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SCIENTIFIC OPINION

Safety in use of dimethyl ether as an extraction solvent[1]

Scientific Opinion of the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids (CEF)

(Question No EFSA-Q-2007-186)

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PANEL MEMBERS

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SUMMARY

Following a request from the Commission, the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing aids (CEF) was asked to give a scientific opinion on the safety in use of dimethyl ether as an extraction solvent.

Dimethyl ether is a solvent to be used in the processing of proteins, in particular collagen, for the meat industry to prepare meat products at levels normally between 0.5 to 1.0 % (w/w) of the finished product.

Dimethyl ether toxicity has been tested mainly upon atmosphere exposure. Upon inhalation dimethyl ether is rapidly taken up and distributed in various tissues and organs. It is reported that upon exposure in the atmosphere to 1000 ppm (equivalent to 1884 mg/m^3) in rats dimethyl ether levels of 14 to 22 mg/kg have been found in different organs and tissues. Organ distribution appears to be proportional with atmosphere concentrations in the range of 750 to 2000 ppm (equivalent to a concentration in atmosphere of 1413 and 3768 mg/m^3).

The Panel considers that in most of the cases inhalation exposure toxicity data cannot be directly extrapolated to an oral exposure situation. However, in this particular case, considering that animal studies have shown that dimethyl ether is distributed in the body following inhalation exposure, similarly as through oral exposure, the Panel estimates that results from inhalation studies can be used to assess dimethyl ether oral toxicity.

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Observations from inhalation studies suggest that dimethyl ether is of low toxicity potential. Dimethyl ether has not shown genotoxicity potential *in vitro* and sub-chronic, chronic and cancerogenicity inhalation studies carried out in rats and hamster exposed to high levels of the compound (up to 47106 mg/m^3) have not identified any significant toxic effect. One of two reproductive and developmental inhalation toxicity studies reported with dimethyl ether has shown no compound related effects at doses up to 52759 mg/m^3, whereas the other study has established a no-effect level of 1250 ppm (equivalent to 2355 mg/m^3). Assuming that the rat body weight is 0.25 kg, that rats have a breathing rate of 240 ml/min and an inhalation absorption efficiency of 75 % for an exposure duration is six h/day, the daily internal exposure to dimethyl ether arising from the lowest no-effect level identified in the embryo-foetal inhalation toxicity study in rats (2355 mg/m^3) can be estimated to be approximately 630 mg/kg bw/day[2].

A residual limit of 9 µg dimethyl ether/kg of extracted animal proteins is proposed by the petitioner. In a worst case scenario in which 1 kg of meat products containing 2 % of dimethyl ether-extracted animal proteins would be consumed daily, the exposure estimate to dimethyl ether would be 0.18 µg/person/day (0.003 µg/kg bw/day for a 60-kg individual). This level of exposure would be about 10^8 times lower than the lowest no-effect levels identified for dimethyl ether in an embryo-foetal inhalation toxicity study (approximately 630 mg/kg bw/day).

The Panel considers thus that the use of dimethyl ether as an extraction solvent, under the intended conditions of use and with a proposed residual limit of 9 µg/kg of extracted animal proteins is of no safety concern.

Key words: Extraction solvent, dimethyl ether, CAS Registry Numbers 115-10-6.

[2] Internal dose (rat) = 0.75 x 240 x 60 x 6/1 000 000 x 2400 / 0.25 = ~ 630 mg/kg bw/d.

TABLE OF CONTENTS

Panel Members 1
Summary 1
Table of Contents 3
Background as provided by the Commission 4
Terms of reference as provided by the Commission 4
Acknowledgements 4
Assessment 5
1. Introduction 5
2. Technical data 5
2.1. Chemistry 5
2.2. Specifications 5
2.3. Manufacturing Process 5
2.4. Methods of analysis 5
2.5. Reaction and fate in foods to which the source is added 5
2.6. Case of need and proposed uses 6
2.7. Exposure 6
2.8. Information on existing authorisations and evaluations 6
3. Biological and toxicological data 6
3.1. Bioavailability, metabolic fate and biological distribution 6
3.2. Toxicity data 7
3.2.1. Genotoxicity 7
3.2.2. Acute, sub-chronic and long-term toxicity 7
3.2.3. Reproductive and developmental toxicity 9
3.2.4. Other information 9
4. Discussion 9
Conclusions 10
Documentation provided to EFSA 10
References 10
Glossary / Abbreviations 13

BACKGROUND AS PROVIDED BY THE COMMISSION

Extraction solvents are regulated under Council Directive 88/344/EEC on the approximation of the laws of the Member States on extraction solvents used in the production of foodstuffs and food ingredients.

A manufacturer has requested the authorisation of dimethyl ether as an extraction solvent to be used during the processing of meat proteins. The dimethyl ether is proposed to be used to remove fat from the raw material in order to produce protein products with a low fat content.

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion, on the safety of in use of dimethyl ether as an extraction solvent.

ACKNOWLEDGEMENTS

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ASSESSMENT

1. Introduction

Dimethyl ether is used as processing aid to extract lipids from proteins used by the meat industry in the preparation of meat products.

2. Technical data

2.1. Chemistry

Dimethyl ether is a vapour at ambient temperature and pressure. Dimethyl ether is reported as having a relative vapour density of 1.59 (air = 1), a density of 2.11 kg/m^3 as a gas at 0 °C, of 669 kg/m^3 (± 0.01) liquefied at 20 °C, a melting point of – 141 °C, a boiling point of - 25 °C (at 101.3 kPa), an autoignition temperature of 235 °C (BAM, DIN 51794), a flash point of - 41 °C. Dimethyl ether has a vapour pressure (20° C) of 510 kPa, an octanol/water partition (log $K_{o/w}$) of - 0.18, and explosion limits of 3.2 - 18.6 % (percentage of volume in air) (Technical dossier, 2007). It is described as being soluble in methanol, ethanol, isopropyl alcohol, chlorinated hydrocarbons and toluene. Its water solubility is reported in the application to be 328 g/l (20 °C at 410 kPa). Synonyms are dimethyl oxide, oxybismethane, methoxymethane, wood ether and others. The CAS registry number is 115-10-6, the EINECS number is 204-065-8. Molecular mass is 46.07 g/mol, chemical formula is CH_3OCH_3.

2.2. Specifications

Dimethyl ether is reported as being 99.99 wt. % pure, colourless with no residual odours, presenting a C1-C4 hydrocarbons (alkanes/alkenes) content of < 50 mg/kg, methanol content is below 1 mg/kg and water content is below 50 mg/kg.

2.3. Manufacturing Process

The manufacturing process is well described. Dimethyl ether is produced by catalysis dehydration of vapourised methanol in a fix-bed reactor and then purified from the reactor effluent by distillation (Technical dossier, 2007).

2.4. Methods of analysis

Specific analytical methods to measure dimethyl ether, methanol and the content of alkanes and alkenes and water are described in detail. A method for the determination of dimethyl ether in collagen is described (Technical dossier, 2007). The method is based on gas chromatography with headspace injection showing a detection limit of 9 µg dimethyl ether/kg collagen.

2.5. Reaction and fate in foods to which the source is added

No specific information was available. Although data was not submitted the petitioner states that dimethyl ether is stable and will not undergo degradation or form reaction products with any type of food.

2.6. Case of need and proposed uses

According to the petitioner dimethyl ether is used to remove fat from protein raw materials, typically beef and pork. Dimethyl ether is used in a closed process system and is recovered. The defatted animal protein is submitted to vacuum which assures that most dimethyl ether remaining in final animal protein products is eliminated.
These proteins can be used by the meat industry in the preparation of meat products, at levels normally between 0.5 to 1.0 % of the finished product. For a description of the extraction capacity of dimethyl ether see Catchpole *et al.* (2007).

2.7. Exposure

The petitioner estimated a worst case exposure scenario to dimethyl ether based on an assumed residual level in extracted animal proteins equal to the described limit of detection (LOD) of the method applied to collagen samples (LOD 9 µg/kg).
The petitioner proposes a residual limit of 9 µg dimethyl ether/kg in extracted animal proteins. Under these conditions and taking into account a maximal use of 2 % of extracted animal proteins in food, the estimated residual concentration of dimethyl ether would be approximately 0.18 µg/kg of food. The Panel considers this to be a conservative estimate as, due to the high volatility of this substance, and given the fact that defatted proteins are submitted to vacuum in practice in final food the concentration of dimethyl ether will be even lower. Processing (*e.g.* cooking) of the food will contribute to a further reduction of the residual concentration of dimethyl ether in the final food.
Considering a worst case scenario in which 1 kg of meat products containing as ingredients 2 % of proteins extracted with dimethyl ether is consumed daily, the exposure to dimethyl ether would be approximately 0.18 µg/person/day.

2.8. Information on existing authorisations and evaluations

Dimethyl ether is listed as propellant and solvent on the inventory of ingredients employed in cosmetic products (EC, 2006; Lucht, 1985).

The petitioner states that dimethyl ether has been identified according to the Clean Air Act Section 612 on the Significant New Alternatives Policy (SNAP) Program as an acceptable substitute (without use limits or conditions) for end-use "CFC-11, HCFC-22, HCFC-142b as aerosol propellants" in the aerosols industrial sector.

3. Biological and toxicological data

3.1. Bioavailability, metabolic fate and biological distribution

Upon inhalation dimethyl ether is rapidly taken up and distributed in various tissues and organs in rats, reaching a steady state concentration 30 minutes after exposure. It is excreted unchanged, largely via exhaled air within a very short time, and levels return to background levels within 90 minutes (Kemper and Eckard, 1978). It has been reported that in rats exposure to 1000 ppm of dimethyl ether (equivalent to[3] 1884 mg/m^3) leads after 60 minutes to concentrations in the order of 14 mg/kg in the muscle, 15 mg/kg in the lungs and liver, 16 mg/kg in the spleen, 17 mg/kg in the kidney and the heart, 18 mg/kg in the brain, and 19 to 22 mg/kg in blood and fat tissue, respectively (Kemper and Eckard, 1978). In this study organ distribution appeared direct proportional with concentrations of dimethyl ether in the atmosphere at the range of 750 to 2000 ppm (equivalent to 1413 and 3768 mg/m^3).

[3] equivalencies were calculated in this opinion according to http://www.cdc.gov/niosh/docs/2004-101/calc.htm

3.2. Toxicity data

Dimethyl ether has been tested mainly via the inhalation route and no information is available on oral exposure. The following text summarises major toxicological findings following inhalation exposure with dimethyl ether reported in the dossier (Technical dossier, 2007).

3.2.1. Genotoxicity

Bacterial mutagenicity Ames tests involving incubation of the plates in atmospheres containing up to 120000 ppm (equivalent to 226110 mg/m^3) dimethyl ether have not shown mutagenic effects, either in *S typhimurium* TA1535, TA1537, TA1538, TA98 and TA100 or *E. coli* WP2 strains with or without metabolic activation (CIVO, 1978a). *In vivo* sex-linked recessive lethal testing on *Drosophila melanogaster* exposed to levels of up to 28000 ppm (equivalent to 52759 mg/m^3) for 14 days in the air show no signs of mutagenic effects. No mutagenic effect of dimethyl ether was observed in a host-mediated assay with *E. coli* K_{12} and *S. typhimurium* TA1538 in N:NIH (sw) mice exposed to atmospheres of up to 20000 dimethyl ether (equivalent to 37685 mg/m^3) for three hours (RIVM, 1981).

One *in vitro* UDS-assay in primary rat liver cells and a HGPRT forward mutation assay in V79 Chinese hamster cells done with dimethyl ether concentrations of up to 75 mmol/l dissolved in the medium have shown no genotoxic effect (RIVM, 1981).

Other unpublished results tend to confirm the lack of genotoxicity potential of dimethyl ether (summarised in IUCLID, 2000).

3.2.2. Acute, sub-chronic and long-term toxicity

Acute exposure to high doses of dimethyl ether (120000 ppm, equivalent to 226110 mg/m^3) has been reported to cause narcotic effects (IUCLID, 2000). Acute exposure for four hours of five-weeks old albino rats (Wistar derived) to an atmosphere containing dimethyl ether at a concentration of 20000 ppm (equivalent to 37685 mg/m^3) did not show any effect (CIVO, 1974).

In a sub-chronic four weeks study with 40 male and 40 female SPF rats (Wistar-derived), exposure to atmospheres of up to approximately 10000 ppm (equivalent to 18842 mg/m^3) dimethyl ether (10 per group per sex), for six hours/day did not show significant changes amongst treated and control groups on behaviour, growth, haematology analysis, urinalysis, organ weights (other than a not dose-related slight increase in kidney weights in males at the lowest dose group of 100 ppm, equivalent to 188 mg/m^3), gross pathology and histopathology examinations (heart, liver, kidney, spleen, respiratory tract) (CIVO, 1976).

In a sub-chronic toxicity study 40 male and 40 female SPF rats (Wistar-derived) were exposed (10 per group per sex) to atmospheres of dimethyl ether for 13 weeks at doses up to approximately 20000 ppm (equivalent to 37685 mg/m^3), six hours per day during 5 days per week (CIVO, 1978b). As in the previous study no changes were observed amongst treated and control groups on behaviour, growth, urinalysis (other than changes in mean specific gravity, organ weights (other than a not dose-related slight increase in adrenal gland weights in males at the lowest dose group of 2000 ppm, equivalent to 3769 mg/m^3), gross pathology and complete histopathology examinations (some cases of dilatation of fundic glands in the stomach were observed in males of the highest dose group). Upon haematology analysis animals exposed to dimethyl ether show reductions in absolute lymphocyte numbers and increases in neutrophilic white blood cells, although this was only significant on day 56 in the highest dose group. At the same dose male rats show a statistically significant increase in serum alanine amino transferase

(ALAT) activity while female rats show a slightly lower total serum protein values with an unchanged albumin fraction and elevated erythrocyte counts only at the intermediate group. These findings were not considered as of biological significance given that histopathology analysis did not show significant changes compared to controls at all doses tested, were not dose-related and were within historical normal ranges of the rat strain.

In a second 13-week sub-chronic toxicity study 50 male and 50 female SPF rats (Wistar-derived) were exposed (10 per group per sex) to atmospheres of dimethyl ether at concentrations up to approximately 20000 ppm (equivalent to 37685 mg/m^3) six hours per day during five days per week (CIVO, 1983a). Exposed animals did not show significant changes compared to control groups on behaviour, growth, relative organ weights, body weights, urinalysis, serum biochemistry, gross pathology and complete histopathology examinations. Upon haematology analysis white blood cell and lymphocyte counts were statistically significant higher in males exposed to almost all doses tested but only at day 28. Neutrophil counts were also statistically significant higher in exposed males but only at day 91 (not significant at the 5000 ppm dose, equivalent to 9421 mg/m^3). Haematology findings were not considered to be of biological significance given that they were not fully dose-related and that according to the authors, controls in this study show lower haematology counts as compared with historical controls of the rat strain.

In a sub-chronic four weeks study 40 male and 40 female Syrian Golden hamsters (Cpb-Ha Ga 51) were exposed to up to approximately 20000 ppm (equivalent to 37685 mg/m^3) dimethyl ether (10 per group per sex), six hours per day, five days a week (CIVO, 1983a). Exposed animals did not show statistically significant changes compared to control groups on behaviour, growth, organ weights, body weights, urinalysis, haematology analysis, serum biochemistry, gross pathology and complete histopathology examinations. Some not statistically significant changes were reported on haematology parameters but they were not dose-related and controls show rather high basal values according to the authors.

In a sub-chronic toxicity study five groups (30 males and 30 females) of Syrian Golden hamsters (Cpb-Ha Ga 51) were exposed to dimethyl ether for 13 weeks at atmospheres of up to approximately 5000, 10000 or 20000 ppm (equivalent to 9421, 18842 or 37685 mg/m^3), six hours per day during five days per week (CIVO, 1983a). Exposed animals did not show significant changes compared to control groups on behaviour, growth, organ weights, body weights, urinalysis, serum biochemistry, gross pathology and complete histopathology examinations. Upon haematology analysis slightly significantly higher blood cell counts were reported in males exposed to the two intermediate doses (5000 and 10000 ppm, equivalent to 9421 and 18842 mg/m^3) at day 56. However, at day 91 blood cell counts were significantly lower in males exposed to 10000 ppm dose. The no-effect level proposed from this study was 5000 ppm (9421 mg/m^3).

A two-years GLP inhalation study conducted in four groups (50 males and 50 females) of Crl:CD (SD)BR rats exposed to atmospheres of 0, 2000, 10000 and 25000 ppm of dimethyl ether (corresponding to 3768, 18842, 47106 mg/m^3, respectively) for six hours per day, five days per week was referenced in the technical dossier submitted (DuPont Co., 1986. Report summarized in IUCLID, 2000). Fourteen haematology and 10 clinical chemistry parameters measured in this study did not show significant changes compared to controls. Histopathological examination did not reveal specific tissue damage at any of the tested doses (approximately 50 organs and/or tissues). A non-significant slight decrease in survival time in animals exposed to 10000 and 25000 ppm dimethyl ether was observed. Exposure up to 25000 ppm dimethyl ether showed no evidence of increased cancer in any of the tissues or organs examined. Based on the slight decrease in survival a no-effect level of 2000 ppm (equivalent to 3768 mg/m^3) was proposed.

3.2.3. Reproductive and developmental toxicity

Exposure of 68 pregnant albino rats of the Wistar strain (Cpb: WU; Wistar Random) to dimethyl ether atmospheres of up to 2.8 % (v/v, equivalent to 28000 ppm or 52759 mg/m^3) from day 6 to day 16 of pregnancy (observed until day 21) did not show teratogenic effects on the foetuses (CIVO, 1981). Body weights, food consumption and food efficiency, autopsy findings and litter data were similar amongst treated and controls. No gross changes attributable to the treatment were observed in pregnant females (organs weights, number of corpora lutea, implantation sites, number of dead and live foetuses per litter). No foetal abnormalities attributable to the treatment were reported. Skeletal abnormalities (super-numerary lumbar ribs) and variations in degree of ossifications (phalanges, cervical and thoracic vertebral bodies) were reported at the two highest dose tested (2.0 and 2.8 %, equivalent to 20000 and 28000 ppm or 37685 and 52759 mg/m^3, respectively). However, these last findings were not dose-related and the differences in ossifications where considered as variations normally found in foetuses of the rat strain. Consequently, a no-effect level of 2.8 % (52759 mg/m^3) was proposed by the authors in a subsequent analysis.

In another study pregnant Crl:CD (SD)BR rats exposed to dimethyl ether atmospheres of 0.125, 0.5 and 2.0 % (equivalent to 1250, 5000 and 20000 ppm or 2355, 9421 and 37685 mg/m^3), from days 6 through 15 of gestation, did not show teratogenic effects (Haskell, 1981). Maternal body weight, maternal organs, gross observations and effects on reproductive organs were not statistically significant different compared to controls. There was some embryo-foetal toxicity reported (decreased foetal body weight, increased incidence on skeletal variation) at the intermediate dose and a no-effect level of 1250 ppm dimethyl ether (equivalent to 2355 mg/m^3) was proposed by the authors.

The authors of the later study considered the skeletal variant findings in Crl:CD rats study as debatable toxic effects since similar findings where not reported in the study carried out in pregnant albino Wistar rats exposed to higher doses of dimethyl ether in the air (CIVO, 1983b).

3.2.4. Other information

In humans inhalation of dimethyl ether can provoke cough, sore throat, confusion, drowsiness, unconsciousness. Contact with eyes can cause redness and pain and in the liquid form dimethyl ether can cause frostbite on skin (ICSC, 2002).

4. Discussion

The Panel considers that in most of the cases inhalation exposure toxicity data cannot be directly extrapolated to an oral exposure situation. However, in this particular case, considering that animal studies have shown that dimethyl ether is distributed in the body following inhalation exposure, similarly as through oral exposure, the Panel estimates that results from inhalation studies can be used to assess dimethyl ether oral toxicity.

Observations from inhalation studies suggest that dimethyl ether is of low toxicity potential. Dimethyl ether has not shown genotoxicity potential *in vitro* and sub-chronic, chronic and carcinogenicity inhalation studies carried out in rats and hamster exposed to high levels of the compound (up to 47106 mg/m^3) have not identified any significant toxic effect. One of two reproductive and developmental inhalation toxicity studies reported with dimethyl ether has

shown no compound related effects at doses up to 52759 mg/m^3, whereas the other study has established a no-effect level of 1250 ppm (equivalent to 2355 mg/m^3). Assuming that the rat body weight is 0.25 kg, that rats have a breathing rate of 240 ml/min and an inhalation absorption efficiency of 75 % for an exposure duration is six h/day, the daily internal exposure to dimethyl ether arising from the lowest no-effect level identified in the embryo-foetal inhalation toxicity study in rats (2355 mg/m^3) can be estimated to be approximately 630 mg/kg bw/day[4] (TGD, 2003).

A residual limit of 9 µg dimethyl ether/kg of extracted animal proteins is proposed by the petitioner. In a worst case scenario in which 1 kg of meat products containing 2 % of dimethyl ether-extracted animal proteins would be consumed daily, the exposure estimate to dimethyl ether would be 0.18 µg/person/day (0.003 µg/kg bw/day for a 60-kg individual). This level of exposure would be about 10^8 times lower than the lowest no-effect-levels identified for dimethyl ether in an embryo-foetal inhalation toxicity study (630 mg/kg bw/day).

The Panel recognizes that the approach taken here comprises route-to-route extrapolation, which is not trivial (Pepelko, 1987, Rennen *et al*., 2004). However, given the absence of toxicity in tissues of first (possible) contact, the limited metabolism and non-reactive character of the substance and the very large margin between the overall NOAEL and the anticipated maximum exposure, in this particular case the Panel considered it appropriate to evaluate the safety of the proposed used of this substance on the basis of the available inhalation toxicity data.

CONCLUSIONS

The Panel considered the intended use of dimethyl ether as an extraction solvent to remove fat from animal protein raw materials. Considering (i) that the defatted animal protein is submitted to vacuum which assures that most of the volatile dimethyl ether is eliminated from final animal protein products (ii) that the maximum residual limit of dimethyl ether is of 9 µg/kg of extracted animal proteins and (iii) that these proteins are used at a level of up to 2 % in the final food, the Panel considered that there is no safety concern.

DOCUMENTATION PROVIDED TO EFSA

Technical dossier, 2007. Application for the approval of dimethyl ether (DME) as an extraction solvent used in the production of foodstuffs and food ingredients according to the provisions of the Council Directive 88/344/EEC (as amended). Submitted by Akzo Nobel Technology & Engineering. 3800 AE Amersfoort. The Netherlands. August 2007.

REFERENCES

Catchpole O.J., Tallon S.J., Grey J.B., Fenton K., Fletcher K., Fletcher A.J. (2007). Extraction of Lipids from Aqueous Protein-Rich Streams using Near-Critical Dimethyl ether; Chemical Engeneering and Technology, 30, 501–510.

CIVO (1974). Report No. R4520. Acute inhalation toxicity study with dimethyl ether in rats. Centraal Instituut voor Voedingsonderzoek. Utrechtseweg 48, Zeist.

CIVO (1976). Report No. 5004. Sub-acute (four weeks) inhalation toxicity study with dimethyl ether in rats. Centraal Instituut voor Voedingsonderzoek. Utrechtseweg 48, Zeist.

[4] Internal dose (rat) = 0.75 x 240 x 60 x 6/1 000 000 x 2400 / 0.25 = ~ 630 mg/kg bw/day.

CIVO (1978a). Report No. R5293. Evaluation of dimethyl ether in the Salmonella/microsome mutagencity test (final report). Centraal Instituut voor Voedingsonderzoek. Utrechtseweg 48, Zeist.

CIVO (1978b). Report No. 5717. Sub-chronic (13-week) inhalation toxicity study with dimethyl ether in rats. Centraal Instituut voor Voedingsonderzoek. Utrechtseweg 48, Zeist.

CIVO (1981). Report No. V81.064/200753/200754. Inhalation embryotoxicity/teratogenicity studies with dimethyl ether in rats. Centraal Instituut voor Voedingsonderzoek. P.O. Box 360. 3700 AJ Zeist. Netherlands.

CIVO (1983a). Report No. V 83.263/201323. Inhalation toxicity studies of dimethyl ether: 4-week study in hamsters and a 13-week study in hamsters and rats. Centraal Instituut voor Voedingsonderzoek. P.O. Box 360. 3700 AJ Zeist. Netherlands.

CIVO (1983b). Report No. V 82.331/220863. Evaluation of embriotoxicity and teratogenicity studies with dimethyl ether (DME) in rats as carried out in two different laboratories. Centraal Instituut voor Voedingsonderzoek. P.O. Box 360. 3700 AJ Zeist. Netherlands.

Du Pont Co. (1986). Report No. 198-86. Unpublished Data, Haskell Laboratory.

EC (2000). Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the production of the health and safety of workers from the risks related to chemical agents at work. OJ L142, 16.6.2000, p. 47.

EC (2006). Commission decision of 9 February 2006 amending Decision 96/335/EC establishing an inventory and a common nomenclature of ingredients employed in cosmetic products. OJ L97, 5.4.2006, p. 1.

Haskell (1981). Dimethyl ether (DME): embryo-fetal toxicity and teratogenicity study in the rat. Report number 459-81. Haskell Laboratory for Toxicology and Industrial Medicine. Central Research and Development Department. Elkton Road. Newark, Delaware 19711.

ICSC (2002). International chemical safety cards. Dimethyl ether. ICSC 0454. http://www.who.int/ipcs/publications/icsc/en/index.html last visited 1 March 2009.

IUCLID (2000). International Uniform Chemical Information Database. Year 2000 CD-ROM edition. European Commission. European Chemicals Bureau.

Kemper F.H. and Eckard R. (1978). Massenfragmentographische Untersuchungen zum pharmakokinetischen Verhalten und zur Organverteilung von Dimethyläther (DME). Universitat Münster.

Lucht (1985). Publikatierreks Lucht 42. Dimethyl ether. A report on examination concerning the safety and environmental aspects of it use as propellant. Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubveheer. Directie Lucht (1985)

Pepelko, W. E. (1987). Feasibility of route extrapolation in risk assessment. Br J Ind Med; 44: 649-651.

Rennen, M.A.J.; Bouwman, T; Wilschut, A.; Bessems, J.G.M and De Heer, C. (2004). Oral-to-inhalation route extrapolation in occupational health risk assessment: a critical assessment. Regulatory Toxicology and Pharmacology, Volume 39, Issue 1, Pages 5-11.

RIVM (1981). Rijksinstituut voor de Volksgezondheid Bilthoven. Rapport nr : 627909001. Onderzoek naar de genotoxiciteit van dimethylether in vier kortdurende testen.

TGD (2003). Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission

Regulation (EC) No 1488/94 on Risk Assessment for existing substances, Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market (2nd edition). European Commission – Joint Research Centre, Institute for Health and Consumer Protection, European Chemicals Bureau (ECB), Ispra, Italy. http://ecb.jrc.ec.europa.eu/tgd/ last visited 1 March 2009.

GLOSSARY / ABBREVIATIONS

ALAT	Alanine Amino Transferase
bw	body weight
CAS	Chemical Abstract Service
GLP	Good Laboratory Practise
IUCLID	International Uniform Chemical Information Database
LOD	Limit of Detection
NOAEL	No-Observed-Adverse-Effect Level
SCF	Scientific Committee for Food