendix 3)

3.2.3.1 Toxicokinetics

DME is rapidly taken up after inhalation and distributed to various organs and tissues, where steady state is reached within 30 minutes. After end of exposure, the concentration of DME in organs and tissues falls very rapidly again. The elimination is described as a two-phase process. No tissue storage is seen.
No data on absorption, distribution or elimination of DME after oral intake or dermal contact were found.

3.2.3.2 Single dose toxicity

The target organ in humans after exposure to very high acute concentrations of DME is the central nervous system, covering effects from incoordination, indistinct vision, and inability to do simple tasks, to unconsciousness (exposure levels from 157000 to 382000 mg/m^3).
In rats, the LC_{50}-value has been reported to be 313000 mg/m^3 after 4 hours exposure; in mice, LC_{50}-values have been reported to be 936000 mg/m^3 after exposure for 15 minutes and 726000 mg/m^3 after exposure for 30 minutes. The effects of DME in rats exposed to sub-lethal doses range from sedation to narcosis.

3.2.3.3 Irritation and sensitisation

No data have been found.

3.2.3.4 Repeated dose toxicity

Short-term studies (2 weeks), in which rats were exposed to concentrations of DME of 96000 mg/m^3, caused sedation, body weight gain suppression, haematology and organ weight changes, but no histopathological organ changes; all changes were completely reversed after cessation of exposure.

At high concentrations of DME, effects on the liver (higher ALT (alanine amino transferase) and AST (aspartate amino transferase) values suggesting a possible onset of a hepatotoxic effect) and changes in white blood cell counts have been observed. The NOEC in subchronic studies (13 or 30 weeks) for haematological effects was reported to be 19000 mg/m^3 for rats and 9600 mg/m^3 for hamsters. In a 30-week study on rats, the NOEC for increased levels of ALT was reported to be 3800 mg/m^3 and for increased levels of AST 380 mg/m^3. In a lifetime study in rats, the NOEC was stated to be 38000 mg/m^3 (ALT and AST were not assessed).
No human data have been found.

3.2.3.5 Toxicity to reproduction

No signs of teratogenicity or embryotoxicity were observed in offspring of female rats exposed to DME at concentrations up to 76000 mg/m^3 from day 6 to 15 of gestation (two studies). In one study, the female animals showed evidence of a narcotic effect from 9600 mg/m^3; no maternal effects were observed in the other study. Retarded ossification of the rib bones and some of the phalangeal bones in the extremities of the foetuses, and an increase in the number of extra ribs was considered as variations reflecting developmental delay rather than a specific effect on the foetuses.
No human data have been found.

3.2.3.6 Mutagenicity and genotoxicity

DME showed no signs of a mutagenic or genotoxic potential in three *in vitro* and two *in vivo* test systems.

3.2.3.7 Carcinogenicity

In a lifetime study in rats (exposed to DME at concentrations up to 48000 mg/m^3), there was no increased incidence of tumours in any of the tissues or organs of the animals.
No human data have been found.

3.2.3.8 Evaluation

The critical target organ at acute high concentrations is the CNS resulting in a narcotic effect. Based on the limited and old data on human exposure to DME, it is not possible to estimate a NOAEC for the narcotic effects in humans. No human data are available in relation to CNS changes such as neurobehavioral disturbances.
Available animal studies show a low order of acute and chronic toxicity, and any capability of DME in being a genotoxic, carcinogenic or developmental toxicant has not been demonstrated. Overall, the NOEC for effects of DME in repeated dose toxicity studies is considered to be 380 mg/m^3 based on the increased levels of AST observed at higher concentrations in the subchronic studies.

3.2.4 Hexamethylenetetramine (Appendix 4)

3.2.4.1 Toxicokinetics

In humans, hexamethylenetetramine was rapidly absorbed following oral administration and distributed to various organs. Following single or repeated oral administration, approximately 82 and 88%, respectively, of the compound was recovered unchanged in the urine. From 10 to 30% of a single oral dose was hydrolysed to formaldehyde and ammonia in the gastric fluid.

3.2.4.2 Single dose toxicity

A case of bladder inflammation was reported following accidental ingestion of hexamethylenetetramine-mandelate. The acute toxicity in animals is low, with reported oral LD_{50}-values in rats from 9200 to over 20000 mg/kg b.w.

3.2.4.3 Irritation and sensitisation

Hexamethylenetetramine has been reported to cause skin and eye irritation in workers. No to mild skin irritation was observed in rabbits and guinea pigs from 2% hexamethylenetetramine. No eye irritation occurred in rabbits from 0.2% hexamethylenetetramine, while a mascara containing 0.1% hexamethylenetetramine caused mild eye irritation in this species. Hexamethylenetetramine was reported to cause allergic contact dermatitis in workers in the rubber, lacquer and plastic industry and positive patch test results have been observed in patients treated with 2% hexamethylenetetramine. Cross-reaction with formaldehyde has been reported. A maximisation test in 25 adults using mascara containing 0.1% hexamethylenetetramine was negative. Hexamethylenetetramine was positive in a Guinea pig maximisation test using a 30% solution for induction and a 50% solution for challenge, while another maximisation test using a concentration of 0.2% was negative.
Occupational exposure to hexamethylenetetramine in a tire manufacturing plant, in mixed exposure with other chemicals, was reported to cause expiratory flow rate reduction, as well as skin rashes. In another study, an intracutaneous skin test with 0.02 ml of a 1% dilution of hexamethylenetetramine gave a positive reaction in 7 workers in the lacquer or plastics industries that had developed asthma, allergic nasal catarrh, contact dermatitis, and allergic conjunctivitis.

3.2.4.4 Repeated dose toxicity

Adverse effects have been reported in less than 3.5% of patients receiving hexamethylenetetramine and its salts orally as a drug. The most frequent findings were gastrointestinal disturbances; some patients showed hypersensitivity reactions.
Mice, rats and cats dosed orally with up to 2500, 1500 and 1250 mg/kg b.w./day, respectively, for 13-104 weeks showed no adverse effects.

3.2.4.5 Reproductive toxicity

No increase in the incidence of congenital abnormalities was observed in 200 newborns exposed to hexamethylenetetramine *in utero* during the first trimester.
No reproductive or developmental effects were seen in 4 studies in rats with doses of up to 2000 mg/kg b.w./day. Pups born of dams treated with hexamethylenetetramine during pregnancy and lactation with 2000 mg/kg b.w./day, and in addition with the same dose for the first 20 weeks of age, had lower body weights. In dogs fed about, 31 mg/kg b.w./day, the percentage of stillborn pups was slightly increased, and the weight gain and the survival to weaning were slightly impaired; no effects were seen at 15 mg /kg b.w./day. In another study, a few pups of dogs fed 94 mg/kg b.w./day had abnormalities.

3.2.4.6 Mutagenicity and genotoxicity

In vitro assays with hexamethylenetetramine showed both positive and negative results. *In vivo* assays were negative except when hexamethylenetetramine was administered at very high doses.

3.2.4.7 Carcinogenicity

No evidence of treatment-related tumours were seen in rats and mice in oral studies with doses up to about 2500 mg/kg b.w./day for up to 2 years or in dermal studies with concentrations up to 30% for up to 2 years.

3.2.4.8 Evaluation

The critical effect of hexamethylenetetramine is evaluated to be sensitisation following exposure by inhalation or by skin contact; the sensitising potential of hexamethylenetetramine is possibly due to its metabolite, the known strong sensitiser formaldehyde.

3.2.5 1-Methyl-1,2-ethanediyl dioleate (Appendix 5)

No toxicological studies regarding effects following exposure to 1-methyl-1,2-ethanediyl dioleate have been found.

Only one reference to 1-methyl-1,2-ethanediyl dioleate has been found in which it was stated that vapour of heated 1-methyl-1,2-ethanediyl dioleate can cause irritation in humans when inhaled. This study is of limited value because of the lack of information on exposure levels and duration. In addition, the irritation might be caused by degradation products of 1-methyl-1,2-ethanediyl dioleate formed by the heating of the substance.

No hazard assessment of 1-methyl-1,2-ethanediyl dioleate is possible because of lack of data.

3.2.6 Isopropyl myristate (Appendix 6)

3.2.6.1 Toxicokinetics

Only 0.25% of the substance was absorbed by monkeys exposed for 5 seconds to a spray containing isopropyl myristate. Dermal application of isopropyl myristate resulted in local penetration in rabbits and guinea pigs, but not in hairless mice. Subcutaneous injection to mice indicated that if absorbed, the substance will be distributed into almost all organs. In humans, isopropyl myristate has been shown to enhance the penetration rate of several other chemicals through human skin.

3.2.6.2 Single dose toxicity

Isopropyl myristate has a low acute oral and dermal toxicity with LD_{50}-values of > 13700 mg/kg b.w. for rats and > 5000 mg/kg b.w., respectively, being reported. No deaths or evidence of systemic toxicity occurred in rats exposed to an aerosol containing 16-20% isopropyl myristate for 6.5 seconds/minute for an hour; the only effect observed was lethargy.

3.2.6.3 Irritation and Sensitisation

No or minimal skin irritation has been observed in humans exposed dermally to isopropyl myristate for up to 21 days. When applied in petrolatum under cover for 48 hours, 10% isopropyl myristate was the lowest non-irritating concentration.

Neither undiluted isopropyl myristate nor products containing the substance caused eye or skin irritation in rabbit studies according to the Draize protocol. In repeated dermal studies in rabbits and in mice lasting 3-28 days, concentrations of 16-100% isopropyl myristate caused moderate to severe irritation, including erythema, oedema, drying, cracking, scaling and fissuring; microscopically, the treated skin of exposed animals showed acanthosis, parakeratosis, hyperkeratosis, and mixed inflammatory cell infiltration.

Rabbits treated dermally on the ears with 1% or more isopropyl myristate in propylene glycol twice daily for 2 weeks developed comedones. Application of isopropyl myristate to the eyes of rabbits daily for 3 days caused no or slight irritation that had vanished after 7 days.
Several experimental studies (repeated insult patch tests, maximisation test) with healthy volunteers have failed to detect any skin sensitising potential of isopropyl myristate. However, one case report exists of strong positive patch test reaction to a spray containing isopropyl myristate and three out of 41 hospital workers with hand eczema had positive skin-prick test reactions to 20% isopropyl myristate. No evidence of photosensitisation or phototoxicity was seen in two human studies with isopropyl myristate.
Two sensitisation tests in guinea pigs with 0.1% isopropyl myristate were negative. A weakly positive response in a local lymph node assay in mice was suggested by the authors to be a false positive response.

3.2.6.4 Repeated dose toxicity

Increased lung weights, but no histological changes, were observed in guinea pigs exposed for an hour three times a day, seven days a week for 4 or 13 weeks to isopropyl myristate (in an aerosol antiperspirant) in concentrations from 10 mg/m^3. Monkeys exposed for 13 weeks to 0.95-6.7 mg/m^3 isopropyl myristate in an aerosol antiperspirant coughed and wheezed. The lung function tests were normal, but histological examination revealed a dose-related accumulation of macrophages within the alveolar and bronchiolar walls of the lungs. No significant effects were seen in rats and hamsters exposed up to 0.16 mg/m^3isopropyl myristate aerosol (in a complex fragrance mixture) for 4 hours/day for 13 weeks.
No effects were seen in rats administered isopropyl myristate in the diet at doses up to 2000 mg/kg b.w./day for 16 weeks or by gavage at doses up to 1000 mg/kg b.w./day for 28 days. Transient changes in some of the organ weights were observed in rats fed 3700 mg/kg b.w./day, and the blood levels of two liver enzymes and the proportion of neutrophilic leucocytes were increased in rats fed 7900 mg/kg b.w./day of isopropyl myristate.

3.2.6.5 Reproductive toxicity

No gross abnormalities were seen in offspring of mice treated with 0.1ml of 1% isopropyl myristate in acetone applied to the skin once a week for 18 months. No human data have been found.

3.2.6.6 Mutagenicity and genotoxicity

Isopropyl myristate was negative in an Ames with and without metabolic activation.

3.2.6.7 Carcinogenicity

No significant differences were observed in the incidence of skin or internal tumours between negative control animals (mice and rabbits) and animals, which were given dermal applications of undiluted (or diluted) isopropyl myristate twice a week in lifetime (or shorter) studies. In a mice skin painting study, a 50% solution of isopropyl myristate accelerated the carcinogenic activity of 0.15% benzo(a)pyrene, a known skin carcinogen. No human data have been found.

3.2.6.8 Evaluation

The critical effect of isopropyl myristate is the local effects (mainly irritation) it might cause. In animals, undiluted isopropyl myristate was moderately to severely irritating to the skin following repeated exposure and at most slightly irritating to the eyes. However, in the majority of studies with human

volunteers no or minimal skin irritation has been observed following repeated dermal administration of undiluted isopropyl myristate. In one human study the highest non-irritant concentration of isopropyl myristate was 10%. The wheezing and coughing of monkeys exposed by inhalation to a formulation containing isopropyl myristate is probably a result of respiratory tract irritation. It should be noted, that in the inhalation studies, isopropyl myristate has only been tested as part of a formulation and not as the pure substance. It is a cause of concern that isopropyl myristate has the ability to enhance the dermal absorption of other chemicals since it, as an inert ingredient in pesticide formulations, might alter the absorption of the active substance or of other of the inert ingredients and thus possibly alter the toxicity of these chemicals.

3.2.7 Sodium ligninsulphonate (Appendix 7)

3.2.7.1 Toxicokinetics

Systemic effects following oral administration indicate that sodium ligninsulphonate is absorbed by this route. However, because of the size of the molecule and its ionisation in solution, the absorption is probably limited.

3.2.7.2 Single dose toxicity

LD_{50}-values for oral administration of sodium ligninsulphonate of 6000 mg/kg b.w. and greater than 40000 mg/kg b.w. have been reported for mice and rats, respectively, and the LC_{50}-value for inhalatory administration to rats was reported to be greater than 480 mg/m^3.

3.2.7.3 Irritation and Sensitisation

Limited data on experimental animals indicate that sodium ligninsulphonate may irritate eyes, skin, and the upper respiratory tract. However, there is no information about the dose levels causing irritation, or whether the irritation was caused by the sodium ligninsulphonate powder or by the chemical in a solution. No human data have been found.
No sensitisation data were found on sodium ligninsulphonate.

3.2.7.4 Repeated dose toxicity

Guinea pigs exposed to sodium ligninsulphonate in the drinking water in doses at or above 1700 mg/kg b.w./day for up to 6 weeks developed ulcers in the upper part of the colon; at higher doses, stomach ulcers as well as weight loss, diarrhoea and deaths also occurred. Rats exposed (drinking water) to doses at about 10000 mg/kg b.w./day for 16 weeks had histological changes of the liver and kidneys, and an increased weight of the same organs as well as the spleen; sodium ligninsulphonate caused no adverse effects at a dose level up to about 2500 mg/kg b.w./per day.

3.2.7.5 Reproductive toxicity

No data have been found regarding reproductive and developmental effects following exposure by inhalation, oral administration, or dermal contact. Sodium ligninsulphonate showed no estrogenic activity in a yeast screening assay.

3.2.7.6 Mutagenicity and genotoxicity

No data were found.

3.2.7.7 Carcinogenicity

No data were found.

3.2.7.8 Evaluation

Based on the available data, the critical effect of sodium ligninsulphonate is probably the irritative that it may cause to the eyes, skin, and upper respiratory tract. However, no details on the exposure were available. The hazard assessment is limited by the lack of data, as no data regarding reproductive and developmental effects, mutagenic and genotoxic potential, and effects following long-term exposure, including carcinogenicity, are available.

3.2.8 Calciumdodecylbenzenesulphonate (CaDBS) (Appendix 8)

3.2.8.1 Toxicokinetics

CaDBS is readily absorbed from the gastrointestinal tract and excreted equally via urine and faeces.

3.2.8.2 Single dose toxicity

CaDBS is of low acute toxicity with reported LD_{50}-values in rats and mice of about 4000 mg/kg b.w.

3.2.8.3 Irritation and sensitisation

No data were available.

3.2.8.4 Repeated dose toxicity

No data were available.

3.2.8.5 Reproductive toxicity

No data were available.

3.2.8.6 Mutagenicity and genotoxicity

No data were available.

3.2.8.7 Carcinogenicity

No data were available.

3.2.8.8 Evaluation

No toxicological studies regarding effects following exposure to CaDBS have been found and thus, no hazard assessment is possible. Analogy considerations with the structural analogues linear alkyl benzene sulphonates (LAS) indicate that CaDBS may be irritating to the skin, eyes and respiratory tract.

3.2.9 Ethylene Glycol (EG) (Appendix 9)

3.2.9.1 Toxicokinetics

EG is rapidly absorbed and distributed following inhalation (rats: 75-80%), oral (rats and mice: 90-100%), and dermal administration (rats: 30%; dermal, mice: 85-100%). EG is metabolised by oxidation via glycol aldehyde and glycolic acid to glyoxylic acid, which is converted either to carbon dioxide or to oxalic acid. Generally, metabolism begins immediately after administration of EG, and excretion of most of the parent compound and metabolites is complete 12 to 48 hours after dosing. The major excretory end products are carbon dioxide in exhaled air, and glycolate and unchanged EG in the urine.

3.2.9.2 Single dose toxicity

There are numerous case reports in the literature of poisoning in humans due to accidental or intentional ingestion of EG; the minimal lethal oral dose for humans has been estimated to be about 1600 mg/kg b.w. for adults.

EG is of low acute oral toxicity in experimental animals, except the cat, with reported oral LD_{50}-values ranging from >2000 to 15400 mg/kg b.w.; a minimal lethal dose of 1000 mg/kg b.w. has been reported for cats. The very limited data on acute inhalation and dermal toxicity in experimental animals also indicate a low acute toxicity by these routes with a reported LC_{50}-value (one hour) of 10900 mg/m^3 in rats and dermal LD_{50}-values of around 10600 mg/kg b.w. in the rabbit.

3.2.9.3 Irritation and sensitisation

EG has not shown a particularly irritating potential to eyes or skin in humans and did not show irritating properties when applied to the skin of rabbits; prolonged dermal exposure to humans can result in skin maceration. The data on eye irritation in experimental animals are conflicting but overall, the data indicate an eye irritating potential of EG. Male volunteers complained of irritation of the throat following exposure to 17 to 49 mg/m^3 and concentrations greater than about 200 mg/m^3 were intolerable due to strong irritation of the upper respiratory tract.

EG is not considered to have a sensitising potential in humans although some case reports are available. No data on sensitisation in experimental animals have been found.

3.2.9.4 Repeated dose toxicity

Numerous studies in experimental animals have revealed that repeated oral administration of EG resulted primarily in toxic effects in the kidneys; overall, a NOAEL for renal effects in male rats, the most sensitive species, of 200 mg/kg b.w./day is considered taking into account the reliability of the various studies.

Male volunteers (exposed for 30 days, 20-22 hours a day, aerosol, mean concentrations of 17 to 49 mg/m^3) did not experience any serious signs of toxicity, including indications of renal toxicity. Similarly, no indications of renal toxicity were observed in rats, guinea pigs, rabbits, dogs and monkeys exposed to EG (vapour) either continuously (12 mg/m^3 for 90 days), or repeatedly (10 or 57 mg/m^3 for 8 hours a day, 5 days per week for 6 weeks).

3.2.9.5 Toxicity to reproduction

Dietary exposure of rats to EG at dose levels up to 1000 mg/kg b.w./day (the highest dose level in the study) for three generations produced no effects on fertility, fecundity, or reproductive performance. When EG was administered to mice in the drinking water for 14 weeks (continuous breeding study), reduced fertility and fecundity, and foetotoxic effects, including malformations were observed at about 1640 mg/kg b.w./day; the NOAEL was about 840 mg/kg b.w./day.

Administration of EG via the gastrointestinal route (gavage) at high concentrations has resulted in developmental toxicity, including teratogenicity in rats and mice. Mice appear to be far more sensitive to the developmental toxicity exerted by EG than are rats and rabbits; a NOAEL for developmental toxicity of 150 mg/kg b.w./day can be considered for mice.

Developmental toxicity, including teratogenicity, has been observed in mice following whole-body exposures to EG respirable aerosol at concentrations from 1000 mg/m^3 (6 hours a day); rats exposed similarly exhibited developmental toxicity, but no teratogenicity at the same exposure levels. The NOAEC for developmental effects was 150 mg/m^3 for rats and at or below

150 mg/m^3 for mice. In a nose-only study performed in mice, the NOAEC for developmental effects, including teratogenicity, was 1000 mg/m^3.
No data on toxicity to reproduction in humans have been found.

3.2.9.6 Mutagenicity and genotoxicity

Most of the mutagenicity and genotoxicity tests available indicate that EG is not a mutagenic or genotoxic substance although some positive results have been reported. In a micronucleus assay in mice, increased numbers of micronuclei was observed following administration (oral, intraperitoneal injection) of very high doses (2800 to 13900 mg/kg b.w.) and thus, the result is not considered as being reliable. Overall, EG is considered not to be a mutagenic or genotoxic substance.

3.2.9.7 Carcinogenicity

No evidence of a carcinogenic effect of EG was observed at dietary concentrations of up to approximately 2000 mg/kg b.w./day for 2 years in rats or of up to approximately 12000 mg/kg b.w./day for 2 years in mice.
No data on carcinogenic effects of EG in humans have been found.

3.2.9.8 Evaluation

The critical effects following exposure to EG are the effects in the kidneys, which are observed in both humans and experimental animals; the developmental effects observed in experimental animals; and the irritative effects observed in humans and experimental animals following inhalation of EG.
A NOAEL of 200 mg/kg b.w./day can be considered for renal effects in male rats, the most sensitive species, from a 2-year dietary study. No data are available regarding renal effects in humans following repeated exposure; however, following acute ingestion of EG, the same type of renal effects are observed in humans as in experimental animals. Therefore, humans are considered to be as sensitive as male rats to the nephrotoxic effects of EG.
Mice appear to be far more sensitive to the developmental toxicity exerted by EG than are rats and rabbits. In a nose-only inhalation study, the NOAEC for developmental effects, including teratogenicity, in mice was 1000 mg/m^3 while the NOAEC was at or below 150 mg/m^3 in a whole-body inhalation study (no concentrations between 150 and 1000 mg/m^3).
Male volunteers complained of irritation of the throat following exposure to mean concentrations of 17 to 49 mg/m^3; a LOAEC for irritative effects of 17 mg/m^3 is considered.

3.2.10 Propylene Glycol (PG) (Appendix 10)

3.2.10.1 Toxicokinetics

PG is rapidly absorbed from the gastrointestinal tract and following dermal contact through damaged skin. It is metabolised to lactic and pyruvic acid, which enter the energy production. From 20 to 45% PG is recovered unchanged in the urine.

3.2.10.2 Single dose toxicity

In humans, high concentrations of PG cause CNS depression and acidosis.
Animal data show low acute oral and dermal toxicity with reported oral LD_{50}-values being of 18000 to 33500 mg/kg b.w. and a dermal LD_{50}-value in the rabbit of 20800 mg/kg b.w.

3.2.10.3 Irritation and sensitisation

Exposure by inhalation did not result in effects in the respiratory tract of humans. In rats, nose bleeding and goblet cell enlargement were reported from inhalation exposure to aerosols at concentrations from 160 and 1000 mg/m^3, respectively, for 90 days, probably related to the hygroscopic character of the substance. PG was reported to be a mild skin and eye irritant in rabbits. It has been reported to cause contact dermatitis in humans, which is considered to be primarily of irritative nature, but which occasionally may be of allergic nature.

3.2.10.4 Repeated dose toxicity

No effects were seen in humans following repeated exposure by inhalation to concentrations up to 94 mg/m^3 for several weeks. Rats exposed by inhalation to 2200 mg/m^3 as an aerosol over 90 days showed an effect (not dose-related) on haematological parameters.

No effects were seen in rats and in dogs treated with 2000 mg/kg b.w./day for 2 years. Effects on the erythrocytes with decreased erythrocyte counts and formation of Heinz bodies were seen in dogs and cats treated orally (diet) with high doses PG (5000 mg/kg b.w./day for 2 years in dogs, 1100 mg/kg b.w./day for 2-17 weeks in cats). However, no effect on haematology was reported in humans exposed to PG.

3.2.10.5 Toxicity to reproduction

No developmental effects were seen in different animal species (rats, mice, hamsters) treated orally with PG at doses greater than 1000 mg/kg b.w./day. No effects on fertility were reported in mice treated orally with doses up to 10000 mg/kg b.w./day or in rats treated by inhalation with up to 354 mg/m^3.

3.2.10.6 Mutagenicity and genotoxicity

Only one of several *in vitro* assays with PG, a chromosome aberration test was positive, and all *in vivo* tests were negative.

3.2.10.7 Carcinogenicity

No carcinogenic effect was reported in a 2-year oral study in rats or in a 120-week dermal study in mice.

3.2.10.8 Evaluation

PG is considered to be of low toxicity, the critical effects being the irritative effects on the skin and the dehydrating effect on the mucous membranes.

3.2.11 2-Butoxyethanol (EGBE) (Appendix 11)

3.2.11.1 Toxicokinetics

EGBE is absorbed and distributed throughout the body (humans and rats) following inhalation, oral administration, and dermal contact. EGBE is metabolised to 2-butoxyacetic acid (2-BAA), the toxic metabolite.

3.2.11.2 Single dose toxicity

EGBE seems of low acute toxicity in humans with haematological changes and metabolic acidosis being the primary effects after acute oral ingestion of large doses of EGBE (combined with other solvents).

EGBE is of moderate acute toxicity whether animals are exposed via the oral, dermal, or respiratory routes with oral LD_{50}-values ranging from 320 to 3100 mg/kg b.w. (rats, mice, guinea pigs, rabbits), dermal LD_{50}-values ranging from 406 to 4800 mg/kg b.w. (rabbits, guinea pigs, rats), and LC_{50}-values of 2200-2400 mg/m^3 (4-hour exposure) for rats.

3.2.11.3 Irritation and sensitisation

Irritation of the nose and throat, and eyes was noted in human volunteers exposed by inhalation to EGBE at concentrations from 490-957 mg/m^3 for 4-8 hours, but not in volunteers exposed to EGBE (98 mg/m^3) for 2 hours. The NOAEL for irritative effects of EGBE in humans is above 100 mg/m^3.
EGBE has shown a moderate to severe skin irritating potential in rabbits and guinea pigs and it is a severe eye irritant in rabbits. Male mice exposed to 750-8200 mg/m^3 EGBE for 10-15 minutes exhibited a 20% decreased in respiratory rate at the lowest concentration and a 40% decrease at the highest concentration.
Human volunteers showed no dermal effects of 10% EGBE in a patch test and EGBE did not result in dermal sensitisation when tested in the guinea pig maximisation test.

3.2.11.4 Repeated dose toxicity

Haematological effects, particularly haemolysis, have been identified as the critical end-point in toxicological studies following both acute and repeated exposures to EGBE. In addition to the haemolytic effect, effects in the liver, spleen and kidney have also been observed following exposure to EGBE; the available data indicate that these effects are secondary to haemolysis. For repeated inhalation exposure, 152 mg/m^3 was a LOAEC for haematological changes for rats (both sexes) and for female mice, and a NOAEC for male mice. For repeated oral exposure, a LOAEL for haematological effects of 69 and 82 mg/kg b.w./day is considered for male and females rats, respectively, and a NOAEL of 357 mg/kg b.w./day for mice. Certain species differences in sensitivity have been observed regarding the haematological effects of EGBE, with rats being particularly sensitive, mice sensitive, and guinea pigs appearing relative insensitive. Humans appear to be less sensitive than are rats to the haemolytic effects of EGBE as no or only very slight haemolytic effects were observed in the poisoning cases after acute oral ingestion of large doses. Furthermore, the only indication of haemolysis (small changes for haematocrit and mean corpuscular haemoglobin concentration MCHC) observed in workers exposed to an average airborne concentration of EGBE of 2.9 mg/m^3 was in the range of normal clinical values; the NOEC for haemolytic effects in humans is therefore above 3 mg/m^3. This difference in sensitivity between rats and humans is supported by *in vitro* studies, which have shown that erythrocytes from humans were unaffected by incubations with 2-butoxyacetic acid (2-BAA, the toxic metabolite of EGBE) at concentrations, which produced total rat erythrocyte haemolysis.

3.2.11.5 Toxicity to reproduction

The reproductive and developmental toxicity of EGBE has been studied in several studies in rats, mice and rabbits following inhalation, oral administration, or dermal application (developmental toxicity only). It can be concluded from these studies that EGBE does not affect the reproductive organs of parents (both males or females), and only results in adverse reproductive and developmental effects at dose levels, which also result in parental toxicity. No malformations were observed in any of the studies. No data have been located regarding toxicity to reproduction in humans.

3.2.11.6 Mutagenicity and genotoxicity

No increases in micronuclei or sister chromatid exchanges were observed in workers exposed to both EGBE and to 2-ethoxyethanol (EGEE).

EGBE has been tested for its potential to induce gene mutations in *in vitro* systems and cytogenetic damage in both *in vitro* and *in vivo* systems. In most of the tests, EGBE has given negative results. Overall, the available data do not support a mutagenic or clastogenic potential for EGBE.

3.2.11.7 Carcinogenicity

Two-year inhalation studies have shown no evidence of carcinogenic activity in male rats, equivocal evidence in female rats, and some evidence in mice. The relevance of the observed tumours to an assessment of the carcinogenicity of EGBE to humans has been questioned. As EGBE is generally negative in the genotoxicity tests and as glycol ethers generally appear unlikely to be carcinogenic, the concern for a carcinogenic potential of EGBE is low.

No data have been located regarding carcinogenic effects in humans.

3.2.11.8 Evaluation

The critical effects following exposure to EGBE are the irritative effects on the respiratory tract and eyes observed in humans and in experimental animals, and the haemolytic effect observed in experimental animals and probably also indicated by the sparse human data available. The NOAEC for irritative effects of EGBE in humans is above 100 mg/m^3. Data indicate that humans are less sensitive to the haemolytic toxicity of EGBE than are rats and mice. For humans, the NOEC for haemolytic effects is above 3 mg/m^3. For repeated inhalation exposure in experimental animals, 152 mg/m^3 was a LOAEC for haematological changes for rats (both sexes) and for female mice, and a NOAEC for male mice. For repeated oral exposure, a LOAEL for haematological effects of 69 and 82 mg/kg b.w./day is considered for male and females rats, respectively, and a NOAEL of 357 mg/kg b.w./day for mice.

3.2.12 1-Methoxy-2-propanol (2PG1ME) (Appendix 12)

3.2.12.1 Toxicokinetics

2PG1ME appears to be absorbed by all routes of exposure. It is primarily metabolised via O-demethylation and oxidation to carbon dioxide; a minor part being excreted via the urine in conjugated form. The toxic metabolite methoxyacetic acid is not formed by 2PG1ME, but only by its β-isomer 2-methoxy-1-propanol, 1PG2ME. 2PG1ME makes out minimum 95% commercial propylene glycol monomethyl ether (PGME) and maximum 5% is the β-isomer.

3.2.12.2 Single dose toxicity

In humans, inhalation exposure to PGME vapours at concentrations from 1125 mg/m3 for 1 to 7 hours caused slight CNS-depression. An LC_{50}-value in rats and guinea pigs of approximately 54600 mg/m^3 has been reported for 4 or 10 hours exposure, respectively. CNS-depression was the major symptom reported from acute inhalation studies in experimental animals. Oral LD_{50}-values of 5000 to 10800 mg/kg b.w. have been reported for rats, mice, rabbits and dogs. A dermal LD_{50}-value of about 13000 mg/kg b.w. has been reported in rabbits.

3.2.12.3 Irritation and sensitisation

Volunteers complained of eye and nose irritation from inhalation exposure to 938 mg/m^3 for 15-30 minutes, and of throat irritation after 45 minutes.

In rats, respiratory tract irritation was reported from 4 hours exposure to 37500 mg/m^3. PGME was not irritating or mildly irritating to the eyes of

rabbits. No information was available on skin irritation from PGME exposure in humans. Rabbits showed no or slight skin irritation following exposure to PGME.
PGME was not sensitising in guinea pigs.

3.2.12.4 Repeated dose toxicity
No human data were available. In animals, CNS depression and effects in the liver (increased weight, hypertrophy, and occasionally slight non-fatty degeneration and granulation)were reported for rats, mice, guinea pigs, and rabbits following repeated exposure to 5450-21800 mg/m^3 for up to 6 months. In a two-year inhalation study in rats, increased liver weight and incidence of eosinophilic hepatocellular foci were observed at 11250 mg/m^3, and development of glomerulonephritis was significantly higher in male F344-rats at this concentration; however, this finding was related to increased levels of α_{2u}-globulin, which is considered specific to male rats of that strain. In dogs, oral administration of PGME for 14 weeks resulted in CNS depression at doses from 920 mg/kg b.w./day.

3.2.12.5 Reproductive toxicity
PGME did not affect the testes of rats following inhalation exposure at concentrations up to 2250 mg/m^3 for 10 days or in mice following oral exposure to 2500 mg/kg b.w./day for 25 days. Occurrence of macrophages in the testes and epididymides of dogs treated orally with 462-2772 mg/kg b.w./day for 14 weeks was reported, but the finding is of unknown significance. Delayed ossification of the sternebrae or the skull was reported in the offspring of rats treated during gestation by inhalation of 11250 mg/m^3 PGME or orally with 739 mg/kg b.w./day, respectively; maternal toxicity was seen in the inhalation at this concentration as well. In a continuous breeding study in mice given PGME in the drinking water, reduced birth weight and weights of epididymides and prostate were observed at 3300 mg/kg b.w./day; no effects were observed in the dams. No foetotoxicity was seen in mice treated orally with doses up to 1848 mg/kg b.w./day,or in rabbits following inhalation of up to 11250 mg/m^3 or orally at doses up to 924 mg/kg b.w./day.

3.2.12.6 Mutagenicity and genotoxicity
PGME was negative in three different *in vitro* tests (Ames test, unscheduled DNA synthesis, chromosomal aberration); no *in vivo* tests were available.

3.2.12.7 Carcinogenicity
No increase in tumour incidence was seen in a 2-year inhalation study in rats and mice exposed to concentrations up to 11250 mg/m^3 PGME.

3.2.12.8 Evaluation
2PG1ME is considered to be of low systemic toxicity, the critical effects being the irritative effects to the eyes, the mucous membranes and the respiratory tract, and depression of the CNS.

3.2.13 Diethylene glycol mono-*n*-butyl ether (DEGBE) (Appendix 13)

3.2.13.1 Toxicokinetics
In rats, the absorption is about 85% following oral administration and following dermal contact, about 30-50% at low dose levels (200 mg/kg b.w.) and about 3-18% at high dose levels (2000 mg/kg b.w.). The major urinary metabolite was 2-(2-butoxyethoxy)acetic acid at both exposure routes; only minor amounts (a few percent) were excreted in faeces and about 5% as

carbon dioxide. No data regarding toxicokinetics following inhalation have been found.

3.2.13.2 Single dose toxicity

DEGBE is of low acute toxicity following oral administration and dermal application in experimental animals with oral LD_{50}-values ranging from 2000 to 9600 mg/kg b.w. (rats, mice, rabbits, and guinea pigs) and dermal LD_{50}-values greater than 2000 mg/kg b.w. (rats and rabbits). An LC_{50}-value of about 73000 mg/m^3 for rats following exposure to the acetate of DEGBE indicate a low order of acute inhalation toxicity for DEGBE as well.
No human data have been found.

3.2.13.3 Irritation and sensitisation

A few human case reports of irritation (skin, eyes, and upper respiratory tract) and sensitisation to DEGBE have been reported.
In rabbits and guinea pigs, DEGBE has shown a very low skin irritating potential in conventional tests for skin irritation whereas it is a moderate eye irritant in rabbits. However, skin irritation, which was concentration dependent in incidence, severity, and time of onset was observed in a repeated dermal toxicity study in rats as well as in a teratogenicity study in rabbits. Based upon these two studies, the NOAEL for skin irritation following repeated dermal application of DEGBE is considered to be between 100 and 200 mg/kg b.w./day.
DEGBE was not sensitising in the guinea pig maximisation test.

3.2.13.4 Repeated dose toxicity

Two-week inhalation studies in rats have revealed effects indicative of local lung effects at exposure levels from 100 mg/m^3; these types of effects were, however, not reported in a 5-week or in a 13-week inhalation study in rats. In the 5-week study, effects on the liver were reported (changes in weight, slight paleness, and slight hepatocyte vacuolisation from 13 mg/m^3). However, in the 13-week study (OECD Guideline 413), no toxicologically relevant effects were observed. Overall, a NOAEC of 95 mg/m^3 is established for the various effects, both systemic as well as local effects in the lungs, observed in the studies of rats following exposure by inhalation to DEGBE.
Two gavage studies (6- and 13-week studies) in rats are available reporting changes in haematological parameters indicative of a haemolytic effect of DEGBE at dose levels (in females) from about 50 mg/kg b.w./day for 13 weeks. However, the results reported in the 6-week and 13-week studies are not consistent and as the studies have not been published, it is impossible to evaluate the results.
The systemic toxicity of DEGBE following dermal application has been studied in rats (2 studies) and rabbits. Overall, a NOAEL for systemic effects, including neurotoxicity, of 2000 mg/kg b.w./day following dermal application of DEGBE is considered based on the two 13-week dermal studies in rats because of the limitations in the dermal rabbit study.
No data on repeated dose toxicity in humans have been found.

3.2.13.5 Toxicity to reproduction

No indications of reproductive and developmental effects were observed in rats in two one-generation studies at dose levels of up to 1000 mg/kg b.w./day (oral study) and 2000 mg/kg b.w./day (dermal study); in the oral study, post-natal effects (decreased weight of pups at day 14 of lactation) were observed in offspring from females administered 1000 mg/kg b.w./day and mated with untreated males whereas no post-natal effects were noted in the dermal study.

Developmental toxicity studies have been performed in rats (oral), mice (oral), and rabbits (dermal, OECD-guideline 414). Overall, NOAELs for developmental toxicity, including teratogenicity of 633, 2050, and 1000 mg/kg b.w./day can be considered for the rat (oral), mouse (oral, developmental only), and rabbit (dermal), respectively. For maternal effects, NOAELs of 500 and 100 mg/kg b.w./day can be considered for mice and rabbits, respectively; in rats, the NOAEL for maternal effects is below 25 mg/kg b.w./day.
No data on toxicity to reproduction in humans have been found.

3.2.13.6 Mutagenicity and genotoxicity
The data on mutagenicity and genotoxicity indicate that DEGBE is not a mutagenic or genotoxic substance neither *in vitro* nor *in vivo*.

3.2.13.7 Carcinogenicity
No data on carcinogenic effects in humans or experimental animals have been found.

3.2.13.8 Evaluation
The critical effects following exposure to DEGBE are the irritative effects on the skin and eyes observed in humans and in experimental animals, and the haemolytic effect observed in studies in experimental animals.
Only a slight skin irritating potential has been observed in conventional tests for skin irritation; however, skin irritation was observed in a repeated dermal toxicity study in rats and in a teratogenicity study in rabbits as well as. Based upon these two studies, the NOAEL for skin irritation following repeated dermal application of DEGBE is considered to be between 100 and 200 mg/kg b.w./day.
DEGBE appears to induce changes in haematological parameters indicative of a haemolytic effect following oral gavage to rats at dose levels from about 50 mg/kg b.w./day for 13 weeks. No changes in haematological parameters have been reported in repeated dose toxicity studies on inhalation and dermal exposure or in the reproductive and developmental toxicity studies using oral or dermal administration routes. The validity of the results of the two oral gavage studies cannot be evaluated; however, DEGBE is considered to have the potential of inducing haemolysis in humans, but probably only at high dose levels and following repeated exposure.

3.2.14 Dipropylene glycol monomethyl ether (DPGME) (Appendix 14)

3.2.14.1 Toxicokinetics
DPGME appears to be readily absorbed by all routes of exposure. Commercial DPGME consists of minimum 95% secondary alcohol isomers, which are metabolised to propylene glycol or dipropylene glycol, or conjugated to glucuronic acid. Excretion primarily occurs through urine. The reproductive toxicant methoxypropionic acid, which is a metabolic product of the primary alcohol isomers, was not found in urine in metabolism studies with DPGME.

3.2.14.2 Single dose toxicity
Inhalation of DPGME (vapour and aerosol) at 3080 mg/m^3 caused CNS depression in rats. Oral LD_{50}-values in rodents and dogs were reported to range from 5000 to 7500 mg/kg b.w., and dermal LD_{50}-values in rabbits to range from 9400 to > 19000 mg/kg b.w.

3.2.14.3 Irritation and sensitisation

In humans, inhalation of 456 mg/m^3 DPGME was irritating to the respiratory tract. Transient eye irritation was reported from application of a 20% aqueous solution of DPGME. Animal data indicated that DPGME is a mild eye irritant, but the substance is not a skin irritant in rabbits. In humans, no skin irritation or sensitisation resulted from a repeated patch test with DPGME. No sensitisation test in animals was available.

3.2.14.4 Repeated dose toxicity

Transient CNS depression was reported in rats exposed to the maximum attainable vapour concentration of 1848 mg/m^3 for 6 to 8 months. Slight granulation and non-fatty vacuolation of the liver was reported in rabbits, guinea pigs and monkeys at 1848 mg/m^3 for 6 to 8 months. No effects were observed in other subchronic inhalation studies (90 days) in rats and rabbits at levels of up to 1232 mg/m^3. No treatment-related effects were noted in rats following dermal application of up to 1000 mg/kg b.w./day for 28 days or in rabbits of up to 4700 mg/kg b.w./day for 90 days.

3.2.14.5 Toxicity to reproduction

No effect on testes was reported in rodents exposed by inhalation at concentrations of up to 1232 mg/m^3 for 90 days (rats, rabbits), or dermally with up to 1000 mg/kg b.w. (rats). Developmental toxicity studies showed no effects of DPGME in rats and rabbits at up to 1756 mg/m^3.

3.2.14.6 Mutagenicity and genotoxicity

DPGME was negative in three different *in vitro* tests (Ames test, unscheduled DNA synthesis, cytogenetic assay); no *in vivo* tests were available.

3.2.14.7 Carcinogenicity

No data were found.

3.2.14.8 Evaluation

DPGME is considered to be of low toxicity, the critical effect being irritation of the eye and the mucous membranes.

3.2.15 Polyethylene glycol dodecyl ether (polyEGDE) (Appendix 15)

3.2.15.1 Toxicokinetics

No data were found.

3.2.15.2 Single dose toxicity

No data on systemic effect in humans from exposure to polyEGDE were available. Oral LD_{50}-values in rats of 4150 and 8600 mg/kg b.w. were reported for polyEGDE.

3.2.15.3 Irritation and Sensitisation

PolyEGDE was reported as a moderate skin irritant in humans. In rabbits, 75-500 mg/kg b.w. polyEGDE was mildly to moderately skin irritating, depending on the chain length. The substance was also moderately eye irritating in rabbits. Severe, but reversible, nasal irritation was caused by direct application of polyEGDE to nostril of rats, but this application way is considered irrelevant in normal use. No information was available on sensitising potential of polyEGDE.

3.2.15.4 Repeated dose toxicity

No data were found.

3.2.15.5 Reproductive and developmental effects
No data were found.

3.2.15.6 Mutagenic and genotoxic effects
PolyEGDE was negative in *in vitro* tests and in *in vivo* tests.

3.2.15.7 Carcinogenicity
No data were found.

3.2.15.8 Evaluation
On the basis on the scarce information available on polyEGDE, the critical effect from this substance is considered to be the irritation to the skin and eyes.

3.2.16 Cyclohexanone (Appendix 16)

3.2.16.1 Toxicokinetics
Cyclohexanone is absorbed by all routes of exposure and rapidly metabolises to cyclohexanol. Excretion occurs mainly through urine as glucuronide conjugates.

3.2.16.2 Single dose toxicity
In animals, cyclohexanone is moderately toxic by inhalation (LC_{50}-values in rats of 6200-32500 mg/m^3), oral administration (LD_{50}-values in rats of 1296-3460 mg/kg b.w), and dermal contact (LD_{50}-values in rabbits of 794-3160 mg/kg b.w.). In humans, CNS symptoms and acidosis have been recorded after accidental ingestion of an unknown dose of cyclohexanone.

3.2.16.3 Irritation and sensitisation
Cyclohexanone was reported to be irritating to eyes, nose and throat of humans following exposure at 306 mg/m^3 for a few minutes, and to skin from 162 mg/m^3. The substance is also a skin and eye irritant in animals.
One case of occupational allergic dermatitis has been reported. Sensitisation studies in guinea pigs and mice were negative. The sensitising potential of cyclohexanone is considered to be negligible.

3.2.16.4 Repeated dose toxicity
Neurological symptoms in the central nervous system, including cognitive changes, have been reported from long-term occupational exposure to concentrations at 162-368 mg/m^3 and confirmed in rat and rabbit studies after short time and prolonged exposure. Also peripheral nervous system effects were reported in humans at this level, but confirmation lacks from animal studies.

3.2.16.5 Toxicity to reproduction
In a two-generation inhalation study in rats, fertility of male rats in the F_1 was reported to be reduced at 5712 mg/m^3, however, no details were available and thus, an evaluation of the effect of cyclohexanone on fertility is not possible on this basis. Slight developmental toxicity was reported in rats and mice following inhalation or oral administration of cyclohexanone, but at maternally toxic levels only.

3.2.16.6 Mutagenicity and genotoxicity
In vitro mutagenicity tests with metabolic activation were negative, a few positive results have been reported without metabolic activation. All *in vivo*

studies but one, of poor quality, were negative. Overall, the available data indicate that cyclohexanone is not a genotoxic or mutagenic substance.

3.2.16.7 Carcinogenicity

In a chronic study in mice and rats exposed orally to cyclohexanone in the drinking water, tumours were reported in the lymphatic tissue, the liver, and in the lungs of mice, and in the adrenals and in the thyroid of rats. Thyroid tumours in rats may, in some cases, not be relevant for humans; however, the carcinogenic mechanism for cyclohexanone is not elucidated and no conclusion can be drawn on this effect. Some of the other tumour-types found are also of questionable relevance for humans, and the lack of dose-response indicate that the substance is not carcinogenic in these studies. However, no conclusive evaluation on the carcinogenic effect of cyclohexanone can be performed on basis of the available data.

3.2.16.8 Evaluation

The available data indicate that CNS-depression and irritation of skin, eyes and respiratory tract are the critical effects of cyclohexanone. However, evaluation of the carcinogenic potential of cyclohexanone cannot be performed on the available data.

3.2.17 1-Methylpyrrolidone (NMP) (Appendix 17)

3.2.17.1 Toxicokinetics

NMP is readily absorbed following inhalation, oral ingestion and dermal contact, and distributed widely to organs and tissues with the highest concentrations occurring (rats) in the liver, small and large intestine, testes, stomach, and kidneys. NMP is rapidly metabolised and excreted in humans and experimental animals with the major route of excretion being the urine (rats: 85-88%).

3.2.17.2 Single dose toxicity

No human data have been found.

NMP is of low acute toxicity in the rat with reported 4-hour LC_{50}-values being greater than 5100 mg/m^3 or in the range of 3100-8800 mg/m^3. The reported oral and dermal LD_{50}-values ranged from 3600-7900 mg/kg and from 2500-10000 mg/kg, respectively, in the rat.

3.2.17.3 Irritation and sensitisation

Several workers have experienced skin irritation and contact dermatitis on the hands after a few days of working with NMP; no signs of contact sensitisation have been reported.

The available studies in experimental animals do not suggest that NMP is a skin irritant or sensitiser, whereas NMP has shown eye irritancy in rabbits.

3.2.17.4 Repeated dose toxicity

Volunteers exposed to NMP at levels up to 50 mg/m^3 for 8 hours did not report any discomfort to eyes or upper airways. Workers have reported severe eye irritation following exposure for a short time (30 minutes) to levels of about 3 mg/m^3 (8-hour TWA), exposures around 66 mg/m^3 were reported as being immediately uncomfortable (within 30 seconds) with minor eye irritation, and exposures above 200 mg/m^3 were found unbearable following a few seconds of exposure.

Following repeated exposure of rats to NMP by inhalation (most studies: 6 hours a day, 5 days per week), histopathological lesions (including testicular damage) were observed only at very high exposure levels (above 3000

mg/m^3). Rats exposed to NMP by inhalation (620 mg/m^3, 6 hours a day, 7 days per week for 90 days) did not show neurotoxic effects. In a 2-year inhalation study, the highest dose level (400 mg/m^3, 6 hours a day, 5 days per week to the vapour predominantly) did not cause any adverse effects and no clinical signs of exposure were reported; thus 400 mg/m^3 is considered as being a NOAEC in the rat for NMP as a vapour with respect to clinical effects as well as to chronic toxicity.

3.2.17.5 Toxicity to reproduction

No reproductive effects were noted in a two-generation study on rats (inhalation, 480 mg/m^3). In a multigeneration study on rats, oral administration (500 mg/kg b.w./day for 13 months) affected reproduction and parental effects were noted. Several teratology studies have investigated the developmental toxicity of NMP in rats (most studies) and in rabbits; generally, no malformations were observed at dose levels, which did not induce maternal toxicity. Foetotoxic effects in form of a lower foetal body weight have been observed in some studies on rats at dose levels (480-620 mg/m^3 (inhalation); 400-500 mg/kg b.w./day (oral administration); 750 mg/kg b.w./day (dermal administration)) that did not induce maternal toxicity. A neurobehavioral teratology study has shown an impairment of higher cognitive functions related to solving difficult tasks in rats exposed at 620 mg/m^3 on gestation days 7-20, a dose level that did not induce maternal toxicity.
No human data are available.

3.2.17.6 Mutagenicity and genotoxicity

The mutagenicity and genotoxicity tests available indicate that NMP is not a mutagenic or genotoxic substance.

3.2.17.7 Carcinogenicity

No carcinogenic effects were observed in rats exposed by inhalation (up to 400 mg/m^3, 6 hours a day, 5 days per week for 2 years).
No human data are available.

3.2.17.8 Evaluation

Based on the available data, the critical effect in humans following exposure to airborne NMP is considered to be the irritative effects on the eyes and the respiratory tract; the critical effect in humans following dermal contact is considered to be skin irritation. Data obtained from studies on experimental animals do not indicate that other effects, including neurotoxic effects, than the irritative ones should be expected to occur following exposure to the levels of NMP eliciting these irritative effects.

3.2.18 4- Hydroxy-4-methyl-2-pentanone (HMP) (Appendix 18)

3.2.18.1 Toxicokinetics

HMP is apparently absorbed both by inhalation and by oral intake. No date have been found regarding metabolism and excretion, but the substance is expected to be eliminated in urine as conjugates, to enter the intermediary metabolism, or to be incorporated in the tissues.

3.2.18.2 Single dose toxicity

Animal data indicate a low acute toxicity by all three routes of exposure, oral LD_{50}-values in rats and mice reported from 2520 to 4000 mg/kg b.w., a dermal LD_{50}-value in rabbits being reported at 13750 mg/kg b.w., while the lowest lethal inhalation exposure in rats was 4830 mg/m^3 over 4 hours.

3.2.18.3 Irritation and sensitisation
In humans, HMP was irritating to the eyes, nose and throat from 15 minutes exposure to 483 mg/m^3. Mucous membrane irritation occurred in animals from 10143 mg/m^3, and the substance is mildly irritating to rabbit eyes and skin. In humans, HMP is defatting to the skin. No data were available on the sensitisation potential of HMP.

3.2.18.4 Repeated dose toxicity
Inhalation exposure of rats at 4830 mg/m^3 HMP for 6 weeks resulted in slight lethargy during and after exposure, increased liver and kidney weights, and unspecified histological changes in the proximal renal tubules of male rats. The kidney toxicity of male rats is evaluated not to be relevant to humans, but a species and gender specific finding associated with accumulation of alpha-2-microglobulin.

3.2.18.5 Toxicity to reproduction
No information was found.

3.2.18.6 Mutagenicity and genotoxicity
HMP was negative in *in vitro* assays, while no *in vivo* assays were available.

3.2.18.7 Carcinogenicity
No information was found.

3.2.18.8 Evaluation
The limited available toxicological information on HMP indicates that the substance is irritating to the eyes and the mucous membranes. Other end-points could not be evaluated because of insufficient data.

3.3 Critical effects and existing regulation

Table 3 summarises the critical effects identified for each coformulant as a result of the hazard assessment as well as the existing regulations for that substance.

The following abbreviations are used in the Table:
-: no regulation; **b.w.**: body weight; **C-value**: quality criteria in ambient air; **CNS**: central nervous system; **L**: the C-value is based on odour, not health based; **LAS**: linear alkyl benzene sulphonate; **LO(A)EL(C)**: lowest observed (adverse) effect level (concentration); **Mn**: manganese; N**O(A)EL(C)**: no observed (adverse) effect level (concentration); **OEL DK**: occupational exposure limit in Denmark; **RDT**: repeated dose toxicity.

Abbreviations related to EU-classification are explained below the Table.

Table 3: Summary table of critical effects and current regulation on selected coformulants
(Tabel 3: Oversigtstabel over kritiske effekter og gældende regulering af udvalgte hjælpestoffer)

Chemical name	Acronym	Critical effects	EU-classification[a,1)]	OEL DK[2)]	C-value[3)]
Manganese (II) sulphate		Neurological effects: LOAEC humans 0.14-1.59 mg Mn/m^3 as total dust	Xn; R48/20/22 N; R51/53	0.2 mg Mn/m^3 (inorganic compounds)	0.001 mg Mn/m^3 (inorganic dust)
Manganese (II) sulphide			-		
Diammonium sulphate		Lung: LOAEC rat 0.5-1 mg/m^3	-	-	-
Dimethyl ether	DME	Acute: CNS depression humans RDT: Liver NOEC rat 380 mg/m^3	Fx; R12	1000 ppm (1885 mg/m^3)	1 mg/m^3
Hexamethylenetetramine		Sensitisation inhalation, skin contact	F; R11 R42/43	-	-
1-Methyl-1,2-ethanediyl dioleate		No data available	-	-	-
Isopropyl myristate		Irritation skin, respiratory tract	-	-	-
Sodium ligninsulphonate		Irritation eye, skin, respiratory tract	-	-	-
Calciumdodecylbenzene-sulphonate	CaDBS	Possibly irritation eye, skin, respiratory tract - by analogy with LAS	-	-	-
Ethylene glycol	EG	Kidney: NOAEL rat 200 mg/kg b.w./day Developmental effects: NOAEC mouse 1000 mg/m^3 Irritation respiratory tract: LOAEC human 17 mg/m^3	Xn; R22	10 ppm (26 mg/m^3)	-
Propylene glycol	PG	Skin and mucous membrane irritation/dehydration	-	-	-
2-Butoxyethanol	EGBE	Haemolysis: NOEC human above 3 mg/m^3 Irritation eye, skin Irritation respiratory tract: NOAEC human above 100 mg/m^3	Xn; R20/21/22 Xi; R36/38	20 ppm (98 mg/m^3)	0.04 mg/m^3 L
1-Methoxy-2-propanol	2PG1ME	Irritation eye, mucous membranes, respiratory tract	-	50 ppm (300 mg/m^3) skin notation	1 mg/m^3
Diethylene glycol mono-*n*-butyl ether	DEGBE	Irritation skin, eye RDT: skin irritation NOAEL 100-200 rat mg/kg b.w./day	Xi; R36	100 mg/m^3	0.02 mg/m^3 L
Dipropylene glycol monomethyl ether	DPGME	Eye and mucous membrane irritation	-	50 ppm (300 mg/m^3) skin notation	1 mg/m^3
Polyethyleneglycol dodecylether	polyEGDE	Skin and eye irritation	-	-	-

Chemical name	Acronym	Critical effects	EU-classification[a,1)]	OEL DK[2)]	C-value[3)]
Cyclohexanone		CNS depression: LOAEC human 162 mg/m^3 Irritation skin, eye, respiratory tract	R10 Xn; R20	10 ppm (40 mg/m^3) skin notation	0.1 mg/m^3
1-Methyl-2-pyrrolidone	NMP	Irritation eye, skin, respiratory tract	Xi; R36/38	5 ppm (20 mg/m^3)	0.5 mg/m^3
4-Hydroxy-4-methyl-2 pentanone	HMP	Irritation eye, mucous membranes	Xi, R36	50 ppm (240 mg/m^3)	0.1 mg/m^3

-: no regulation; **b.w.**: body weight; **C-value**: quality criteria in ambient air; **CNS**: central nervous system; **L**: the C-value is based on odour, not health based; **LAS**: linear alkylbenzene sulphonate; **LO(A)EL(C)**: lowest observed (adverse) effect level (concentration); **Mn**: manganese; N**O(A)EL(C)**: no observed (adverse) effect level (concentration); **OEL DK**: occupational exposure limit in Denmark; **RDT**: repeated dose toxicity.

1) The Statutory Order from the Ministry of the Environment no. 439 of June 3, 2002, on the List of Chemical Substances.
2) Grænseværdier for stoffer og materialer. Arbejdstilsynets At-vejledning C.0.1, oktober 2002.
3) B-værdivejledningen. Vejledning Nr. 2 2002, Miljøstyrelsen, Miljøministeriet.

[a] EU-classification and labelling system consists of classes of danger and risk phrases noted in abbreviated form as shown below. R-phrases can be combined in order to indicate the route of exposure, e.g. R48/20/22 "Harmful: Danger of serious damage to health by prolonged exposure by inhalation and if swallowed".

Symbols

F Highly flammable
Xi Irritant
Xn Harmful
N Dangerous for the environment

R-phrases:

R10 Flammable
R12 Extremely flammable
R20 Harmful by inhalation
R21 Harmful in contact with skin

R22 Harmful if swallowed
R36 Irritating to eyes
R37 Irritating to respiratory tract
R38 Irritating to skin
R42 May cause sensitisation by inhalation
R43 May cause sensitisation by skin contact
R48 Danger of serious damage to health by prolonged exposure
R51 Toxic to aquatic organisms
R53 May cause long-term adverse effects in the aquatic environment

4 Discussion

The results of this project on hazard assessment of 18 selected coformulants give information on two levels: data availability and toxicological effects observed for the 18 substances according to the public available literature.

4.1 Data availability on the selected coformulants

The literature searches performed on the 18 coformulants clearly demonstrate, that the toxicological database for this class of substances is limited.

Data are available on all end-points (acute toxicity, irritation, sensitisation, repeated dose toxicity, toxicity to reproduction, mutagenicity and genotoxicity, and carcinogenicity) for 8 substances: Hexamethylenetetramine, isopropyl myristate, ethylene glycol (EG), propylene glycol (PG), ethylene glycol mono-*n*-butyl ether (EGBE), 1-methoxy-2-propanol (2PG1ME), cyclohexanone, and 1-methyl-2-pyrrolidone (NMP).
For 6 substances, data are available on four to six end-points: Manganese (II) sulphate / manganese (II) sulphide, dimethyl ether (DME), diammonium sulphate, diethylene glycol mono-*n*-butyl ether (DEGBE), dipropylene glycol monomethyl ether (DPGME), and 4-hydroxy-4-methyl-2-pentanone (HMP).
For 3 substances, the data are limited to a few information about one to three end-points: sodium ligninsulphonate, calciumdodecylbenzene sulphonate (CaDBS), and polyethylene glycol dodecyl ether (polyEGDE).
For 1 substance, no relevant data were found at all: 1-methyl-1,2-ethanediyl dioleate.

Human data are available for 16 of the selected substances; however for most of these substances, the data are scarce. The 2 substances for which no human data were found are sodium ligninsulphonate and CaDBS. For one substance (1-methyl-1,2-ethanediyl dioleate), the human data are not considered as being relevant for the hazard assessment of this substance. For most of the substances, data have been found primarily on irritative effects (14 substances), and in some cases also on acute toxic effects (7 substances). Reports on skin sensitisation in humans are present for 9 substances, but most of these are case reports on very few individuals; for one of these substances (hexamethylenetetramine), data on sensitisation by inhalation is also available. Human data were found on effects following repeated exposure for 7 substances, while reporting on toxicity to reproduction is only available for two substances. No data are available in humans for mutagenicity and genotoxicity, or for carcinogenicity.
The available human data are in most cases obtained from case reports (e.g., poisonings), clinical examinations, studies on volunteers, and experiences from the working environment; no epidemiological studies have been located for any of the substances. For the major part of substances and end-points, the information is
qualitative and do not relate to specific exposure levels. Furthermore, the data are often not very well reported, and mixed exposures cannot always be

excluded. Consequently, a hazard assessment could not be performed for any of the selected substances based on the human data only.

Animal data are available for all of the 18 substances, but one (1-methyl-1,2-ethanediyl dioleate). For one substance (CaDBS), the animal data are not specifically describing the selected substance, but a mixture (LAS) containing the substance, and the relevance of the data is therefore questionable. For the remaining substances, animal data are available on acute toxicity (16 substances) and local irritation (15 substances). Data for sensitisation are very scarce, with only 7 substances reported tested for skin sensitisation. Repeated dose toxicity data are available for 15 substances and data for toxicity to reproduction are available for 12 substances. *In vitro* mutagenicity/genotoxicity data are available for 15 substances and *in vivo* genotoxicity tests for 10 substances. Data on carcinogenicity in animals are available for 10 substances.
A large number of the available animal studies have been performed many years ago and therefore not in accordance with GLP or with agreed test guidelines as e.g., OECD test guidelines or the testing methods (Annex V Part B) adopted within the EU. The reporting of the studies is in many cases not appropriate, leaving out some information that would have been useful for the interpretation of the results. For several of the substances, most of the various end-points have not been examined thoroughly and therefore, data gaps exist. The problem of data gaps is most important for end-points such as sensitisation, repeated dose toxicity, toxicity to reproduction, *in vivo* mutagenicity/genotoxicity, and carcinogenicity.
The relatively high percentage of data on developmental toxicity and/or adverse effects on fertility may be due to the overrepresentation of glycol ethers, a chemical class including known reproductive toxicants.
The selected coformulants used in low tonnage are poorly documented with respect to effects following repeated administration, e.g. polyEGDE, HMP, and 1-methyl-1,2-ethanediyldioleate. However, this is also the case for several coformulants used in higher tonnage as e.g., DPGME, CaDBS, and sodium ligninsulphonate. Thus, there is no consistent relation between data availability and tonnage, and the adverse health effects of coformulants used in Denmark in high tonnage are not necessarily studied more extensively than coformulants used in low tonnage.

4.2 Toxicological effects of the selected coformulants

The toxicological evaluations of the 18 coformulants selected for this project showed that these substances have various toxicological effects:

The most common critical effect indicated by the available data is local effects - predominantly irritation of the eye, the skin, and/or the respiratory tract. For 13 of the coformulants, irritative effects are identified as the critical effect based on results from animal studies and/or from human experience. However, the severity of the irritative effects is difficult to evaluate as an effect level could only be derived for 3 of these irritative coformulants (EG: respiratory tract; EGBE: respiratory tract; DEGBE: skin).
One other coformulant (hexamethylenetetramine) is associated with development of allergic asthma in humans by inhalation; this coformulant is also a skin sensitiser in humans and in guinea pigs.
Another coformulant (manganese (II) sulphate) is shown to be a serious neurotoxicant at low exposure levels by inhalation, while a number of coformulants, predominantly organic solvents, have CNS-depressing effects

following acute exposure to relatively high concentrations and/or following repeated exposure.
One coformulant is nephrotoxic (EG), one causes haemolytic anaemia (EGBE), and one affects the liver (DME).
One coformulant (EG) is probably a developmental toxicant following exposure at very high concentrations (above 1000 mg/m^3).
None of the 18 selected coformulants are considered to possess a mutagenic and/or genotoxic potential although it is acknowledged that some positive results have been obtained in some test systems for two of the selected coformulants (manganese (II) sulphate, hexamethylenetetramine) and no data are available for 3 of the coformulants.
A carcinogenic potential has not been identified for any of the 10 coformulants for which this end-point has been examined.

Thus, none of the selected coformulants can be considered as harmless based on the hazard assessments performed in this project. A number of the coformulants had even serious adverse health effects. This finding is especially alarming as the data availability was very limited for a number of coformulants. Some of the coformulants selected may thus have additional toxicological effects than the ones identifiable on the available database.

4.3 Present regulation

Eight of the 18 selected coformulants are classified for health effects by the EU. Three substances are classified for acute toxicity (EG, EGBE, cyclohexanone), 4 substances for irritative effects (EGBE, DEGBE, NMP, HMP), 1 substance for sensitisation (hexamethylenetetramine), and 1 substance for effects following repeated exposure (manganese (II) sulphate). For 10 of the 18 coformulants, an occupational exposure limit has been established in Denmark and for 9 of the coformulants, a C-value (quality criteria value in air) has been set in Denmark.

According to the present regulation, classification of a pesticide for health effects will reflect the toxicological effects of the coformulants with respect to acute toxicity and local irritation, which are the end-points where data are required for the pesticide product. However, classification will not include information on effects following repeated exposure as well as on a number of specific effects (sensitisation, toxicity to reproduction, mutagenicity/genotoxicity, carcinogenicity) unless the coformulants themselves are adopted on the list of dangerous substances.

4.4 Limitation of the project

The limited number of coformulants included (18 substances) in this project in comparison to the very high number of different coformulants used in Denmark makes the project vulnerable to bias. It is difficult to ensure that the prioritisation of the coformulants does not introduce parameters that influence the results with respect to the two elements investigated in this project, namely the data availability and the toxicological assessments of the coformulants. Also, the criteria for prioritisation of coformulants set under point 2.1 give rise to the following comments on the representativity of the coformulants evaluated in the project:

1. By setting tonnage as the primary criteria for selection, the many different functions of coformulants are probably not represented among the 18 selected substances as some functions can be fulfilled by only small amounts of coformulants, (e.g., perfume) while other functions require large amount of the chemical (e.g., fillers, dispersing agents, solvents). Thus, there is a risk that the latter functions are over represented in the project.
   It can be seen from Table 1 that a number of glycol ethers are included in the project. Many solvents, including glycol ethers, are irritative to the eyes, the skin and the respiratory tract, and some are CNS-depressants. These effects are all represented among the coformulants selected in this project; however, because of the possible overrepresentation of a certain chemical class in the project, it is not possible to use this knowledge on coformulants in general.

2. The criteria exempting substances classified as mutagens, carcinogens or toxic to reproduction may have biased the representativity of the results both on data availability and on toxicological effects.

The purpose of this project was to compile and evaluate the available toxicological information on the 18 selected coformulants in order to perform a hazard assessment for these substances. Therefore, proper risk assessments cannot be performed for these substances as no exposure assessments have been carried out in this project. Thus, no conclusions can be made exclusively based on the results obtained in this projects whether exposures to these coformulants in pesticides may constitute a risk for humans of experiencing adverse health effects during the use of these pesticides.

5 Conclusions

5.1 Data availability on the selected coformulants

The results of this project demonstrate that the data availability for the 18 selected coformulants is limited.

Toxicological data are available for 16 of the selected coformulants; however, for many of these coformulants, various end-points have not been examined thoroughly. For two of these coformulants (sodium ligninsulphonate, polyEGDE), relevant data are only available for acute toxicity and irritation. For two other coformulants (1-methyl-1,2-ethanediyl dioleate, CaDBS), no relevant data are available at all.

In conclusion, the hazard assessments of most of the 18 selected coformulants may be hampered by the data gaps identified.

5.2 Toxicological effects of the selected coformulants

The available data on the selected coformulants indicate that coformulants in pesticides are not toxicologically inert ingredients, but that they may possess a range of toxicological effects.

For 13 of the selected coformulants, irritative effects on the eye, the skin, and/or the respiratory tract are identified as the critical effect based on results from animal studies and/or from human experience; however, the severity of the irritative effects is difficult to evaluate as an effect level could only be derived for 3 of these irritative coformulants. Other critical effects identified include sensitisation, neurotoxicity, CNS-depressing effects, nephrotoxicity, haemolytic anaemia, and liver effects. One coformulant is probably a developmental toxicant following exposure at very high concentrations. No mutagenic/genotoxic or carcinogenic substances were identified among the selected coformulants for which these end-points have been examined (15 and 10 coformulants, respectively).

Eight of the 18 selected coformulants are classified for health effects by the EU (3 for acute toxicity, 4 for irritative effects, 1 for sensitisation, and 1 for effects following repeated exposure (neurotoxicity)).

In conclusion, a number of the selected coformulants have serious adverse health effects. This finding is particularly of concern as the data availability is very limited for some of coformulants. Thus, it cannot be excluded that some of the selected coformulants may have additional toxicological effects than the ones identifiable on the available database.

However, it should be born in mind that it is not possible based exclusively on the results obtained in this project to evaluate whether exposures to any of the 18 selected coformulants in pesticides may constitute a risk for humans of

experiencing adverse health effects during the use of these pesticides as no exposure assessments have been carried out within this project.

5.3 Limitation of the project

The limited number of coformulants evaluated (18 substances) in this project as well as the criteria for selection of the substances to be evaluated in the project (section 2.1) may give rise to some bias regarding the results obtained in the project. The predominant concern is that the 18 selected substances are not representative for the very high number of different coformulants used in Denmark.

6 Recommendations

The results of this project demonstrate that serious adverse health effects are observed for a number of the 18 selected coformulants. This finding is particularly of concern in the light of the limited data availability for some of the selected coformulants and thus, it cannot be excluded that some coformulants may have additional toxicological effects than the ones identifiable on the available database. Consequently, this project points at a need for an improvement of the toxicological database on coformulants.

On the basis of the results obtained in this project, it is recommended that the authorities take further measures to ensure that humans are protected from experiencing adverse health effects following exposure to coformulants used in pesticide formulations.

One measure could be to improve the toxicological database on coformulants in order to enable a detailed hazard assessment of every end-point of relevance to human health e.g., by a revision of the current approval scheme in order to include data requirements on all relevant toxicological end-points either for all the specific coformulants to be used in a given pesticide formulation or for the pesticide formulation itself. As the approval scheme for pesticide formulations already includes data requirements for acute toxicity and for skin and eye irritation, focus could particularly be put on other end-points such as sensitisation, repeated dose toxicity, neurotoxicity, toxicity to reproduction, mutagenicity/genotoxicity, and carcinogenicity.

Another measure could be a further regulation on the use of coformulants in pesticide formulations in order to ensure that the coformulants for which serious health effects are identified are not allowed for use in pesticide formulations.

It should be born in mind that the 18 selected substances may not be representative for the very high number of different coformulants used in Denmark and therefore, the results obtained in this project may be subjected to some bias. Thus, a first measure could be to perform hazard assessments for more of the coformulants used in Denmark in order to evaluate if the coformulants generally possess toxicological effects of concern for human health.

7 References

Allanou R, Hansen B and van der Bilt Yvonne (1999): Public Availability of Data on EU High Production Volume Chemicals (EUR 18996 EN).

Bichel Committee (1999a): The Bichel Committee: Report from the main Committee.

Bichel Committee (1999b): Bichel Udvalget: Rapport fra underudvalget om Miljø- og Sundhed.

EEC (1967): Council Directive 67/548/EEC of June 1967 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous substances.

EEC (1978): Council Directive78/631/EEC of 26 June 1978 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging of dangerous prepartions (pesticides).

EEC (1988): Council Directive of 7 June 1988 on the approximation of the laws, regulations and administrative provisions of the Member States relating to classification, packaging and labelling of dangerous preparations.

EEC (1991): Council Directive 91/414/EEC on the marketing of plant protection products.

EC (1999): European Parliament and Council Directive 1999/45/EC of 31 May 1999 on the approximation of the laws, regulations and administrative provisions relating of the Member States to classification, packaging and labelling of dangerous preparations.

Miljø- og Energiministeriet (1998): Miljø- og Energiministeriets bekendtgørelse nr 241 af 27. april 1998 om bekæmpelsesmidler med senere ændringer.

Miljøministeriet (2002a): Miljøministeriets bekendtgørelse nr 329 af 16 maj 2002 om klassificering, emballering. Mærkning, salg og opbevaring af kemiske stoffer og produkter.

Miljøministeriet (2002b): Miljøministeriets bekendtgørelse nr. 439 af 3. juni 2002 af listen over farlige stoffer.

Miljøstyrelsen (1992): En vurdering af mængden af hjælpestoffer og toksikologisk viden om disse I ukrudtsmidler. Pilot project, MST, j. nr. 7041-0229, brev nr 2, 1992.

Miljøstyrelsen (1998): List of Undesirable Substances. Enviromnental Review no 7, 1998, Danish EPA.

Miljøstyrelsen (2001): Environmental project no 636, 2001: Report on the Advisory list for selvclassification of dangerous substances, Danish EPA.

Miljøstyrelsen (2003): Personal communication from the Danish EPA.
Nordic Council of Ministers (2003) in press: Auxilliary substances in plant protection products – their impact on health and environment.