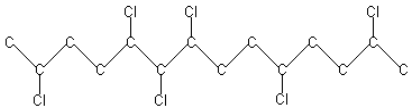
JRC Scientific and Technical Reports

European Union
Risk Assessment Report

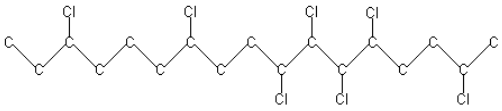
CAS: 85535-85-9 **EINECS No: 287-477-0**

ALKANES, C14-17, CHLORO

Part II
Human Health



$C_{14}H_{24}Cl_6$



$C_{17}H_{29}Cl_7$

EUROPEAN COMMISSION

Institute for Health and Consumer Protection

EUR 25202 EN - 2011

The mission of the JRC-IHCP is to protect the interests and health of the consumer in the framework of EU legislation on chemicals, food, and consumer products by providing scientific and technical support including risk-benefit assessment and analysis of traceability.

European Commission
Joint Research Centre
Institute for Health and Consumer Protection

Contact information
Address: Via E. Fermi 2749 - 21027 Ispra (VARESE) - Italy
E-mail: jrc-ihcp-communication@ec.europa.eu
Tel.: +39 0332 785959
Fax: +39 0332 785730

http://ihcp.jrc.ec.europa.eu/
http://www.jrc.ec.europa.eu/
http://esis.jrc.ec.europa.eu/

JRC66049

EUR 25202 EN

ISBN 978-92-79-23046-2

ISSN 1831-9424

doi:10.2788/86466

Luxembourg: Publications Office of the European Union, 2011

Printed in Italy

RISK ASSESSMENT
Part II – Human Health

OF
ALKANES, C_{14-17}, CHLORO

(MEDIUM-CHAINED CHLORINATED PARAFFINS)

CAS No. 85535-85-9
EINECS No. 287-477-0

Final Report, 2008

Contact Details of the Rapporteur(s)

Rapporteur: **United Kingdom**

Contact - human health:
Health & Safety Executive
Industrial Chemicals Unit
Redgrave Court
Merton Road
Bootle, Merseyside
L20 7HS

ukesrhh@hse.gsi.gov.uk
Tel: (44) 0151 951 3791
Fax: (44) 0151 951 3308

Foreword

I am pleased to present this updated Risk Assessment Report on Alkanes, C14-17, Chloro (MCCP), which is the result of in-depth work carried out by experts in The United Kingdom, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93 on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94 , which is supported by a technical guidance document . Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.

This Risk Assessment improves our knowledge about the risks to human health from exposure to chemicals. I hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals

.

Elke Anklam
Director
Institute for Health and
Consumer Protection

OVERALL RESULTS OF THE RISK ASSESSMENT

CAS Number: 85535-85-9

EINECS Number: 287-477-0

Alkanes, C_{14-17}, chloro

Medium-chained chlorinated paraffins (MCCPs)

Human health assessment

Workers

( ) i) There is a need for further information and/or testing.
(x) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.
(x) iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) is reached for workers exposed during oil-based MWF use. The calculated margins of safety for this scenario in relation to repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are unacceptably low. For all remaining scenarios, there are no concerns in relation to repeat dose effects, carcinogenicity, effects mediated via lactation and effects at the time of parturition, and hence, conclusion (ii) is reached.

Consumer exposure

( ) i) There is a need for further information and/or testing.
(x) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.
( ) iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Consumer exposure to MCCPs is generally very low. Most applications of MCCPs are not designed for consumer contact and most exposures are negligible. The only consumer exposure scenarios for which significant exposures could occur are the wearing of leather clothes treated with MCCPs and the use of metal working fluids.

The calculated margins of safety (MOS) for repeated exposure toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are sufficient to provide reassurance that adverse effects would not occur and thus conclusion (ii) is reached.

Exposure via the environment

( ) i) There is a need for further information and/or testing.
(x) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.
( ) iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Regional exposures

For exposures at a regional level, the calculated margins of safety for repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are

considered to provide sufficient reassurance that adverse health effects would not occur and thus conclusion (ii) is reached.

Local exposures

For local sources of exposure, the calculated margins of safety for repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are considered to provide sufficient reassurance that adverse health effects would not occur and thus conclusion (ii) is reached.

Infants exposed via breast milk and cow's milk

Very large margins (5 orders of magnitude) have been calculated between the estimated infant intake of MCCPs and the levels at which adverse effects mediated via lactation have been seen in animals. Also, due to concerns identified by the environmental risk assessment, an environmental risk reduction programme is currently under development and this could lead to reductions in point source and diffuse environmental emissions in due course. Furthermore, industry has shown a formal commitment to initiating a monitoring programme of levels of MCCPs in breast and cow's milk. Therefore, overall, conclusion (ii) is reached.

Combined exposure

A combined exposure scenario, taking account of the potential for exposure as a consumer and via environmental sources is not relevant, given that consumer exposures are infrequent, rather than repeated daily exposures. Therefore no risk characterisation for this scenario has been performed.

Risks from physicochemical properties

( ) i) There is a need for further information and/or testing.
(x) ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.
( ) iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

There are no significant risks to humans from the physicochemical properties of medium-chained chlorinated paraffins. Therefore conclusion (ii) is reached.

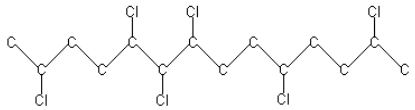
CONTENTS

TABLES AND FIGURES

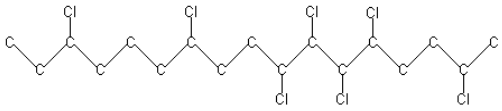
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 85535-85-9
EINECS No: 287-477-0
IUPAC Name: Alkanes, C_{14-17}, chloro
Molecular formula: $C_xH_{(2x-y+2)}Cl_y$, where x=14-17 and y=1-17
Example structural formulae:



$C_{14}H_{24}Cl_6$



$C_{17}H_{29}Cl_7$

Molecular weight: see Section 1.2.1
Synonyms: chlorinated paraffin (C_{14-17}); chloroalkanes, C_{14-17}; chloroparaffin; chloroparaffine, C_{14-17}; medium-chain chlorinated paraffins; paraffine clorurate (C_{14-17}); paraffine clorurate a catena media.

In this assessment the name medium-chain chlorinated paraffin (or MCCP) will be used for the substance as this is the more common name. The commercially supplied products are usually mixtures of different carbon chain lengths (reflecting the carbon chain length distribution in the parent n-paraffin feedstocks used), and have different degrees of chlorination, although all have a common structure in that no secondary carbon atom carries more than one chlorine atom. MCCPs are produced by the chlorination of straight-chain hydrocarbons of 14-17 carbon atoms in length. The degree of chlorination can vary generally from 20-70% by weight, although most commercially available products fall in the range 40-70%. Because of the variation in combinations of carbon chain length and degree of chlorination, a wide range of products are available with an average chain length usually being specified by the manufacturer and a chlorination degree being random but defined by weight. Information on chain length distribution is not available for commercially available MCCP products.

Two other groups of chlorinated paraffins are made commercially. These are known as short-chain (typically C_{10-13}) and long-chain (typically C_{20-30}). This assessment is only concerned with the medium-chain (C_{14-17}) chlorinated paraffins, but some information on the other types is included when it is considered to be useful and relevant to the assessment. The short-chain chlorinated paraffins have been assessed previously under Regulation (EEC) 793/93.

1.2 PURITY/IMPURITIES, ADDITIVES

1.2.1 Purity

Table 1.1 shows the theoretical % weight chlorine content of several compounds that can be considered as medium-chain chlorinated paraffins. The amount of chlorine present in the commercial products is usually expressed as a percentage by weight (% wt. Cl), but since the

commercial products contain a number of components with different carbon chain lengths, it is not possible to identify exactly which compounds are present in a given product, although **Table 1.1** can be used as a guide. Wherever possible in this report, the actual carbon chain length (or range of chain length) and the degree of chlorination (% wt. Cl) will be given.

Although it is theoretically possible to produce MCCPs with chlorine contents up to 70% wt. Cl, such products are not manufactured commercially. The highest chlorine content of the commercial MCCPs normally available is around 58-60% wt. Cl, although products with a chlorine content of up to 62-63% have recently been developed. The lowest chlorine content of the commercial MCCPs is around 40% wt. Cl, but the largest tonnages of MCCPs have chlorine contents between 45 and 52% wt. Cl (Euro Chlor, 1999).

The purity of the produced chlorinated paraffin is related to the purity of the n-paraffin feedstock. In Western Europe, chlorinated paraffins are made from purified n-paraffin feedstocks containing no more than 1-2% isoparaffins and <100 mg aromatics/kg (the aromatics are removed by treatment of the n-paraffin with sulphuric acid). For some high-stability applications, n-paraffin fractions with <1% isoparaffins and <10-100 mg aromatics/kg are used (BUA, 1992).

Table 1.1 Theoretical chlorine content of some MCCPs

Formula	Molecular weight	% Cl by weight	Formula	Molecular weight	% Cl by weight	Formula	Molecular weight	% Cl by weight
Formula	232.5	15.3	$C_{15}H_{24}Cl_8$	488.0	58.2	$C_{16}H_{18}Cl_{16}$	778.0	73.0
$C_{14}H_{27}Cl_3$	301.5	35.3	$C_{15}H_{20}Cl_{12}$	626.0	68.1			
$C_{14}H_{24}Cl_6$	405.0	52.6	$C_{15}H_{17}Cl_{15}$	729.5	73.0	$C_{17}H_{35}Cl$	274.5	12.9
$C_{14}H_{21}Cl_9$	508.5	62.8				$C_{17}H_{32}Cl_4$	378.0	37.6
$C_{14}H_{18}Cl_{12}$	612.0	69.6	$C_{16}H_{33}Cl$	260.5	13.6	$C_{17}H_{29}Cl_7$	481.5	51.6
$C_{14}H_{16}Cl_{14}$	681.0	73.0	$C_{16}H_{30}Cl_4$	364.0	39.0	$C_{17}H_{26}Cl_{10}$	585.0	60.7
			$C_{16}H_{27}Cl_7$	467.5	53.2	$C_{17}H_{23}Cl_{13}$	688.5	67.0
$C_{15}H_{31}Cl$	246.5	14.4	$C_{16}H_{24}Cl_{10}$	571.0	62.2	$C_{17}H_{21}Cl_{15}$	757.5	70.3
$C_{15}H_{28}Cl_4$	350.0	40.6	$C_{16}H_{21}Cl_{13}$	674.5	68.4	$C_{17}H_{19}Cl_{17}$	826.5	73.0

Commercial products are complex mixtures of isomers and standard analytical methods do not permit separation and identification of these. Work by Könnecke and Hahn (1962) provides a basis for estimating the distribution of the chlorine contents present in a given product (although this work was actually carried out with C_{26} chlorinates, it is thought that similar distributions will apply to all chlorinated paraffins). This work gives a prediction of approximately 80% of the isomers present lying within ±10% of the stated average chlorine content and 90% within ±15%. Thus in a medium-chain 50% wt. Cl product, there is likely to be only around 5% of mono- and dichloro isomers present (with a corresponding low percentage of highly chlorinated material) (ICI, 1995).

Any impurities present in the commercial chlorinated paraffins are likely to be related to those present in the n-paraffin feedstock, in which the major non-paraffinic impurity is a small proportion of aromatics (generally in the range 50-100 ppm). However, there is some evidence that the chlorination reaction does not favour chlorination of aromatics. No specific analytical methods are currently available for the detection of possible impurities present in the commercial products (ICI, 1995).

The levels of chlorinated paraffins of chain lengths other than C_{14-17} present in the current commercial products are <1%. The producers of MCCPs (represented by Euro Chlor) have, since 1991, used paraffin feedstocks in the production process with a C_{10-13} content of <1% (the actual levels are often much lower than this), and a $>C_{18}$ content of <1% (Euro Chlor, 1999).

1.2.2 Additives

It is known that additives/stabilisers such as long-chain epoxidised soya oil or glycidyl ether are added to some chlorinated paraffins to inhibit the release of HCl at elevated temperatures. These are used at concentrations of <1% by weight. For some high thermal stability formulations, other additives e.g. organophosphorus compounds, have been reported to be used in conjunction with these (BUA, 1992).

1.2.3 Medium-chain impurities present in other chlorinated paraffin products

It has recently been reported that some long-chain chlorinated paraffins based on a C_{18-20} carbon chain length may contain a substantial proportion of C_{17} chlorinated paraffins, with only very small amounts of chlorinated paraffins of shorter chain lengths (EA, 2001). The typical levels reported were 17% C_{17} and <1% C_{16}, although the range of the C_{17} impurity was given as 10-20%. The amounts of chlorinated paraffins with carbon chain lengths of C_{15} or lower present in the C_{18-20} liquid products would be negligibly small.

These impurities are considered later in the regional exposure estimates for C_{14-17} chlorinated paraffins, and the risk characterisation.

1.3 PHYSICOCHEMICAL PROPERTIES

The physicochemical properties of MCCPs are discussed below and summarised in **Table 1.2**.

Since the products produced contain many components, the physicochemical properties of the various products can vary, reflecting the different components of the products. Representative values have therefore been selected for the key parameters used for environmental modelling. The effect of the variation of these properties on the risk characterisation is analysed in Appendix H.

Table 1:2 Physicochemical properties of some MCCPs

Property	Chlorine content (% wt)	Value	Remarks
Physical state (at ntp)	**40-63**	**Liquid**	
Pour point		-45 °C to 25 °C	commercial mixtures - no distinct melting point
Boiling point (at ntp)		>200 °C	decomposition with release of HCl
Density	41	1.095 g/cm³ at 20 °C	
	56	1.315 g/cm³ at 20 °C	
	40-58	1.1-1.38 g/cm³ at 25 °C	
	56	1.28-1.31 g/cm³ at 60 °C	
Vapour pressure	45	2.27×10^{-3} Pa at 40 °C	
		0.16 Pa at 80 °C	
	52	1.3×10^{-4}-2.7×10^{-4} Pa at 20 °C	
		1.07×10^{-3} Pa at 45 °C	
		6.0×10^{-3} Pa at 60 °C	
		0.051 Pa at 80 °C	
Water solubility		0.005-0.027 mg/l	
Log octanol-water	45	5.52-8.21	measured by a high
partition coefficient	52	5.47-8.01	performance thin layer chromatography method
Flash point	>40	>210 °C	closed cup
Autoflammability		not stated	
Explosivity		not applicable	
Oxidising properties		none	

Note: ntp = normal temperature and pressure.

1.3.1 Physical state (at ntp)

MCCPs are liquids at room temperature.

1.3.2 Melting point

Commercial MCCPs do not have a distinct melting point. Pour points in the range -40°C to -7°C and -45°C to 0°C have been reported for these materials in IUCLID. BUA (1992) reports a similar pour point range of -50°C to 0°C. It has been reported that MCCPs with a very high chlorine content (62-63% wt. Cl) have a pour point of around 25°C (Euro Chlor, 1999).

1.3.3 Boiling point

The exact boiling point of MCCPs is unknown as they start to decompose (with liberation of HCl) at temperatures of around 200°C. The boiling point can therefore be considered to be >200°C.

1.3.4 Relative density

The density varies with chlorine content of the product. Values reported in IUCLID include 1.095 g/cm^3 for 41% wt. Cl product and 1.315 for 56% wt. Cl product at 20°C, 1.1-1.38 g/cm^3 at 25°C for products with chlorine contents in the range 40-58% wt. Cl and 1.275-1.305 g/cm^3 at 60°C for a 56% wt. Cl product.

Kirk-Othmer (1993) gives the following similar values for the density of C_{14-17} chlorinated paraffins at 25°C: 1.10 g/cm^3 for a 40% wt. Cl product, 1.16 g/cm^3 for a 45% wt. Cl product; 1.25 g/cm^3 for a 52% wt. Cl product and 1.36 g/cm^3 for a 58% wt. Cl product.

1.3.5 Vapour pressure

A vapour pressure of 2.27×10^{-5} hPa (2.27×10^{-3} Pa) at 40°C has been reported in IUCLID for MCCPs with a chlorine content of 45% wt. Cl. A vapour pressure of 0.16 Pa has been reported for a similar chlorinated paraffin at 80°C (BUA, 1992).

The vapour pressure of a C_{14-17}, 52% wt. Cl product has been reported as 1×10^{-6}-2×10^{-6} mmHg (1.3×10^{-4}-2.7×10^{-4} Pa) at 20°C by Campbell and McConnell (1980). Vapour pressures for a C_{14-17}, 52% wt. Cl product at elevated temperatures have been reported as 1.07×10^{-3} Pa at 45°C, 6×10^{-3} Pa at 60°C and 0.051 Pa at 80°C (BUA, 1992).

It has been reported that the volatility of chlorinated paraffins in general decreases with increasing chlorine content (Kirk-Othmer, 1993), and this is borne out by the above figures.

Recently, Drouillard *et al* (1998) determined the vapour pressures of a series of short-chain (C_{10-13}) chlorinated paraffins at 25°C using a vapour pressure - gas-liquid chromatography technique. They found that vapour pressures of the short-chain chlorinated paraffins decreased with both increasing carbon chain length and degree of chlorination. They derived the following equation relating vapour pressure (in Pa at 25°C) to the number of carbon and chlorine atoms present in a molecule:

$$\log (\text{vapour pressure}) = -(0.353 \times \text{no. of C atoms}) - (0.645 \times \text{no. of Cl atoms}) + 4.462$$

Using this equation, vapour pressures for all possible medium-chain chlorinated paraffin congeners can be estimated. This is shown in Appendix B for all possible combinations of carbon and chlorine numbers. It should be noted that the reliability of this equation for the medium-chain chlorinated paraffins is unknown, however the values estimated for C_{14-17}, ~51-53% Cl chlorinated paraffins are in the region 5×10^{-5} Pa for C_{14}, 2×10^{-5} Pa for C_{15}, 2×10^{-6} Pa for C_{16} and 9×10^{-7} Pa for C_{17}, which agrees reasonably well with the measured data above, particularly as the measurements on the commercial mixture will be dominated by the more volatile components (shorter chain length, lower chlorinated components).

For the environmental assessment, the vapour pressure of 2.7×10^{-4} Pa at 20°C measured by Campbell and McConnell (1980) will be used as a representative value for a commercial product. The vapour pressures of individual isomers are likely to cover a large range of values, being dependent on the carbon chain length and number of chlorine atoms present.

1.3.6 Water solubility

The water solubility of a ^{14}C-labelled chlorinated n-pentadecane (51% wt. Cl) has been determined to be 0.005 mg/l by parent compound measurement and 0.027 mg/l by ^{14}C

analysis after 6 months at 20°C. The test substance was prepared by mixing n-pentadecane-8-^{14}C with unlabelled C_{14-17} paraffin prior to chlorination to 51% wt. Cl. Approximately 50 mg of the test substance was weighed out onto a glass microscope slide and this was then placed in 5 litres of water. The test was carried out by stirring the chlorinated paraffin in water for 91 days and then allowing the solution to settle (no stirring) for a further 87 days to ensure that equilibrium was reached. Light was excluded from the test solution. The authors suggested that the discrepancy between the water solubility obtained by the two methods may indicate that some degradation had occurred during the test (Madeley *et al*, 1983a). However, this discrepancy could also, in part, be due to the different analytical methods used. Given that the substance tested is a complex mixture, the solubility values obtained by the different methods are in reasonable agreement.

Campbell and McConnell (1980) reported the solubility at 16-20^{o}C of a C_{16}, 52% wt. Cl chlorinated paraffin to be 10 µg/l in freshwater and 4 µg/l in seawater, based on radioactivity measurements. Few other details are available about the method used, but the results obtained are comparable with those reported by (Madeley *et al*, 1983a) above.

A water solubility value of 0.027 mg/l will be used in the assessment. It is likely that the water solubility will vary with both carbon chain length and degree of chlorination.

1.3.7 Partition coefficient

Calculated values for log Kow between 5.5 and >6 are reported in IUCLID for medium-chain chlorinated paraffins.

Log Kow values of 6.95 for $C_{14}H_{26}Cl_4$ (42.2% wt. Cl), 6.37 for $C_{14}H_{23}Cl_7$ (56.5% wt. Cl), 8.54 for $C_{17}H_{32}Cl_4$ (37.5% wt. Cl) and 7.94 for $C_{17}H_{27}Cl_9$ (58.0% wt. Cl) have been calculated using the CLOGP 3.4 computer program (BUA, 1992).

Renberg *et al* (1980) determined the octanol-water partition coefficients for medium-chain chlorinated paraffins using a high performance thin layer chromatography (HPTLC) method. The partition coefficients determined (log values) were 5.52-8.21 for a C_{14-17}, 45% wt. Cl product and 5.47-8.01 for a C_{14-17}, 52% wt. Cl product. The range quoted reflects the different HPTLC retention times, and hence octanol-water partition coefficients, of the various components of the commercial products. These measured values are in good agreement with the values estimated above.

Fisk *et al* (1998b) determined the octanol-water partition coefficients of two ^{14}C-labelled medium-chain chlorinated paraffins of single carbon chain length (C_{16}). The two compounds used were $C_{16}H_{21.7}Cl_{3.3}$, 35% wt. Cl and $C_{16}H_{20.6}Cl_{13.4}$, 69% wt. Cl. The mean log Kow values determined by a HPLC method were reported to be 7.2 for the 35% wt. Cl substance (range of log Kow was 4.7-6.6, 6.6-7.8, 7.8-8.0 and 8.0-8.3 for the four main components of this substance) and 7.4 for the 69% wt. Cl substance (range of log Kow was 6.9-7.8). These are consistent with the other values determined above.

For the environmental assessment, a log Kow value of 7 (approximately the middle of the range of measured values) will be used as a representative value.

1.3.8 Flash point

A flash point of >210°C (closed cup) is reported in IUCLID for a C_{14-17}, >40% wt. Cl product.

1.3.9 Autoflammability

Decomposition starts to occur above 200°C with liberation of hydrogen chloride.

1.3.10 Explosivity

Not explosive.

1.3.11 Oxidising properties

No oxidising properties.

1.4 CLASSIFICATION

Classification (according to the 30th ATP of Directive 67/548/EEC)

N;R50/53

R64

R66

Environment

This classification is based on the toxicity seen with *Daphnia magna* (48-hour EC_{50} = 0.0059 mg/l), a high fish bioconcentration factor of 1,087 and the lack of biodegradability in standard biodegradation test systems, N Dangerous for the environment

R50/53 Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Human health

R64 May cause harm to breast-fed babies

R66 Repeated exposure may cause skin dryness or cracking

S-phrases

(S1/2 Keep locked up and out of reach of children). *For use only if sold to the public.*

S36 Wear suitable protective clothing

S37 Wear suitable gloves

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

Medium-chain chlorinated paraffins are currently manufactured at five sites in the EU. The current total production capacity as reported in IUCLID is in the range 45,000-160,000 tonnes/year.

Chlorinated paraffins are manufactured by adding chlorine gas into the starting paraffin in a stirred reactor. Depending on the chain length of the paraffin feedstock, the temperature of the reaction is maintained between 80 and 100 °C, with cooling if necessary. Catalysts are not usually needed for the reaction to proceed, but ultraviolet light may be used to aid the reaction. Once the desired degree of chlorination has been reached (as determined by density, viscosity or refractive index measurements), the flow of chlorine gas into the reaction is stopped. Air or nitrogen is then used to purge the reactor of excess chlorine and hydrochloric acid gas and small quantities of a stabiliser (e.g. epoxidised vegetable oil) may be added to the product. The product is then typically filtered and piped to batch storage tanks for filling drums, tankers or bulk storage tanks. The main by-product from the process is hydrogen chloride gas. This is collected by absorption in water and re-used as hydrochloric acid (BUA, 1992).

2.2 USES

The main uses of medium-chain chlorinated paraffins are as secondary plasticisers in polyvinyl chloride (PVC), as extreme pressure additives in metal working fluids, as plasticisers in paints, as additives to adhesive and sealants, in fat liquors used in leather processing and as flame retardants in rubbers and other polymeric materials.

Estimates for the amounts of medium-chain chlorinated paraffins used in the various applications within the EU are given in **Table 2.1** (Euro Chlor, 1998).

Figures have been provided for the use of medium-chain chlorinated paraffins in the EU in 1998 (Euro Chlor, 1999). These were provided in a slightly different form to those in **Table 2.1** but indicate that the overall use of medium-chain chlorinated paraffins during 1998 had fallen from the 1997 level to a similar level as in 1994. The reduction in use of medium-chain chlorinated paraffins compared with 1997 was generally spread over all the uses, with the exception of metal cutting working/cutting fluids, which showed a small increase in use, and paints, sealants and adhesives, which remained approximately at the 1997 level. The 1997 consumption figures are used in the environmental assessment to represent a realistic worst case for the amounts used in the various applications.

In a previous assessment of the short-chain (C_{10-13}) chlorinated paraffins, risk reduction measures were identified for use in metal cutting/working fluids and leather fat liquors. The medium-chain chlorinated paraffins have similar uses, and can be considered as replacements for the short-chain chlorinated paraffins in some of these applications. Any reductions in use of the short-chain chlorinated paraffins in these areas could lead to an increased use of medium-chain chlorinated paraffins as replacement. The effect of such substitutions on the amounts of medium-chain chlorinated paraffins likely to be used in the future as a result of risk reduction measures applied to the short-chain chlorinated paraffins is currently unknown,

although an increasing trend in use in metal working/cutting fluids is evident from **Table 2.1**. Appendix E considers this issue further.

Table 2:1 Use of medium-chain chlorinated paraffins in the EU

Application	Industry category	Use category	Quantity used (tonnes/year) (Percentage of total use given in brackets)			
			1994	1995	1996	1997
PVC	11 (polymers industry)	47 (softeners) or 22 (flame retardant and fire preventing agents)	45,476 (80.2%)	48,640 (82.9%)	49,240 (83.0%)	51,827 (79.4%)
Metal working/ cutting	8 (metal extraction, refining and processing industry	35 (lubricants and additives)	2,611 (4.6%)	2,765 (4.7%)	3,302 (5.6%)	5,953 (9.1%)
Paints, adhesives and sealants*	14 (paints, lacquers and varnishes industry) and 15 (others)	47 (softeners) or 22 (flame retardant and fire preventing agents)	3,079 (5.4%)	2,392 (4.1%)	2,638 (4.4%)	3,541 (5.4%)
Rubber/polymers (other than PVC)	11 (polymers industry)	47 (softener) or 22 (flame retardant and fire preventing agents)	2,497 (4.4%)	2,767 (4.7%)	2,324 (3.9%)	2,146 (3.3%)
Leather fat liquors	7 (leather processing industry)	47 (softeners)	1,614 (2.8%)	1,270 (2.2%)	1,172 (2.0%)	1,048 (1.6%)
Carbonless copy paper	12 (pulp, paper and board industry)	48 (solvent)	1,296 (2.3%)	837 (1.4%)	630 (1.1%)	741 (1.1%)
Total			56,673	58,671	59,306	65,256

Note: *approximate split is 2/3 used in sealants and 1/3 used in paints (CEFIC, 1999).

It is thought that around 50% of the leather fat liquor formulations produced in the EU are exported for use outside the EU.

For use in PVC and other polymers, it is possible that pellets (masterbatch) containing medium-chain chlorinated paraffins could be manufactured outside the EU and then imported into the EU for further processing to give the final product. Similarly, such pellets could be manufactured within the EU and exported for subsequent processing. A similar situation may also exist with finished products containing medium-chain chlorinated paraffins. The actual amounts of medium-chain chlorinated paraffins imported into and exported out of the EU in this way are very difficult to estimate. For the purpose of this assessment it will be assumed that net import into the EU of these products will be small compared with the amount presented in **Table 2.1**.

Some information is available on the amounts of total PVC (flexible and rigid) manufactured and imported into the EU (ECVM, 2000) that is useful in this issue. The total Western European market for PVC was estimated to be 5,594,000 tonnes/year in 1997, compared to the total amount of PVC produced in Western Europe of 5,528,000 tonnes/year in the same year. This gives a net import of PVC into the EU of around 66,000 tonnes/year, or 1.2% of the total produced. This indicates that the net import of medium-chain chlorinated paraffins into

the EU in PVC or masterbatch is likely to be small compared to the amounts produced in the EU presented in **Table 2.1**.

In Sweden, the use of all chlorinated paraffins in metal working fluid has been reduced by 80% overall (a 95% reduction in water-oil emulsions (i.e. 160 tonnes in 1986 and 8.5 tonnes in 1993) and a 75% reduction in straight oil based cutting fluids (i.e. 520 tonnes in 1986 and 130 tonnes in 1993)) between 1986 and 1993, and is expected to reduce further (Stenhammar and Björndal, 1994). More than 80% of the chlorinated paraffins used in emulsion cutting fluids and at least 20% of the chlorinated paraffins used in straight oil applications were reported to be C_{10-13} chlorinated paraffins (the remainder would include the C_{14-17} chlorinated paraffins).

Further information on the use of medium-chain chlorinated paraffins has been obtained from the Danish product register. In the register, 28 tonnes/year of medium-chain chlorinated paraffins were reported in a total of 42 products. The product types identified included fillers/sealants (typically 10-20% chlorinated paraffin content), cutting fluids, process regulators (e.g. hardeners) and paints, lacquers and varnishes (typically 1-5% chlorinated paraffin content). Most products contained medium-chain chlorinated paraffin in the range 10-20% by weight of the formulation.

Information has been provided on the breakdown of use of medium-chain chlorinated paraffins by country (Euro Chlor, 1999). This information is considered confidential but did indicate that the main user countries are Italy and the United Kingdom, with use in the United Kingdom accounting for just over 25% of the total EU use. The use pattern in the main user countries was broadly in line with that outlined in **Table 2.1**.

2.2.1 Use as a plasticiser

2.2.1.1 PVC

Medium-chain chlorinated paraffins are used as secondary plasticisers mainly in PVC. The primary plasticisers used are generally phthalates or phosphate esters (Kirk-Othmer, 1993). The phosphate esters are normally used only when flame retardant benefits are needed (Euro Chlor, 1999). The medium-chain chlorinated paraffins may also be used in some other plastics, but here the major function is likely to be as a flame retardant rather than as a plasticiser (see Section 2.2.2.2).

Primary plasticisers in PVC are used to increase the elongation properties and softness of the polymer. Secondary plasticisers, when used in combination with primary plasticisers, cause an enhancement of the plasticising effects and so are also known as extenders. The majority of secondary plasticisers used in PVC applications are medium-chain chlorinated paraffins with chlorine contents around 45% wt. Cl or 50-52% wt. Cl, with only very small amounts (<1% of total sales) of medium-chain chlorinated paraffins with higher (e.g. 56-58% wt. Cl) or lower (e.g. ~40% wt. Cl) chlorine contents being used in PVC (Euro Chlor, 1999).

There are two main types of PVC produced e.g. suspension and paste-forming (emulsion) PVC, and the methods for incorporation of plasticisers in the two types are different. Worldwide, approximately 70% of PVC resin is suspension, with 20% emulsion and small amounts of bulk (9% of total resin production; produces irregular particles with little or no

impurities) and solution (1% of total resin production; used to make specialised resins for metal coatings, record manufacture, powder coatings and surface coatings) (Rubin, 1990).

Polymers of suspension PVC (also known as pearl, bead or granular) are produced by suspending vinylchloride monomer in water and carrying out the polymerisation using a monomer-soluble initiator. This results in the PVC particles formed having a relatively large particle size (e.g. 100-150 µm). These particles are highly porous and so can absorb large amounts of plasticiser. The PVC particles are typically processed using a dry-blend cycle. In this cycle, all the polymer formulation ingredients, including plasticisers, are heated to around 70-110°C and mixed to form a dry powder product. This can be either stored or further processed immediately. Processing of the dry powder can take the form of extrusion, injection moulding or calendering. The powder can also be extruded and chipped to form pellets of PVC compound which can subsequently be further processed to give the final product. Many producers of PVC products purchase PVC compound as it is easy to store and similarly many companies exist that produce PVC compound (Kirk-Othmer, 1996).

Paste-forming (plastisol) PVC polymers are produced as a paste or plastisol rather than a dry powder (a plastisol is a suspension of a solid in a liquid in which it does not dissolve, but does form an homogenous mixture at elevated temperatures; the term organosol is used for a plastiol that contains more than 10 parts of a solvent per 100 parts of resin (Rubin, 1990)). Microsuspension polymerisation or emulsion polymerisation is usually used to form the PVC for these applications. Both these processes result in the formation of PVC particles with a much smaller particle size than produced by suspension polymerisation processes. The small particle size means that the initial product has low porosity and so formulation with additives (e.g. plasticisers) is not possible using a dry-blending cycle, and instead a paste is formed. This paste or plastisol can then be spread, coated, rotationally cast or sprayed onto the desired item, or may be semi-gelled for storage (i.e. heat is applied to convert it into a semi-solid form). A wide range of plasticisers are used in these applications as the choice affects the viscosity of the plastisol, which is important in the further processing steps, and it is common for 2 or 3 different plasticisers to be used in a single formulation to achieve the desired final properties (Kirk-Othmer, 1996).

During the formation of finished products, the PVC formulation may be exposed to temperatures of 180 °C for up to several minutes. In some processes, for example sheet and film production by calendering or spread coating there is the potential for volatilisation of the plasticiser as the hot plastic is exposed to the surrounding air. Processes involving injection moulding and extrusion are carried out in closed equipment and so little exposure of the hot product to air occurs and so the potential for volatilisation of the plasticiser is reduced. In some facilities filtering or incineration of the exhaust gas is used to reduce the air emissions from the process. It has been reported that concentrations of primary plasticiser (e.g. di-(2-ethylhexyl) phthalate (DEHP)) are typically 500 mg/m^3 in air extracted from spread coating ovens, which can be reduced to <20 mg/m^3 by the use of filtration equipment, with exhaust air incineration reducing the emission to practically zero (Kirk-Othmer, 1996). It has been reported (Kirk-Othmer, 1996) that the use of filters and/or incinerators in calendering and spread coating plants has been steadily increasing in recent years. Figures for 1990 are shown in **Table 2.2**. The figures refer to the percentage of the total phthalate plasticiser processed in each application. Of the processes listed in **Table 2.2**, medium-chain chlorinated paraffins are used mainly in spread coating (e.g. for wall coverings and PVC “leather cloth”) and calendered flooring.

Table 2:2 Exhaust air treatment in Western Europe by process in 1990 (Kirk-Othmer, 1996)

Process	Amount of phthalate plasticiser used in process	Percentage of phthalate use undergoing exhaust air treatment	
	(tonnes/year)	Filter treatment	Incineration
Spread coating	192,000	53%	22%
Slush, dip and rotational moulding	17,000	26%	6%
Automotive underseal	67,000		100%
Calendered sheet and film	138,000	23%	25%
Calendered flooring	31,000	15%	56%

The majority of flexible PVC is thought to be used in applications such as flooring, wall covering, upholstery, and sheaths for wire and cable.

The properties and compatibility of the chlorinated paraffin with both PVC and the primary plasticiser vary with both the carbon chain length and the degree of chlorination. Generally, as the chain length of the chlorinated paraffin is increased, its volatility decreases and so the potential for migration from the finished PVC is reduced. At the same time, however, the compatibility with PVC and the primary plasticiser is reduced. On the other hand, the compatibility of chlorinated paraffins with PVC and the primary plasticiser increases with increasing chlorination, and so the potential for migration is reduced, but the flexibility of the final product is also reduced. As a result of these properties, medium-chain chlorinated paraffins with varying degrees of chlorination are used in most applications (BUA, 1992).

For soft PVC products that require a high flexibility at normal and low temperatures, medium-chain chlorinated paraffins with chlorine contents around 40-45% wt. Cl are used as secondary plasticiser. Examples of applications for this type of PVC include coatings, some types of flooring, garden hose and shoe compounds. The secondary plasticiser is added at 10-15% by weight of the total plastic (BUA, 1992; Euro Chlor, 1999).

Medium-chain chlorinated paraffins with higher degrees of chlorination (typically around 50-52% wt. Cl) are more compatible with PVC and have a lower volatility than lower chlorinated analogues. They are used as secondary plasticisers in calendered flooring, cable sheathing and insulation and in general purpose PVC compounds. In heavily filled products, such as some types of calendered flooring, they can be used as the sole plasticiser at levels of around 10% in the finished product (Euro Chlor, 1999).

The more highly chlorinated medium-chain paraffins (e.g. 56-58% wt. Cl) are less volatile still and are used for softening plastics that are subject to higher temperatures during processing (BUA, 1992).

2.2.1.2 Paints and varnishes

Medium-chain chlorinated paraffins, with chlorine contents around 50-60% wt. Cl are used as plasticisers in some paints, varnishes and other coatings. The main areas of application appear to be in corrosion or weather resistant coatings/paints for steel constructions, ships, industrial flooring, containers, swimming pools, facades and road markings (BUA, 1992).

The medium-chain chlorinated paraffins can be used as plasticisers in paints based on many resins, but are most commonly used in chlorinated rubber or vinyl copolymer-based paints.

The chlorinated rubber-based paints are used in aggressive marine and industrial environments whereas the vinyl copolymer-based paints are used principally for the protection of exterior masonry.

A survey of the use of chlorinated paraffins in paints and coatings in the United Kingdom has been carried out (BCF, 1999). A total of 141 companies were contacted and initial responses were obtained from 106 of these. Of the companies responding, 22 (~21%) indicated that they used medium-chain chlorinated paraffins or other chlorinated paraffins. More detailed information on the use of chlorinated paraffins was obtained from 12 (~55%) of the 22 companies. The chlorine content of the chlorinated paraffins used range from around 40% wt. Cl to 70% wt. Cl (with the 70% wt. Cl substances being long-chain length ($<C_{18}$ products). The types of paint/coating and the typical chlorinated paraffin contents are shown in **Table 2.3**.

Table 2:3 Chlorinated paraffin content of paints (BCF, 1999)

Coating type	Chlorinated paraffin content (% by weight)
Organic solvent borne chlorinated rubber primers and topcoats	1-5
Organic solvent borne chlorinated rubber systems for swimming pools/fishponds	5-20
Organic solvent borne zinc rich (epoxy) primers	2-5
Organic solvent borne acrylic container coatings	2-10
Organic solvent borne chemical and water resistant coatings	5-20
Organic solvent borne vacuum metallising lacquers	1-5
Organic solvent borne flame retardant coating for wood	1-5
Organic solvent borne intumescent coating for structural steel	20-30
Organic solvent borne floor paints	5-10
Organic solvent borne water-proofing coatings for walls	5

Euro Chlor (1999) reported that the typical level of a medium-chain chlorinated paraffin in the formulated paint would be 4-15% by weight. After drying (evaporation of solvent) the medium-chain chlorinated paraffin content of the coating would be around 5-20% by weight.

In tonnage terms, the amount of chlorinated paraffins used in the United Kingdom in paints/coatings appears to be small, with a total of up to around 34 tonnes/year being identified in the BCF survey (it is not possible to extrapolate this figure to give the total United Kingdom or EU usage). Further, it was found that paints containing chlorinated paraffins make up only a very small proportion of the total paint manufactured at a site (typically <1-2% of the total, up to 5% in some cases). The total number of sites in the United Kingdom manufacturing paints and coatings containing medium-chain chlorinated paraffins is estimated at around 30 (BCF, 1999).

The BCF (1999) survey also tried to identify the number of sites where coatings containing medium-chain chlorinated paraffins might be used in the United Kingdom, but this did not prove to be possible. The major users of the paints are professional painters and specialist applicators, but some DIY paints containing medium-chain chlorinated paraffins may be used by the general public. In the United Kingdom, it was estimated that there would be around

40,000 users of coatings containing medium-chain chlorinated paraffins for water proofing of walls, with around 1,000-1,500 users of paints and coatings for other uses.

2.2.1.3 Adhesives/sealants

Chlorinated paraffins, including medium-chain ones, are used as plasticisers/flame retardants in adhesives and sealants. Examples include polysulphide, polyurethane, acrylic and butyl sealants used in building and construction and in sealants for double and triple glazed windows. The chlorinated paraffins are typically added at amounts of 10-14% wt. of the final sealant but could be added at amounts up to 20% wt. of the final sealant in exceptional cases. The medium-chain chlorinated paraffins used in these applications generally have a chlorine content of 50-58% wt. Cl (BUA, 1992; Euro Chlor, 1999).

The difference between an adhesive and sealant can be fairly blurred in that some sealants are used as adhesives and *vice versa*. Generally, sealants are considered to be materials that are installed into a gap or joint to prevent water, wind, dirt or other contaminants from passing through the joint or crack. Adhesives, on the other hand, are used to transfer loads and are typically designed with much higher tensile and shear strength than sealants (Palmer and Klosowski, 1997). The main use of medium-chain chlorinated paraffins in this area is in sealants.

2.2.2 Use as a flame retardant plasticiser

Chlorinated paraffins are used as flame retardant additives in some applications. However, when used primarily as a flame retardant, chlorinated paraffins with a high chlorine content (e.g. 70% wt. Cl) are used. As medium-chain chlorinated paraffins are not produced with these high chlorine contents, then they are not considered primarily as flame retardants. However, some applications make use of both their plasticising and flame retardant properties.

2.2.2.1 Rubber

Medium-chain chlorinated paraffins are used as softener (or process oil) additives with flame retardant properties for rubber. The chlorinated paraffins used generally have a high chlorine content and are present at up to 15% wt. of the total rubber. The rubber is used in conveyor belts and also in building and automotive applications (BUA, 1992).

2.2.2.2 Plastics

As well as acting as (secondary) plasticisers in PVC and plastics, chlorinated paraffins also act as flame retardants in these materials. When used as a plasticiser, the chlorinated paraffin with moderate chlorine contents (e.g. >50% wt. Cl) will reduce to some extent the flammability of the final product, but when used specifically as a flame retardant, chlorinated paraffins with a high degree of chlorination (e.g. $>C_{20}$ 70-72% wt. Cl) are used, along with a synergist e.g. antimony trioxide. When used as a flame retardant additive, up to around 5% wt. for PVC and up to 15% wt. for polystyrene and unsaturated polyester resins of the chlorinated paraffin may be added (BUA, 1992; Euro Chlor, 1999).

There are no medium-chain chlorinated paraffins available with a 70-72% wt Cl contents and so they are not considered as specific flame retardant additives in plastics. The medium-chain chlorinated paraffins are generally used as flame retardant plasticisers (Euro Chlor, 1999).

2.2.2.3 Adhesives/sealants

Medium-chain chlorinated paraffins are used as flame retardant additives in some sealants. They also act as plasticisers and so have a dual function and no distinction is made between the two functions in this report as the amount (and types) of chlorinated paraffin used in a given sealant is similar regardless of whether the primary function is as a plasticiser or as a flame retardant (chlorinated paraffins with higher chlorine contents may be more effective as flame retardants).

2.2.3 Extreme pressure additive (metal cutting/working fluids)

Medium-chain chlorinated paraffins are used in a wide variety of cooling and lubricating fluids used during metal cutting, grinding and forming operations. The two main types of lubricants used are water-based emulsions, whose function is mainly cooling, and oil-based lubricants. The medium-chain chlorinated paraffins used generally have a chlorine content of between 40 and 55% wt. Cl. The amount of chlorinated paraffin present in a given fluid depends on the final application (BUA, 1992).

For oil-based fluids the chlorinated paraffin content of the fluid ranges from about 5% wt. for light machining to up to 70% wt. for heavy drawing processes (metal forming fluids) (BUA, 1992).

The market for metal forming fluids in the United Kingdom is around 500 tonnes/year. These contain up to 70% by weight of chlorinated paraffin, but the average content is around 50% by weight. (Euro Chlor, 1998). The chlorinated paraffin used in these applications is likely to be short-chain (C_{10-13}), for which no suitable alternative appears to be currently available.

The amount of medium-chain chlorinated paraffin present in the water-based cooling lubricant concentrate is up to 4% as chlorine (i.e. around 8% as chlorinated paraffin). This is diluted with water to give a 3-5% aqueous emulsion that is used in grinding, rough machining and sawing applications (BUA, 1992). Thus the concentration of medium-chain chlorinated paraffin in the final water-based fluid is around 0.4% wt.

2.2.4 Fat liquors (for leather)

Medium-chain chlorinated paraffins are used in fat liquors for leather. They are used in conjunction with sulphated or sulphonated oils (Kirk-Othmer, 1993), chlorosulphonated paraffins, natural fats and oils (Euro Chlor, 1998). Typically, medium-chain chlorinated paraffins with a relatively low chlorine content (e.g. 40% wt. Cl) are used in these applications.

In general the chlorinated paraffins are used in leathers for the top end of the quality range and give the following advantages (Euro Chlor, 1998):

- High light-fastness

- Strong binding to the leather compared to other additives (low migration)
- Dry feel surface finish with excellent suppleness.

The formulation of leather fat liquors is by a simple mixing process using an enclosed system at ambient temperature. The main components of the fat liquor are water, natural fats (e.g. fish oils), surfactants and the chlorinated paraffin. The chlorinated paraffin accounts for about 10% (range 5-15%) by weight of the formulated fat liquor.

The fat liquor is applied to the leather as a diluted solution. The fat liquoring step is the last stage of leather preparation. The amount of fat liquor used in this step is around 7-12%, based on the shaved weight of the leather to be treated (i.e. around 70-120 g of fat liquor/kg of leather). Since the fat liquor typically contains around 10% (range 5-15%) chlorinated paraffin, the amount of chlorinated paraffin used in this step is around 7-12 g chlorinated paraffin/kg leather (range 3.5-18 g chlorinated paraffin/kg leather). The process itself takes place in enclosed rotating drums at temperatures in the region of 40-60^{o}C, with each batch taking around 1-4 hours depending on the end product being produced. The pH of the reaction is carefully controlled throughout the process by the addition of formic acid to the emulsion (pH is changed from around 5.5 at the start to 3.6 at the end of the process). The pH is used to affect the nature of the leather surface, the rate of absorption of the fat liquor and the stability of the emulsion. The high binding efficiency of the leather for the chlorinated paraffin means that the relative composition of the additives in the fat liquor solution change with time during the process. It is believed that not more than 2% of the original amount of chlorinated paraffin is present in the spent fat liquor solution at the end of the process. (Industry estimate based on experience of the process (Euro Chlor, 1998)).

2.2.5 Carbonless copy paper

Another use that has been reported for chlorinated paraffins in general is as a solvent used in carbonless copy paper (BUA, 1992). The European consumption of carbonless copy paper was around 710,000 tonnes/year in 1996, but was predicted to fall to around 660,000 tonnes/year by 1998. Only a small proportion of this paper will contain medium-chain chlorinated paraffins. The most common applications for carbonless copy paper include delivery dockets, credit card slips and business forms.

Carbonless copy paper consists of at least 2 sheets of paper. It is produced by coating the back side of the top piece of paper with gelatine (or synthetic polymer) capsules containing a colour former in a solvent. Medium-chain chlorinated paraffins can be used as the solvent in some applications. Binders, such as modified starch, polyvinylalcohols, acrylates or carboxylated styrene-butadiene rubber latices, are used to attach the gelatine capsules to the paper. The upper surface of the bottom sheet is coated with reactive montmorillonite clay. For copy paper with three or more sheets, the middle sheets would be coated with the reactive clay on the upper surface and the gelatine capsules on the lower surface. Writing pressure results in breakage of the gelatine capsule which releases the colour former. This then reacts with the clay to form the colour on the surface of the lower sheet.

The majority of European manufacturers of carbonless copy paper are members of the Association of European Manufacturers of Carbonless Paper (AEMCP). About 6 years ago, all members of the AEMCP agreed to stop using chlorinated paraffins in the production of carbonless copy paper, and this agreement still remains in force today. Members of the AEMCP account for around 95% of the carbonless copy paper that is used in Europe.

Based on the figures reported, the amount of carbonless copy paper containing medium-chain chlorinated paraffins in the EU is at most 5% of the 660,000 tonnes/year i.e. 33,000 tonnes/year. This assumes that the 5% of companies not covered by the AEMCP agreement use medium-chain chlorinated paraffins in all the carbonless copy paper that they produce, which would appear to be unlikely.

2.3 EXISTING CONTROL MEASURES

In Germany, chlorinated paraffin-containing wastes e.g. metal working fluids with >2 g halogen/kg and halogen-containing plasticisers, are classified as potentially hazardous waste and are incinerated (BUA, 1992).

3 ENVIRONMENT

An environmental risk assessment of alkanes, C_{14-17}, chloro (medium-chain chlorinated paraffins or MCCPs) produced in accordance with Council Regulation (EEC) 793/93[1] was published in December 2005 and subsequently updated in August 2007.

1 O.J. No. L 084, 05/04/1993 p. 0001-0075.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational Exposure

4.1.1.1.1 General Introduction

Definitions and limitations

The general discussion sections summarise the important issues arising from the exposure assessments and brings together measured exposure data and predictions from the EASE (Estimation and Assessment of Substance Exposure) model. EASE is a general purpose predictive model for workplace exposure assessments. It is an electronic, knowledge based, expert system which is used where measured exposure data are limited or not available. The model is in widespread use across the European Union for the occupational exposure assessment of new and existing substances.

All models are based upon assumptions; their outputs are at best approximate. EASE is only intended to give generalised exposure data and works best in an exposure assessment when the relevance of the modelled data can be compared with and evaluated against measured data.

EASE is essentially a series of decision trees. For any substance, the system asks a number of questions about the physical properties of the substance and the circumstances of its use. For most questions, the EASE user is given a multiple-choice list from which to select the most appropriate response. Once all the questions have been answered, the exposure prediction is determined absolutely by the choices made. EASE can be used to estimate inhalation and dermal exposure - dermal exposure is assessed as the potential exposure rate to the hands and forearms (a total skin area of approximately 2,000 cm^2). The dermal model is less developed than the inhalation model, and its outputs should be regarded as no more than first approximation estimates.

The output ranges generated by EASE relate to steady-state conditions, and estimate the average concentration of the substance in the atmosphere over the period of exposure which in this review is taken to be the working shift.

Where real exposure data is not available, EASE has been used to predict exposures. Details of the reasoning behind any assumptions made during the course of EASE predictions are made clear in the relevant sections.

In this document, unless otherwise stated, the term exposure is used to denote personal exposure as measured or otherwise assessed without taking into account the effect of any personal protective equipment (PPE) which might be in use. This definition permits the effects of controls other than PPE to be assessed and avoids the problem of trying to quantify the actual protection provided by PPE in use.

In addition, with the exception of the use of MWFs, the predicted exposures by both the inhalation and dermal routes do not take account of the fact that the MCCPs will only constitute a proportion of the volatile components in the various formulations containing them. Although the percentage of MCCPs in the formulations are known, we do not know the actual concentration available for both the inhalation and dermal exposure. Where MCCPs are contained in formulations it was not possible to establish the extent to which they would be trapped in the polymer, and thus the extent to which dermal or inhalation exposure may occur. Also there may be preferential volatilisation of MCCPs due to its higher volatility, thus this would increase its percentage in the vapour for inhalation exposure and would decrease the percentage in any surface contamination for dermal exposure. The predicted exposures to MCCPs are therefore expected to be overestimated. The extent of the overestimate is not known but will depend upon the proportion of the MCCP in the formulation and the extent of the above factors.

Following discussion at the TM, industry have collected some exposure data at PVC compounding, plastisol manufacture and use, calendering, extrusion and at rubber manufacturing. This data is presented in Section 4.1.1.3.

Overview of exposure

Occupational exposure to MCCPs occurs during the:

- manufacture of MCCPs;
- manufacture of PVC formulations containing MCCPs and their use;
- manufacture and use of paints containing MCCPs;
- manufacture and use of sealants and adhesives containing MCCPs;
- manufacture of rubber containing MCCPs;
- manufacture and use of MWFs containing MCCPs;
- manufacture and use of fat liquors for leather treatment; and
- manufacture of carbonless copy paper containing MCCPs.

HSE's National Exposure Database does not have any measurements of exposure to airborne C_{14} to C_{17} chlorinated paraffins (MCCPs) during their manufacture and use. Industry has provided exposure data for PVC compounding, plastisol manufacture and use, calendering, extrusion and rubber manufacture. Data have also been provided for paint spraying. Where MCCPs are used in metal working fluids, the exposure to MCCP has been estimated using data gathered on exposure to metal working fluids themselves and knowledge of the concentrations of MCCPs in these fluids. For all other scenarios the EASE model has been used to predict exposures of workers to airborne MCCP.

MCCPs are viscous liquids with very low vapour pressures. For the environmental assessment (see Section 1.3.5) a vapour pressure of 2.7×10^{-7} kPa at 20 °C for the 52% chlorinated MCCP has been used as a representative value for all MCCPs regardless of the percentage chlorination. This vapour pressure corresponds to a saturated vapour concentration (SVC) of 0.0027 ppm or 0.051 $mg.m^{-3}$ (assuming a molecular weight of 450) at 20 °C and has been used for the workplace exposure assessment. Thus personal exposures to MCCP vapour at ambient temperature in the workplace will be very low, the maximum theoretical vapour concentration being 0.0027 ppm (0.051$mg.m^{-3}$). This was taken into account when considering values of exposures to vapour at workplace ambient temperature predicted by the EASE model. Although processing temperatures are often in excess of 20°C, the temperature of the working environment will usually be about 20°C. Therefore this prediction for

maximum vapour concentration based on the SVC will still hold where the process is at a higher temperature. At the point of release of hot vapour from the process there will be a mixture of vapour and mist. The mist is formed as the hot vapour cools and condenses to form liquid droplets, thus in the worker's breathing zone there will be vapour, at a maximum of the SVC, and mist. The extent of the exposure to the mist will be dependent on the processing temperature and the controls. This is discussed in the following sections.

Four personal sampling results from plastisol manufacture were provided by industry from two different operators: there are 0.02, 0.03, 0.03 and 0.08 $mg.m^{-3}$ 8hr TWA. Sampling data were also provided by industry from plastisol use: 12 personal samples (8hr TWA) were collected over two days. Values ranged from <0.1 to 0.12 $mg.m^{-3}$, with a median of 0.02 $mg.m^{-3}$ and a 90^{th} percentile of 0.12 $mg.m^{-3}$. However, the results indicated that exposures were higher on day 1, ranging from <0.01 to 0.12 $mg.m^{-3}$, than day 2 which ranged form <0.01 to 0.02 $mg.m^{-3}$. This was attributed to a malfunctioning extraction system on one of the ovens on day 1 which was repaired by day 2. Most of the small number of measured data are below the EASE value of 0.05 $mg.m^{-3}$ and range from 0.02 to 0.08 $mg.m^{-3}$. The highest value of 0.08 $mg.m^{-3}$ will be taken forward to risk characterisation as the RWC. A range of <0.003 to 0.44 $mg.m^{-3}$ MCCP exposures was found from 32 personal samples taken from 4 EU sites carrying out PVC compounding. The median of these exposures is 0.03 $mg.m^{-3}$ and the 90^{th} percentile is 0.15 $mg.m^{-3}$. Four samples were taken at a site carrying out the application of PVC insulation, by extrusion, to electrical cables. The values are <0.01, <0.01, 0.03 and 0.44 $mg.m^{-3}$. A range of 0.01 to 0.07 $mg.m^{-3}$ MCCP exposures was found during rubber manufacture from 7 personal samples taken at one site.

A range of 9-18 $mg.m^{-3}$ 8hr TWA was derived from EASE data for the mist in situations where poor control of this mist was felt to be a possibility. These were calendering of plasticised PVC, compounding of plasticised PVC, extrusion and moulding of plasticised PVC, and rubber manufacture.

In addition to the possibility of exposure to MCCP aerosols created by condensation, there are situations where aerosols may be created by mechanical agitation, in particular, during the use of metal working fluids (MWFs) containing MCCP in the engineering industry and during the spraying of paints which contain MCCP. Values for exposure to airborne MCCP derived from exposure in a recent unpublished survey of the exposure of workers to metal working fluids indicate reasonable worst case (RWC) 8-hour TWA exposures of 0.03 $mg.m^{-3}$ for water-based MWFs and 2.4 $mg.m^{-3}$ for oil-based MWFs. NB. Metal working fluids constitute only 10% of the total EU usage of MCCPs.

De Pater *et al.*, 1999 (draft), provides a model for predicting exposure to non-volatile compounds during spray painting, which gave a result of 5 $mg.m^{-3}$ 8hr TWA.

The measured exposure data, with the exception of PVC calendering, clearly shows that personal exposures are significantly lower than the values derived from EASE predictions. Where relevant, the measured data will be used to determine the values taken forward to risk characterisation in preference to the EASE predictions.

Because of the very low level of exposure to MCCP vapour, skin contact will constitute the major source of personal exposure to MCCP.

The number of persons potentially exposed to MCCP in the EU is not known but is expected to be of the order of many thousands.

Occupational exposure limits

There are no occupational exposure limits for MCCPs.

4.1.1.1.2 Occupational exposure during manufacture of MCCPs

As already described in Section 2.1, the chlorination of C_{14} to C_{17} paraffins is carried out as a batch process within closed chemical plant at process temperatures in the region of 100 °C. Blending and holding tanks are maintained at temperatures between 40 and 80 °C to maintain workable viscosities. The containment in these vessels will be breached when filters are removed for cleaning and when product samples are taken. For tanker filling and drumming of the MCCP product similar temperatures are maintained to ensure adequate mobility of the material.

At each MCCP manufacturing plant it is likely that in the region of 30 to 40 workers may be involved with operating the process, including drum and tanker filling. It is also likely that various patterns of job rotation will be followed. It is estimated that between 150 and 200 workers may be potentially exposed to MCCPs during their manufacture within the EU. Because of the degree of containment exposure to MCCP is only likely to occur when the containment is breached, for example, during sampling, filter cleaning, maintenance and during drumming off and tanker filling.

Modelled inhalation exposure data

Neither the HSE nor industry has made measurements of exposure to airborne MCCP during its manufacture.

EASE predicts that, for substances with a vapour pressure which is less than 0.001 kPa at the processing temperature, exposures to airborne substance will be within the range 0-0.1 ppm, regardless of pattern of use or pattern of control. Thus because the vapour pressure of MCCP, as calculated within the EASE model, remains below 0.001 kPa for processing temperatures up to 125 °C the predicted exposure for processes temperatures below 125 °C will be independent of patterns of work or control and will be within the range 0-0.1 ppm. Predicted inhalation exposures to MCCP during the manufacture of the substance will therefore clearly be within the range 0-0.1 ppm as all the activities associated with manufacturing process operate at temperatures below 125 °C. Furthermore, as the saturated vapour concentration at ambient temperature (20 °C) is only 0.0027 ppm ($0.051 mg.m^{-3}$), the upper limit of this range of predicted exposures to MCCP vapour will be reduced to 0.0027 ppm. (see Overview of Exposure above).

These predictions of exposure to vapour do not take account of the possibility that there might in some instances be a slight, transient exposure to a fine mist of MCCP formed by the cooling of vapour emitted by hot MCCP when the plant containment is breached for sampling, filter cleaning, and possibly maintenance. This small release of fine mist is likely to quickly dissipate and therefore the contribution to the worker's total exposure is likely to be minimal. EASE is not capable of addressing such circumstances. There is no activity during the manufacture of MCCPs which involves vigorous agitation which might produce a mist or spray to which workers could be exposed

Modelled dermal exposure

In the manufacturing process the activity leading to the greatest likelihood of dermal exposure will be for the workers engaged in drumming off. Assuming that semi-automated drumming plant is utilised, the appropriate EASE scenario is non-dispersive use with direct handling and intermittent contact for which the model predicts that exposure to 210cm^2 will be in the range 0.1-1 mg/cm^2/day. In practice, dermal exposures will be reduced by the workers wearing PPE, in particular gloves.

4.1.1.1.3 Occupational exposure during use in PVC formulating

Introduction

The major application of MCCPs in the EU is in the plasticisation of PVC. The properties of suspension and emulsion grade polymers and the function of plasticisers have been discussed at Section 2.2.1.1. In PVC formulations the MCCPs act as secondary plasticisers. Sometimes referred to as plasticiser extenders, they enable the formulator to reduce the amount of the more expensive primary plasticisers such as phthalate and phosphate esters. The MCCPs may also be used to enhance the flame retardant properties of the formulation.

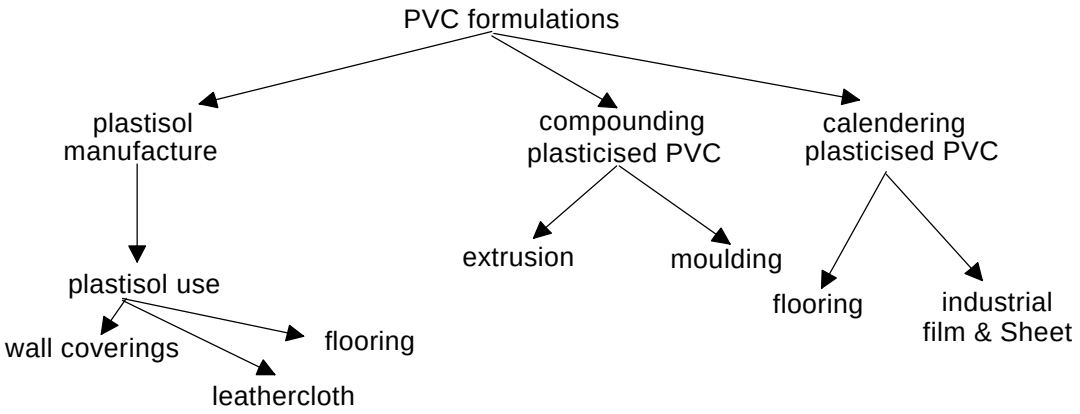
There are two main categories of PVC polymer, namely, emulsion polymer and suspension polymer:

a) *PVC emulsion polymer* when mixed with plasticisers at ambient temperature forms a mobile, liquid mass known as a plastisol. This can be coated onto a variety of substrates before being passed through heated ovens to gel and fuse the plastisol and produce laminates such as wallcoverings, floor coverings, leathercloth for upholstery, luggage and garments, tarpaulins and conveyor belting.

b) *PVC suspension polymer* when mixed with plasticisers initially produces a "dry mix" known as pre-mix which is subsequently mixed at elevated temperature to produce a plastic mass. This may in turn be calendered to form PVC sheeting or extruded and chipped to produce material which can be subsequently co-extruded as cable insulation or sheathing, extruded into profiles, or moulded into shaped articles.

Industry has made some measurements of exposure to airborne MCCPs during their use as secondary plasticisers in PVC. It is not known how many workers may be potentially exposed to MCCPs during the manufacture and use of plasticised PVC formulations containing MCCPs in the EU.

Figure 1 Use profile of MCCPs in PVC formulations (not an exhaustive list)



The exposure to MCCPs in the plasticisation of PVC is considered under the following headings: PVC plastisol manufacture, PVC plastisol use, calendering of plasticised PVC, compounding of plasticised PVC, and extrusion and moulding of plasticised PVC.

PVC plastisol manufacture

The ingredients of the plastisol formulation are added to the enclosed mixing vessel, the plasticisers including MCCPs being piped from bulk storage, and blended together by means of mechanical stirring. In general the MCCP used in plastisols is 45% chlorinated and may be used within the range 5-30% of the mix. The plastisol is finally put through a sieve to remove undispersed particles before being piped to intermediate storage for in-house use or to containers for transporting to third party user companies. Throughout the mixing cycle the plastisol is maintained at a temperature below 40 °C to prevent premature gelation. Thus only relatively gentle mechanical stirring is used in order to prevent heat build-up which could occur if high shear forces were to be created by, for example, by the use of high speed stirring. Such gentle agitation will be insufficient to create a spray.

Industry inhalation data

Sampling data was provided by industry for one site (Hughson 2003b). This site manufactures various grades of PVC flooring, on one of two continuous coating lines. Plastisol is prepared by adding the necessary ingredients, including MCCP to a mixer via a charge hopper. The mixing process is contained with in a closed vessel, though this needs to be opened up for short periods of time for inspection and for cleaning, although this is only done after purging. The hoppers are fitted with local exhaust ventilation. Four personal samples were collected over two days from two different operators: 0.02, 0.03, 0.03 and 0.08 $mg.m^{-3}$ 8hr TWA.

Modelled inhalation exposure data

As for manufacturing of MCCPs, the predicted exposure, for processing temperatures up to 125 °C will be within the range 0-0.1 ppm. The upper limit of the range of predicted exposures to MCCP vapour will again be reduced to 0.0027 ppm ($0.051mg.m^{-3}$) at 20 °C (i.e. the SVC).

The possibility that there might be any exposure to a fine mist of MCCP formed by the cooling of vapour emitted by plastisols containing MCCPs when the temperature is kept below 40 °C is discounted. There is no activity during the manufacture of plastisols containing MCCPs which involves vigorous agitation which might produce a mist or spray to which workers could be exposed.

Conclusion

Most of the small number of measured data are below the EASE value of 0.05 mg/m^3 and range from 0.02 to 0.08 mg/m^3. The highest value of 0.08 mg/m^3 will be taken forward to risk characterisation as the RWC.

Modelled dermal exposure data

In the manufacture of PVC plastisols containing MCCP a number of activities may give rise to the potential for dermal contact with MCCP or formulations containing it, for example during weighing out and transfer to the mixing vessel, during sieving, during transfer to holding tanks, and during sampling for laboratory testing. It is likely that on any one workshift these activities will be shared among 2 or 3 workers making about 4 or 5 batches of plastisol per shift. It seems reasonable therefore to assume an EASE model scenario of either non-dispersive use with direct handling and intermittent contact or incorporation in a matrix with direct handling and intermittent contact for both of which the prediction is that exposure to 420 cm^2 will be in the range 0.1 to 1mg/cm^2/day. For maintenance workers, such a prediction would probably represent a worst case situation. In practice dermal exposures will be reduced where workers wear PPE, in particular gloves, when handling MCCP or plastisol containing it.

PVC plastisol use

PVC plastisols may be used in a variety of ways. The predominant process involves the spread coating of plastisol onto a substrate material before passing it through a curing oven in which the plastisol coating is gelled and fused. Products so formed are wallcoverings, floorcoverings and leathercloth, the latter being used, for example, in the manufacture of upholstery. Alternatively for example a textile web may be dip coated with plastisol before undergoing a similar oven curing to form conveyor belting. The temperature of the coated web whilst passing through the curing oven generally rises to between 160 and 180 °C with a maximum in the region of 200 °C. The curing ovens are normally subjected to exhaust ventilation which feeds the contaminated air to an incinerator or to an electrostatic precipitator from which the liquid condensate may be recovered for re-use. The escape of volatile material such as plasticiser, i.e. MCCP, from the oven into the work environment is thus minimised. The curing oven may be divided into zones of different temperature allowing the plastisol coating to be subjected to a gradual rise in temperature as it is gelled and fused. There may be a cooling zone through which the hot web passes before exiting from the oven. As the web leaves the oven it may also pass immediately between a pair of chilled embossing rollers to impart a particular surface pattern. This embossing process has the added benefit of reducing the temperature of the cured plastisol thereby further reducing the emission of volatile material from the coated web into the general work atmosphere.

Industry inhalation data

Sampling data was provided by industry for one site (Hughson 2003b). This site manufactures various grades of PVC flooring, on one of two continuous coating lines. Mixed batches of plastisol are loaded onto open tank trailers and transported to the production line using an electric tow-truck. Liquid is automatically pumped to the coating head and evenly spread out

onto a roll. The product then passes through ovens for curing. At the end of the coating line the product is automatically trimmed before being fed through the packing station where it is inspected, cut to length and wrapped in polythene. The curing ovens are fitted with extract ventilation. Twelve personal samples (Table 4.1) were collected over two days. Values ranged from <0.1 to 0.12 $mg.m^{-3}$, with a median of 0.02 $mg.m^{-3}$ and a 90^{th} percentile of 0.12 $mg.m^{-3}$. However, the results indicated that exposures were higher on day 1, ranging from <0.01 to 0.12 $mg.m^{-3}$, than day 2 which ranged form <0.01 to 0.02 mg. m^{-3}. This was attributed to a malfunctioning extraction system on one of the ovens on day 1 which was repaired by day 2.

Table 4:1 Industry data from PVC plastisol use

Sample Code	Job	Sample Time (minutes)	Concentration MCCPs ($mg.m^{-3}$)
Day 1			
UK/02/03	Tug driver	424	0.04
UK/02/04	1st coat spreader operator	226	0.12
UK/02/05	2nd coat spreader operator	233	0.09
UK/02/06	Back coat operator	234	0.04
UK/02/07	Base coat operator	222	0.12
UK/02/08	Process leader	227	<0.01
Day 2			
UK/02/10	Process leader	482	0.01
UK/02/11	1st coat spreader operator	481	0.01
UK/02/12	Tug driver	405	<0.01
UK/02/13	2nd coat spreader operator	478	0.01
UK/02/14	Base coat operator	471	0.02
UK/02/15	Back coat operator	476	<0.01

Modelled inhalation exposure data

The primary potential source of exposure to airborne MCCP will be the curing oven. The appropriate EASE scenario for the curing process is inclusion into a matrix with the provision of LEV. Using this scenario the EASE model predicts an exposure to MCCP in the range of 0.5-1 ppm for processes operating between 126 and 282 °C. However, the range for exposure to vapour will be markedly less than that predicted because of the very low value of the saturated vapour concentration at ambient temperature. The upper limit for vapour exposure at 20 °C will thus be 0.0027 ppm ($0.051 mg.m^{-3}$). It is possible that there might be some escape of hot vapour laden air from the curing oven, either through leaks or from the hot, cured web as it leaves the oven. Such vapours could, on cooling, give rise to the formation of a fine mist containing MCCP and could thereby provide exposure over and above that caused by the airborne vapour. Nevertheless, as most curing ovens are likely to be efficiently exhausted as described above, there should be relatively little escape of hot vapour laden air from the oven which might in turn condense on cooling to form a fine airborne mist in the workplace environment.

The actual plastisol coating of the substrate takes place at ambient temperature prior to the oven gelling and fusion. The application of the plastisol is carried out by means of roller

devices which transfer an even and measured coating of plastisol from a holding trough to the moving substrate. Alternatively the textile web may be dip-coated by being passed through a trough containing the plastisol. As already indicated above, because the coating operation takes place at ambient temperature (i.e. substantially below 126 °C), EASE predicts worker exposure to MCCP at the coating process will be in the range 0-0.1 ppm regardless of pattern of use or pattern of control. Moreover because the saturated vapour concentration is 0.0027 ppm at ambient temperature the actual exposure range will be 0-0.0027 ppm ($0.051 mg.m^{-3}$).
There is no likelihood of exposure to a fine mist of MCCP formed by the cooling of vapour emitted by plastisols containing MCCP as the coating takes place at ambient temperature. In addition, neither method used for the coating process will give rise to the mechanical production of plastisol spray.
Thus the exposure to MCCP vapour of the one or two workers operating a plastisol coating line will be within the range 0-0.0027 ppm ($0.051 mg.m^{-3}$), with the possibility of slight exposure to MCCP mist if there is any leak of hot vapour laden air from the oven(s).

Conclusion

Although the range of the measured data was from <0.1 to 0.12 $mg.m^{-3}$ the higher values came from day 1 when the extraction system was not working correctly. On day 2 when the extraction was working correctly the values ranged from <0.01 to 0.02 $mg.m^{-3}$. The EASE value predicted for this scenario is 0.05 $mg.m^{-3}$ and as most of the measured results on day 2 were below this value, 0.05 $mg.m^{-3}$ will be taken forward to risk characterisation as the RWC.

Modelled dermal exposure data

In the use of PVC plastisols containing MCCP, only in transferring plastisol to the coating head and in setting and adjusting the coater is there potential for skin contact. It is likely that on any one workshift these activities will be shared among 1 or 2 workers per coating line per shift. It seems reasonable therefore to assume an EASE model scenario of incorporation in a matrix with direct handling and intermittent contact, for which the prediction is that exposure to 420 cm^2 will be in the range 0.1-1 $mg/cm^2/day$. This estimate can be further reduced taking into account that a maximum of 30% of the plastisol is MCCPs, giving a range of 0.03 – 0.3 $mg/cm^2/day$ over 420 cm^2. In practice dermal exposures will be reduced by the workers wearing PPE, in particular gloves, when handling plastisol containing MCCP.

Calendering of plasticised PVC

There appears to be relatively little use of MCCPs in calendered PVC sheet formulations. Where MCCPs are used their main purpose it is to contribute to the flame retardant properties of the product. The 52% chlorinated product is normally used in this application.

The ingredients of the formulation, namely suspension grade PVC, primary plasticiser, MCCP and other components are added to a closed mixing vessel in which they are blended to form the pre-mix. The plastisers, including the MCCP, will normally be piped directly into the mixer. During this first mixing stage the temperature of the mix can rise to temperatures between 60 and 110 °C depending upon the type of mixer employed and the shear forces imparted to the mix. The pre-mix is then transferred, usually by gravity, to a sealed internal mixer specifically designed to impart high shear forces to the mix. During this mixing the high shear forces raise the temperature of the mix to between 150 and 175 °C and bring about gelation and fusion. From the internal mixer hot mix is discharged into an extruder, which is used to provide an extrudate to continuously feed the top nip of the calender. An additional mixing step may sometimes take place between the internal mixer and the extruder whereby

the hot plastic mass is blended on a two roll mill on which the mix is subjected to further high shear mixing. On the calender the hot plastic mass is sequentially passed through three nips, provided by four large rollers usually in an inverted "L" configuration, which gradually squeeze the material into a continuous sheet of the desired width and thickness. The temperature of the mass as it travels through the calender may rise to values in the region of 200 °C. As the sheet leaves the bottom calender roller it passes through a series of cooling rollers so that it is at a temperature close to ambient before being wound up.

Modelled inhalation exposure data

At each stage where the hot plastic mass is open to the atmosphere there is generally some provision of LEV which exercises a good degree of control of exposure of the workers to the volatile emissions from the material. The MCCP vapour, which is evolved by the hot plastic mass will, because of its low vapour pressure, quickly condense to a fine mist as it comes into contact with cool ambient air. Thus any MCCP to which workers will be exposed will comprise both vapour and mist.

It is not known how many workers are potentially exposed to MCCP during its use in calendering PVC either in the UK or in the EU. However, it is likely that between 3 and 5 workers will be involved per shift in running a calender line.
The EASE scenario that best represents the calendering of PVC is inclusion into a matrix with provision of LEV. For the initial mixing operation for which process temperatures may be between 60 and 110 °C the predicted exposure to MCCP vapour is in the range 0-0.1 ppm whereas the prediction for the subsequent mixing and calendering operation, where temperatures may be between 150 and 200 °C, is in the range 0.5-1.0 ppm. As the operations are likely to all be in the same vicinity it would seem appropriate to take the latter higher prediction as representing the exposures experienced by all the workers on the calendering line. However, both predictions overstate the exposure to MCCP vapour. As has already been discussed for other processes, the upper limit of predicted exposure to MCCP vapour can be no greater than the saturated vapour concentration at ambient temperature, namely, 0.0027 ppm (0.051mg.m^{-3}). There will also be some exposure to the mist formed by MCCP vapour condensation, but the EASE model is not able to address such a situation. Mist that is not removed by the local exhaust ventilation is likely to quickly condense on nearby cold surfaces and contribute to dermal exposure. It is likely that most plants will have a reasonable standard of LEV and therefore the level of uncontrolled mist will be minimal.
Where the extraction is insufficient there is the potential for more significant release of mist into the workplace and therefore increased occupational exposure. The EASE predictions for vapour at 200 °C are overestimates, since the actual working environment will be closer to ambient and the SVC is only 0.0027 ppm. However, we can use the EASE predictions for vapour as a rough approximation for exposure to mist. If we assume that all the vapour condenses to form mist then the vapour range of 0.5-1.0 ppm becomes 9-18 mg.m^{-3} 8-hour TWA to represent the mist. These figures are likely to be overestimates and only representative of a poor standard of control of the vapour and mist.

Industry Data

Industry inhalation data

Good quality sampling data was provided by industry for one site (Hughson 2003c). At this site sheets of PVC flooring are manufactured from raw materials using a calendering process. PVC resin, MCCP and other ingredients are blended in one of two mixer and the products discharged to 2-roll mills where they are compressed into thin sheets. Each mill has a fume

extraction hood situated above it. Strips of material from the mills are conveyed to a rotary shredder and the mixture passed through the marbling mill. The output is fed to the calender mill where the material is blended. The calender mills are fitted with a fume extraction system. A continuous sheet of PVC from the calender passed through a heating unit and embosser and finally a cooling/conditioning unit before being cut into sections and stacked onto pallets.

Eighteen measurements were collected over two days (Table 4.2). Values ranged from 0.03 to 1.2 mg/m^{-3}, with a median of 0.35 mg.m^{-3} and a 90th percentile of 1.01 mg.m^{-3}. However, the results indicated that exposures were higher for mill, calender and relief operators than for all other workers who are not directly involved in working with hot PVC. The values recorded for the mill, calender and relief workers ranged from 0.18 to 1.2 mg.m^{-3}, whereas the values for the other workers ranged from 0.03 to 0.22 mg.m^{-3}. The report concluded that fume emissions from the mills and calender were not being controlled by the ventilation equipment currently provided.

Table 4:2 Industry data from PVC calendering

Sample Code	Job	Sample Time (minutes)	Concentration MCCPs (mg.m^{-3})
Day 1			
UK/04/08	Premix operator	379	0.03
UK/04/02	Mill No. 1 operator	385	0.95
UK/04/01	Mill No. 2 operator	385	0.40
UK/04/05	Relief operator	374	0.43
UK/04/03	Calender operator	377	0.68
UK/04/04	Calender operator	383	0.56
UK/04/06	Foreman	376	0.09
UK/04/07	Panel man	366	0.04
UK/04/09	QC Inspector	365	0.03
Day 2			
UK/04/10	Premix operator	401	0.04
UK/04/11	Mill No. 1 operator	402	1.2
UK/04/13	Mill No. 2 operator	397	0.18
UK/04/12	Relief operator	213	0.35
UK/04/14	Calender operator	395	0.93
UK/04/15	Calender operator	394	1.1
UK/04/18	Foreman	393	0.21
UK/04/16	Panel man	396	0.22
UK/04/17	QC Inspector	397	0.17

Two data points are also available from calendering during rubber manufacture, 0.01 and 0.03 mg.m^{-3} MCCP (see section 4.1.1.1.6). The calendering process in these two industries are likely to be similar and therefore it is possible to consider these data here, although we have no information as to how representative they would be.

Conclusion

Although we have no indication of how representative the new data from industry (Hughson 2003c) would be of calendering as a whole, they do indicate that the exposures of the mill, calender and relief workers are likely to be higher than previously thought. At the specific factory where the sampling was carried out calendering of plasticised containing MCCPs was not carried out every day, usually 2-3 days per week. This is likely to similar in other manufacturers as a wide range of different PVCs are available and there appears to be relatively little use of MCCPs in calendered PVC sheet formulations.

Taking this new data into account it is proposed that $1mg.m^{-3}$ be taken forward as the RWC.

Modelled dermal exposure data

In the calendering of plasticised PVC containing MCCP, there is a potential for skin contact with MCCP itself or the PVC material containing it. There is, as described above, the potential for dermal contact with contaminated surfaces. For the 3 to 5 workers involved it seems reasonable therefore to assume an EASE model scenario of either non-dispersive use or incorporation in a matrix with direct handling and intermittent contact, for both of which the prediction is that exposure to $420cm^2$ will be in the range 0.1-1 mg/cm^2/day. For maintenance workers, such a prediction would also apply. In practice dermal exposures will be reduced by the workers wearing PPE, in particular gloves, when handling MCCP or any PVC material containing it other than the finished sheet.

Compounding of plasticised PVC

MCCP is used as a secondary plasticiser and flame retardant in flexible grades of PVC (Hughson 2006a). The primary plasticiser is di-octylphthalate (DOP). It is common practice in the PVC manufacturing industry to vary the proportion of MCCP and DOP according to their respective market prices. This is done without affecting the performance specifications of the PVC, so it is difficult to be certain about how much MCCP is used in a particular product.

The purpose of compounding plasticised PVC is to provide a chipped form of the product suitable to feed directly to an extruder or injection moulding machine. For these applications the 52% chlorinated MCCP is used at concentrations between 12 and 30%, with most being between 15 and 20%. The MCCP is primarily present as a plasticiser extender, but it does confer some flame retardancy on the formulation. The product goes mainly into the electrical cable insulation and sheathing. The activity is undertaken by specialist compounding firms. It is not known how many workers are involved in compounding PVC for these applications either in the UK or in the EU.

The mixing process is similar to that described for calendering of plasticised PVC, except that a 2 roll mill is not usually employed. The material after leaving the high shear mixer is transferred to an extruder fitted with a die face cutter which produces a chipped material. The chip is enclosed and air conveyed to the packaging line by which time it has cooled to temperatures only a little above ambient.

New information (personal communication) has recently been provided by industry on PVC compounding. Many PVC compounders do not use MCCPs at all, and of the compounders that do use MCCPs all the larger ones only run MCCP formulations about once a month. A significant proportion of the MCCPs is used for plastisols, although some big users have

recently stopped using MCCPs when they have reformulated away from the primary plasticiser DOP.

Modelled inhalation data

By analogy with the mixing regime which precedes calendering of plasticised PVC, the workers engaged in compounding plasticised PVC will have exposures to MCCP vapour in the range 0-0.0027 ppm (0.051mg.m^{-3}). Although there may be some exposure to mist from condensing hot MCCP vapour, it is likely to be less than that experienced in calendering as there are no activities such as the use of the 2 roll mill and the calender for which the hot PVC mass is more open to the workplace atmosphere.

Where the control is again insufficient as described with calendering of plasticised PVC the exposure to mist is again predicted to be 9-18 mg.m^{-3} 8-hour TWA as rough approximation. These figures are likely to be overestimates.

Industry data

Sampling data were provided by industry from four sites in the UK, Italy and Spain and are given in Table 4.3.

Table 4:3 Industry data from PVC compounding

Site	Number of samples	Minimum (mg.m^{-3})	Maximum (mg.m^{-3})
1	7	<0.003	<0.02
2	4	<0.01	0.02
3	13	0.03	0.44
4	8	0.02	0.15

The median of all 32 samples is 0.03 mg.m^{-3} and the 90th percentile is 0.15mg.m^{-3}. The work at all four sites was essentially the same and is believed to be representative of this type of work throughout the EU.

Site 1 used a batch process, with many different grades of PVC and different colours necessitating cleaning of mixers and extruders after each batch. Control at this site appeared to be good, as even though there was a spillage of MCCP during the sampling period and the operators had to clean it up all results are below the limit of detection.

Site 2 used a continuous process, with few different colours, thereby reducing the amount of cleaning (and potential exposure) the operators did.

Site 3 also used a batch process, with cleaning after each run. One operator spent the majority of the working time in the control room with the other three in the production area. This site appeared to have less good control than sites 1 and 2. A significant amount of airborne dust was created when the mixers were cleaned, using hand brushes, scrapers and compressed air jets. There also appeared to be significant leakage of dust from gaps in the intake manifold of the mixer. The two highest levels (0.32 and 0.44 mg.m^{-3}) were taken from the same worker on different days and probably reflect the working methods of this particular operator as the rest of the results were all below 0.15 mg.m^{-3}.

Site 4 had 2 production lines, one batch and one continuous. Cleaning was carried out at the end of each run on the batch line. This site also appeared to have less good control than sites 1

and 2. There were potential exposure points that did not have LEV, e.g. at the discharge from the mixer to the feed hopper. There were also indications that the ventilation system was not operating as intended, e.g. there was a net outward flow of air from the enclosure round the extruders and a significant amount of dust spillage around the mixing vessels.

The 90th percentile of the measured data is 0.15 mgm^{-3} will be taken forward to the risk characterisation as the RWC.

Modelled dermal exposure data

In the compounding of plasticised PVC containing MCCP, there is relatively little potential for skin contact with MCCP itself or the PVC material containing it, except during cleaning of mixers. For the workers involved it seems reasonable therefore to assume an EASE model scenario of either non-dispersive use or incorporation in a matrix with direct handling and incidental contact, for both of which the prediction is that exposure will be in the range 0 - 0.1 mg/cm^2/day over 840cm^2. Incidental contact has been used as the task will only be carried out infrequently and it is unlikely to be done more than once per day when MCCP containing PVC is being made.

A small number (two people sampled from 2 workplaces) of dermal sampling results have been provided by industry (Hughson 20006a) from a study whose purpose was to develop a dermal sampling method for MCCPs. The measured dermal exposure levels from the compounding workers were collected from worst-case situations where contact with MCCP and MCCP contaminated surfaces was most likely and the samples were collected immediately after the tasks were completed, thereby minimising the potential for skin absorption or transfer from the skin to other surfaces.

The dermal exposures for the hands were all in the range 2.2 - 14.1 µg/cm^2, with very similar levels for the forearms. However, the levels for the neck and face were higher at 23.1 – 60.3 and 27.5 – 113µg/cm^2 respectively. This is simply due to the fact that the face and neck were unprotected and exposure has perhaps resulted from deposition of MCCP from the air or from transfer to the skin from contaminated clothing.

Given the small number of measurements and that the method is still in development the EASE value of 0.1 mg/cm^2/day over 840cm^2 will be used for risk characterisation.

In practice dermal exposures will be reduced by the workers wearing PPE, in particular gloves, when handling MCCP or any PVC material containing it other than the finished chipped compound.

Extrusion and moulding of plasticised PVC compound

For co-extrusion of plasticised PVC in wire insulation and cable sheathing, apart from the extrudate itself, the hot mass of PVC is enclosed. The exit from the extruder is rapidly cooled and provided with LEV. The same conditions are likely to apply to any other extrusion application of plasticised PVC which is formulated with MCCP. Injection moulding of PVC compound takes place within closed moulds which are cooled before opening.

Modelled inhalation data

The EASE model scenario for extrusion of plasticised PVC formulations containing MCCP is incorporation in a matrix with LEV provision. The range of exposures for such scenario with process temperatures between 126 and 282 °C is 0.5-1.0 ppm. However, as in all the PVC scenarios, this range will reduces to 0-0.0027 ppm (0.051mg.m^{-3}) because of the very low

vapour pressure of MCCP at ambient temperature. The cooling and LEV arrangements will minimise the possibility of exposure to mist resulting from the cooling of hot vapours escaping from the hot process.

Where the control is again insufficient the exposure to mist is again predicted to be 9-18 $mg.m^{-3}$ 8-hour TWA as rough approximation. These figures are likely to be overestimates and only representative of a poor standard of control of the vapour and mist.

Industry Data

Site 2 (see above) also had a separate area where PVC insulation is applied , by extrusion, to electrical cables. Various sizes of cables are produced, from computer signal to heavy electrical power cable. There are 4 extrusion machines, which apply a coating of PVC to the cable as it passes through the coating head. Each extrusion head has LEV and the cable is quenched in a water bath as it leaves the head. The operators spend the majority of their time at the workstation, near the extruder. However, they do move away from there at certain times to set up or remove cable drums. On each day sampling took place, the cables being processed were large diameter power cables, which use a relatively large quantity of PVC and therefore likely to represent a worst case scenario.

Four personal sample results were collected from different operators; <0.01, <0.01, 0.03 and 0.44 $mg.m^{-3}$. The last result appears to be atypical for this process as all the other results are substantially below this. Also, two static samples were taken at the workstations and gave levels of <0.01 and 0.09 $mg.m^{-3}$, which also indicates that the 0.44 $mg.m^{-3}$ result is likely to be spurious.

Taking all of this into consideration it is proposed to take 0.1 $mg.m^{-3}$ forward to the risk characterisation as the reasonable worst case.

Modelled dermal exposure data

In the compounding of plasticised PVC containing MCCP, there is no possibility of skin contact with MCCP itself although there may be some contact the PVC material containing it. For the workers involved it seems reasonable therefore to assume an EASE model scenario of incorporation in a matrix with direct handling and incidental contact, for which the prediction is that exposure to $210cm^2$ will be in the range 0-0.1 mg/cm^2/day. For maintenance workers, such a prediction would also apply. In practice dermal exposures will be reduced by the workers wearing PPE, in particular gloves, when handling any PVC material containing MCCP.

4.1.1.1.4 Occupational exposure during manufacture and use in paints

MCCPs are used as plasticisers in a limited number of specialised paint systems, for example, in water proofing paints for walls, in chlorinated rubber systems for lining swimming pools and ponds and in solvent based floor paints. The MCCPs used have chlorination values between 40 and 52% and are added mainly in the range 4-15% of the paint as manufactured. It is not known how many workers may be exposed during the manufacture of these products or during their use.

Industry inhalation data

Sampling data has been provided by industry from 2003 (Hughson 2003). Sampling was carried out at 2 locations, (i) a college of further education and (ii) a residential property. At

the college the area painted was an external brick wall and at the residential property the area painted was the internal concrete walls of a prefabricated garage. Although these tasks were small scale operations, they can be considered representative of typical spray painting tasks.

The same paint, a modified acrylic, containing 5.6% MCCP was used for both tasks. At the college the spray paint equipment used was a Titan 440 airless sprayer with a tip size of 0.48mm. The paint was not tinned prior to use, in accordance with the manufacturers instructions. During the spraying the weather was dry with a light wind, and the work area was sheltered from direct sunlight and from the wind. The work was carried out by one experinced and qualified painter. One coat of paint was applied to the wall and this took 20 minutes. A second coat was applied one hour later and again took 20 minutes to complete. The painter wore disposable overalls and nitrile gloves as well as a a disposable organic vapour respirator (3M type 4251). At the residential property the area painted was the internal walls of a self-contained concrete garage. The walls had been cleaned prior to the sampling. The equipment used was a Graco G-max airless spray paint system, with a 0.53mm tip. During the survey there was a light wind. The painter was a vehicle mechanic with experince of spray painting. During spray painting the cantilever garage door was closed in order to prevent over-spray affecting adjacent vehicles and properties. The painter wore a cotton overall, nitrile rubber gloves and a North organic vapour respirator with twin A2 filters. The paint was applied in 2 coats, leaving approximately 1 hour between coats. The total spraying time was 35 minutes.

The results are shown in Table 4.4.

Further inhalation sampling data has been provided by industry (Hughson 2006) from a survey of one site, where a spray painting trial was carried out specifically to obtain exposure measurements for this assessment. However, the work was designed to be representative of a typical outdoor industrial spray painting job, done by an experienced spray painter. The surface being painted was a steel storage container and two different paints were applied, both suited to the aggressive marine and industrial atmospheres and are used for painting ships, chemical plant, storage tanks, bridges and sewerage works. The first paint used was a modified acrylic, containing 5.7% MCCP by weight, with a chlorination level of 52%. The second paint was a chlorinated rubber paint and contained 8.2% MMCP by weight, with a chlorination level of 52%.

The spray painting tasks were of short duration and air monitoring was carried out only during the spraying work. The levels presented are therefore task specific measurements rather than 8 hr TWAs. During the survey period the weather was cold with a persistent fog and there was no noticeable wind. The relative humidity was about 90% due to the fog. Spray painting would not normally be done under these environmental conditions as the paint finish would be adversely affected. This however, was not a consideration for this exercise.

A Graco G-Max airless spray paint system, with a tip size 0.53mm was used. This is a heavy-duty airless spray unit intended for industrial application of all types of paint. The container was sprayed until the acrylic paint (20l) was used up. This exercise was repeated using 25 litres of chlorinated rubber paint. The spray painter wore disposable overalls, PVC coated gloves and a Sundstrom SR100 half mask respirator, with A2 organic vapour filter cartridge.

Samples were collected using an OSHA versatile sampler (SKC type 226-30-16) and analysed using gas chromatography with mass spectrometry. As there was a limited time available for collecting measurements the painter was fitted with 2 samplers, one worn on each side of the body. The results are shown in Table 4.4. The measured values for all sampling periods were

in the range 0.3 – 5.1 mg/m^3, with a median value of 2.7 mg/m^3 and a 90th percentile value of 3.9 mg/m^3. 8-hr TWAs have been calculated, assuming that there was no further exposure to MCCP-containing paint in that day. The results range from 0.004 – 0.19 mg/m^3, with a median value of 0.04 mg/m^3 and a 90th percentile value of 0.1 mg/m^3. The exposure data do not indicate that airborne concentrations were higher or lower for the different paint types.

Table 4:4 Results of task-based personal inhalation sampling for MCCP during paint spraying task

Sample	Task	Duration (minutes)	Concentration MCCP (mg/m^3)	8-Hr TWA MCCP (mg/m3)
2006 data -Modified acrylic paint				
1	Fenced side (preparation and 5 min spray time)	49	0.3	0.03
2	ditto	49	0.4	0.04
3	Spraying fenced side	6	1.5	0.02
4	Ditto	6	2.7	0.03
5	Spraying open side &end door	10	2.1	0.04
6	Ditto	10	1.5	0.03
7	Spraying monoflex extension	10	3.0	0.06
8	Ditto	10	2.5	0.05
9	Spraying monoflex extension	6	3.3	0.004
10	ditto	6	2.5	0.03
2006 data - Chlorinated rubber paint				
11	Spraying fenced side	10	4.0	0.08
12	Ditto	10	3.8	0.079
13	Spraying open side and end door	10	2.8	0.06
14	Ditto	10	2.7	0.06
15	Spraying monoflex extension	18	3.5	0.13
16	ditto	18	5.1	0.19
2003 data -modified acrylic paint				
17	external brick wall	40	0.05	0.002
18	ditto	40	0.08	0.006
19	self-contained prefabricated concrete garage	35	0.6	0.04
20	ditto	35	0.58	0.04

Taking into account all of the data from Table 4.4 the 8-hour TWA exposures for paint spraying range from 0.002 – 0.19 mg.m^{-3}, with a median value of 0.04 mg.m^{-3}and a 90th percentile value 0.085 mg.m^{-3}.

Modelled inhalation exposure data

As there are no other measurements of exposure available to airborne MCCP during its use in paints, the EASE model has been used to predict the personal exposure of workers to airborne MCCP arising from this use.

As with previous scenarios the exposure predicted using EASE is 0 to 0.1 ppm, for processing temperatures up to 125 °C. The mixing processes used to prepare paints containing MCCP are carried out in closed vessels. The processing temperature is mostly at ambient, with a possible rise to a maximum between 50 and 60 °C during the initial pre-mixing involving high shear forces. Thus the predicted inhalation exposures to MCCP during its use in the production of paints will clearly be within the range 0-0.1 ppm and can be reduced to an upper limit of 0.0027 ppm (0.051mg.m^{-3}) at 20 °C. The processing temperatures for paint manufacture are such that the possibility of the creation of a mist resulting from the cooling of hot vapours can be discounted. In addition, the process will not produce mechanically induced spray formation to which workers could be exposed.

It is understood that some 90% of the paint formulations incorporating MCCPs are applied by brushing. As already explained for such a procedure carried out at room temperature exposures of workers to MCCPs present in the formulation will be in the range 0-0.0027 ppm. There will be neither exposure to mist from condensation of hot vapour nor to mechanically generated spray. Some 10% of the paint formulations containing MCCPs may be applied using spraying techniques. For such procedures the application of the EASE model is confounded by the very low volatility of the MCCPs. Thus exposure predictions cannot be derived. This spraying is understood to be usually undertaken outside, for example, to line swimming pools. De Pater et al, 1999, provides a model for predicting exposure to non-volatile compounds during spray painting. Data is provided for polyisocyanates, HDI monomer and dusts, and from these reasonable worse case scenarios (RWS) of 10 mg.m-3, 0.2 mg.m-3 and 50 mg.m-3 respectively are provided in the report. Using the polyisocyanate data for this scenario as a similar non-volatile liquid the report suggests the following formula to take account of the concentration of the substance in the formulation.

$$E = 10 \times C / 30$$

E = estimated exposure in mg.m^{-3}
C = the percentage of substance in the paint
10 = RWS exposure for polyisocyanates in mg.m^{-3}
30 = RWS concentration of polyisocyanate in the paint
Since the paint considered in this assessment contains 15% MCCP, the equation becomes.

$$E = 10 \times 15 / 30$$

The predicted exposure is therefore 5 mg.m^{-3} 8-hour TWA MCCP.

There are many complicating factors that make it difficult to simply accept this result. The report does state that more work is needed to refine this method. The exact method of application will influence exposure. For example, whether the spraying is inside or outside, the extent of any ventilation used, and the type of spray guns being used. The MCCPs based paints are applied to surfaces outside, whereas the polyisocyanate paints were probably applied inside. The nature of the paint will also affect exposure. Some components maybe chemically or physically bound with the polymer matrix of the paint. In the absence of other data the above is a reasonable first approximation.

Conclusions

Although the measured data provided by industry are task specific, 8hr TWAs can be calculated. It is assumed that no other exposure to MCCPs occurs in the same day. This would appear to be a reasonable assumption given that complete tasks were sampled. Overall the exposures ranged from 0.002 to 0.19 mg.m^{-3}, with a median value of 0.04 mg.m^{-3} and a 90^{th} percentile value of 0.085 mg.m^{-3}.

Spray painting can be used as the worst case scenario for painting tasks and is likely to produce higher exposures. The de Pater model predicts that exposure for non-volatile compounds during spray painting would be 5 $mg.m^{-3}$ 8-hour TWA MCCP. Although the task specific values produced by the sampling exercises are within the same order of magnitude of this, the comparable 8hr TWA values are not. Therefore it is proposed to take forward the highest 8hr TWA value (0.19 $mg.m^{-3}$) forward to risk characterisation. This value is preferred to the 90^{th} percentile value to take into account the potential variability of exposures during paint spraying.

Industry dermal exposure data

Hughson 2006 also presents some dermal exposure measurements, which were collected as a pilot exercise during the method development phase of a study to assess dermal exposure to MCCPs. A total of 18 separate tape strip samples were collected at the same time as the inhalation samples during the paint spraying exercise (see above). While the worker wore protective gloves and a disposable overall, there were measurable levels of MCCP in the skin contaminant layer, from the hands, forearms, face and neck. The dermal exposures were generally low (i.e. typically 1-3 µg/cm2). As the sampling and analytical procedures are still in the process of being validated, these data can only be considered to be preliminary estimates and will not be used in determining the value for risk characterisation.

Modelled dermal exposure data

In the manufacture of paints containing MCCP, there is possibility of skin contact with MCCP itself during its addition and with material containing it. For the workers involved the appropriate EASE model scenarios will be either non-dispersive use or incorporation in a matrix, both with direct handling and incidental contact. The predictions for both scenarios are that MCCP exposure to 420 cm^2 (assuming manual addition of liquid) will be in the range 0-0.1 $mg/cm^2/day$. For maintenance workers, such a prediction would also apply. In practice dermal exposures will reduced if the workers wear PPE, in particular gloves, when handling any MCCPs and paints containing them.

For workers applying paints containing MCCP with brush or by spraying, the appropriate EASE scenario will be incorporation into a matrix with direct handling and intermittent handling. The prediction for this scenario is that MCCP exposure will be in the range 0.1-1 $mg/cm^2/day$ over $840cm^2$.When the percentage (15%) of MCCPs in the paint is taken into account the prediction becomes 0.015 – 0.15 $mg/cm^2/day$ over $840cm^2$. In practice, dermal exposures will be reduced if the workers wear PPE, in particular gloves, when handling any paints containing MCCPs.

4.1.1.1.5 Occupational exposure during manufacture of sealants

MCCPs are used as plasticisers in a number of sealant systems. They also are used because they confer in some formulations a degree of flame retardancy. The MCCPs used have chlorination values between 50 and 60% and are added mainly in the range 15-20% of the formulation. It is not known how many workers may be exposed during the manufacture of these products or during their use.

Modelled inhalation exposure data

Neither the HSE nor industry has made measurements of exposure to airborne MCCP during its use in sealants. Consequently the EASE model has been used to predict the personal exposures of workers to airborne MCCP arising from this use.

As with previous scenarios the exposure predicted using EASE is 0-0.1 ppm, for processing temperatures up to 125 °C. The mixing processes used to prepare sealants containing MCCP are carried out in closed vessels. The processing temperature is mostly at ambient, with a possible rise to a maximum between 50 and 60 °C, during mixing which involves fairly high shear forces. The temperature of the mix when transferred from the mixer to the packaging system is between 35 and 40 °C. Thus the predicted inhalation exposures to MCCP during its use in the production of sealants will clearly be within the range 0-0.1 ppm and can be reduced to an upper limit of 0.0027 ppm (0.051mg.m^{-3}) at 20 °C. The processing temperatures for sealant manufacture are such that the possibility of the creation of a mist resulting from the cooling of hot vapours can be discounted. In addition, the process will not produce mechanically induced spray formation to which workers could be exposed.

Modelled dermal exposure data

In the manufacture of sealants containing MCCP, there is possibility of skin contact with MCCP itself during its addition and with material containing it. For the workers involved the appropriate EASE model scenarios will be either non-dispersive use or incorporation in a matrix, both with direct handling and incidental contact. The predictions for both scenarios are that exposure to 420cm^2 will be in the range 0-0.1 mg/cm^2/day. For maintenance workers, such a prediction would also apply. In practice dermal exposures will reduced if the workers wear PPE, in particular gloves, when handling any MCCPs and sealants containing them.

4.1.1.1.6 Occupational exposure during rubber manufacture

There is some use of the MCCPs of higher degree of chlorination (60-70%) as flame retardant additives in rubber. The main application is in manufacture of conveyor belting. The initial addition and mixing of ingredients is very similar to that employed in the compounding and calendering of PVC and will give rise to comparable worker exposures. (See Section 4.1.1.1.3) The final hot moulding of the rubber sheet will take place in closed presses which are equipped with LEV to capture any rubber fume including MCCP emitted when the presses are opened. Although somewhat different to the calendering of PVC, the process is considered to give rise to a similar degree of exposure. It is understood that throughout the EU, there may be a few hundred workers involved in producing rubber which contains MCCPs.

Modelled inhalation exposure

The EASE model has been used to predict the personal exposures of workers to airborne MCCP arising from this use.

By analogy with use of MCCPs in PVC formulation, workers exposure will be in the range 0-0.0027 ppm (0.051mg.m^{-3}). Mist that is not removed by the local exhaust ventilation is likely to quickly condense on nearby cold surfaces and contribute to dermal exposure. Where the extraction is insufficient there is the potential for more significant release of mist into the workplace and therefore increased occupational exposure.

Where the control is again insufficient as with the use of MCCPs in PVC formulation the exposure to mist is again predicted to be 9-18 $mg.m^{-3}$ as rough approximation. These figures are likely to be overestimates and only representative of a poor standard of control of the vapour and mist.

Industry Data

Industry have provided sampling results from one rubber compounding manufacturing site in Italy. The plant produces an intermediate rubber compound from raw materials using a Banbury mixer and a calender mill. The product is shipped to customers for secondary processing into cables and other rubber goods. Production using MCCP is by a batch process, which on average only runs two days per month. There were four operators on the production line, two usually present in the mixer area, one at the calender and one at the packaging machine. There is no rotation of tasks and the operators remain at their workstations for the majority of the shift.

The MCCP is delivered to the mixer via enclosed pipelines. The mixer and the calender plant have LEV, which appeared to efficiently capture the process emissions. At the packaging area, the operator supervises the material as the rubber strips load into open storage baskets. There was no visible emissions from the product. The sampling results are shown in Table 4.5.

Table 4:5 Industry data from rubber manufacture

Job	Sampling result ($mg.m^{-3}$)
Mixer operator	0.02
Calender operator	0.01
Packaging operator	0.02
Mixer operator	0.01
Calender operator	0.03
Packaging operator	0.01
Mixer operator	0.07

Taking into consideration the measured results and the similarities in process with PVC compounding and calendering it is proposed to take the highest measured value of $0.07mg.m^{-3}$ forward to the risk characterisation as the reasonable worst case.

Modelled dermal exposure

Again by analogy with PVC formulation it is assumed that predicted dermal exposures for $420cm^2$ of workers involved in the manufacture of rubber will be in the range 0.1-1 $mg/cm^2/day$. In practice this exposure will be reduced if workers wear PPE, in particular, gloves.

4.1.1.1.7 Occupational exposure in the manufacture and use of metal working fluids

MCCPs are used as extreme pressure additives in a wide variety of cooling and lubricating fluids used during metal cutting, grinding and forming operations. These fluids are commonly referred to as metal working fluids (MWFs). The MCCPs used may be between 45 and 55 % chlorinated and added at concentrations ranges between 5 and 10% in water-based MWFs and typically between 5 to 10% in oil-based MWFs, although for some heavy duty applications MCCP content is typically between 50 and 70% (Cherrie, 2006). In terms of tonnage used in Europe, water-based MWF containing between 5 and 10% MCCP vastly outsell those with higher contents. Also, in practice, it is usual for the end user to dilute the water-based MWF products with water. This has the effect of reducing the in-use concentration of MCCP. The recommended dilution is about 5% aqueous emulsion. Therefore, the estimated maximum in-use concentration of MCCP in water-based MWFs is approximately 0.5%. Oil-based MWFs are not diluted by the end user, with MWF products containing as little as 2% MCCP and as high a level as 100% MCCP, which is used for heavy duty applications such as broaching. However, the main uses for oil-based MWFs are for those containing 5 to 10% MCCP. The usage of this type of MWF differs between European countries. However, some heavy-duty applications are also used, in which there are higher levels of MCCP, typically 50 – 70%.

The components of both oil and water-based MWFs are blended by the manufacturers in closed vessels at ambient temperatures, although on occasion temperatures may rise to about 40 °C. The application of MWFs to rotating workpieces produces a mechanically induced mist to which the worker may be exposed.

For metal forming operations, MCCPs with higher levels of chlorination are used and are present in the oil at concentrations up to 50%. These metal forming activities do not give rise to mechanically produced mist.

The number of people potentially exposed to MCCPs in the manufacture of MWFs is not known, but many thousands are likely to be potentially exposed to MCCPs in their use in MWFs throughout the EU.

Modelled and derived inhalation data

Neither the HSE nor industry has made measurements of exposure to airborne MCCP during the manufacture and use in MWF formulations containing it. Therefore the EASE model has been used to predict worker exposures during the manufacture of MWFs.

For the use of MWFs, exposures are derived from measured data on exposure to oil mist and to spray from water-based MWFs.

EASE predicts that, for substances with a vapour pressure which is less than 0.001 kPa at the processing temperature, exposures to airborne substance will be within the range 0-0.1ppm, regardless of pattern of use or pattern of control. Thus because the vapour pressure of MCCP, as calculated within the EASE model, remains below 0.001 kPa for processing temperatures up to 125 °C the predicted exposure for processes temperatures below 125 °C will be independent of patterns of work or control and will be within the range 0-0.1 ppm. Predicted inhalation exposures to MCCP during the use of the substance in the production of MWFs will therefore clearly be within the range 0-0.1 ppm as all the activities associated with manufacturing process operate at temperatures very much below 125 °C. Furthermore, as the saturated vapour concentration at ambient temperature (20 °C) is only 0.0027 ppm, the upper limit of this range of predicted exposures to MCCP vapour will be reduced to 0.0027 ppm

(0.051mg.m^{-3}). In this situation the possibility of production of mechanically induced spray or of mist formation by the condensation of hot vapour can be discounted.

A HSE report describes results of a wide ranging survey of worker exposure to MWFs; 31 sites were surveyed. At 12 of these sites a total of 40 personal exposures to oil-based MWF were measured and at 28 sites a total of 298 personal exposures to water-based MWF were measured. In the latter case the results are quoted as MWF concentrate. For the oil-based MWF the 95th percentile result was 3.4 mg.m^{-3} 8-hour TWA and for the water-based MWF the 95th percentile result was 1.6 mg.m^{-3} 8-hour TWA. Assuming the upper limit of MCCP concentration in oil-based MWF to be 70% then this corresponds to 8-hour TWA exposures of 2.4 mg/m^3. For water-based MWF the maximum in-use concentration is 0.5%. These results correspond to 8-hour TWA exposures of 0.008 mg/m^3 MCCP. Although, HSE's work found poorly prepared concentrate strengths of up to 37.5%, the more recent water-based MWF concentration values of 1 to 15% (median 7%) from Semple et al, indicate that 0.5% is a realistic maximum in-use concentration. Therefore the value of the 95th percentile 8-hr TWA, 0.008 mg/m^3 will be used as a reasonable worse case scenario for water-based MWFs, without adjustment. These results relate to exposure to liquid droplets containing MCCP, i.e. the MCCP is in liquid form. There will also be some exposure to MCCP vapour. However, as explained already the fact that the saturated vapour concentration of MCCP is 0.0027 ppm at 20 °C (equivalent to 0.051mg.m^{-3}) means that the contribution of the vapour to the total exposure to MCCP will be quite small.

The HSE survey did not include an investigation of exposure to MCCP into the use of MWFs in metal forming. For this application there may be exposure to a mist formed by the condensation of hot vapour. The extent of this will depend upon the extent to which the oil/MCCP mixture is heated.

Modelled and derived dermal exposure data

For the exposure to MCCPs in the manufacture of MWFs the appropriate EASE scenario for predicting dermal exposure is non-dispersive use with direct contact and incidental exposure. The corresponding prediction for dermal exposure to 420cm^2 is in the range 0-0.1 mg/cm^2/day.

A report has been commissioned by industry (Cherrie, 2006) to provide estimates of dermal exposure to MCCPs during use of MWFs based on data from existing studies, taking into account technical information on the use of MCCP in MWFs for use in this RAR.

Although dermal exposure data were evaluated from 3 published studies: Semple et al. (2005), Roff et al. (2004) and van Wendel de Joode et al. (2005), only the data from Semple et al. (2005) were used to produce the final estimates of exposure for MCCP from the use of MWF. The data reported by Semple et al. (2005) provided the largest available set of information about MWF exposure and is the only source that represents exposure data from workers without protective gloves. From experience and the observations of the other authors it was believed that gloves are not commonly worn in this work situation and they may not be consistently worn throughout the workshift. The data from this study along with information on the range and average MCCP content in MWF were used to extrapolate estimates of the typical and RWC dermal exposures of MCCP exposure when using MWFs. Because the estimates of dermal exposure to MCCP in MWF were obtained from surrogate data, allowance was also made for the uncertainties associated with the overall estimates to ensure that the final information did not underestimate likely dermal exposure.

Semple et al. (2005) collected data on MWF exposure from six engineering companies in Scotland, which although not representative of the entire engineering sector, did cover a wide range of product and service delivery. The study was designed as an intervention study to assess the effectiveness of different safety training approaches. Five of the six sites employed over 100 workers, whilst the sixth employed less than 50 people; although the numbers involved in the machine tool department were much lower than this. The number of workers directly exposed to MWF was between 10 and 40. The samples were collected by wipe sampling and the samples analysed by ICP/AES using boron as a marker of MWF contamination. There are no standardized methods for measurements of demal exposure. Use of boron as a marker for MWF contamination is based on MDHS 95/2 – Measurement of personal exposure of metal working machine operators to air-borne water mix MWFs (HSE, 2003). In total there were 196 pairs of measurements of exposures on right and left hands and there was no statistical difference between left and right hand measurements. For the purposes of this assessment the average exposure measurement for both hands was used. Further analysis showed that the training intervention resulted in a reduction of dermal exposure and so this analysis was only carried out on the baseline data from each of the sites and repeat visit data for the 3 control sites. This resulted in 16 measurements being available for work with oil-based MWF and 96 for work with water-based MWF. The concentration of water-based MWF in the sump was also measured as part of this study and data were available for 93 of the dermal samples. The values ranged from 1 to 15%, with a median of 7%.

Use of water-based MWF

For the use of water-based MWFs the EASE scenario is non-dispersive use with direct handling and extensive handling for which the predicted range is 1-5 mg/cm^2/day. Taking into account the fact that for water mix MWFs the MCCP is present at a maximum in-use concentration of 0.5% (Cherrie, 2006) the predicted range of dermal exposure for use of water-based MWFs will be to 0.0005 to 0.025 mg/cm^2/day over 840cm^2. The predicted reasonable worst-case exposure would be 21 mg MCCP per day.

From Semple et al. (2005) the 90th percentile exposure measurements of MWF on the hands was 36,000 mg. The data from the two types of MWF were not significantly different from each other. Assuming the maximum in-use concentration of MCCP in water-based fluids to be 0.5%, the RWC hand exposure (90th percentile) would be 180 mg.

Use of oil-based MWF

For the use of MWFs the EASE scenario is non-dispersive use with direct handling and extensive handling for which the predicted range is 1-5 mg/cm^2/day. For oil-based fluids, if it is assumed that there will be 70% MCCP in the fluid and as there is no further dilution the EASE predicted range would be 0.7 to 3.5 mg/cm^2/day, over 840 cm^2. Therefore the EASE predicted RWC would be 2,940 mg/day.

From Semple et al. (2005) the 90th percentile exposure measurements of MWF on both hands was 36,000 mg. The data from the two types of MWF were not significantly different from each other. For oil-based fluids it is not necessary to adjust the in-use exposure for dilution effects. It is assumed, therefore that the maximum typical in-use concentration is 70% MCCP. This gives a RWC estimate (90th percentile exposure with highest proportion MCCP) of 25,000 mg MCCP on the hands.

Conclusions

Dermal exposure to MCCPs during use of MWFs will be assessed separately for the two different types of MWF; water-based and oil-based.

EASE predicts that the exposure to MCCP during use of water-based MWFs is 0.005 to0.025 mg/cm^2/day over 840cm^2. Therefore the predicted RWC would be 21 mg MCCP per day. For oil-based fluids, the predicted range is 0.7 to 3.5 mg/cm^2/day, over 840 cm^2. Therefore the predicted RWC would be 2,940 mg/day.

Cherrie (2006) gives estimates for dermal exposure during the use of both water-based and oil-based MWFs. Using the information from this report the RWC exposure given for water-based MWFs is 180 mg/day and for oil-based MWFs the RWC is 25,000 mg/day.

There is a large difference between the EASE predicted exposures and the estimates produced from real sampling data of dermal exposure to MWF. As the estimates in Cherrie (2006) are based on 112 good quality real sampling data as well as information on MWF formulations, these data will be preferred to the EASE estimates in deciding the RWC levels for both water-based and oil-based MWFs. Therefore, the values taken forward for risk characterisation are 180 mg/day for water-based MWFs and 25,000 mg/day for oil-based MWFs.

4.1.1.1.8 Occupational exposure in the manufacture and use of fat liquor in leather treatment

Leather fat liquor is made via a simple mixing process in an enclosed system at ambient temperature, the main components being water natural fats, surfactants and MCCP. The MCCP, which may be chlorinated at levels between 40 and 50%, accounts for about 10% w/w of finished fat liquor. The fat liquor is transported in drums or FBCs to the tanneries.

At the tannery the liquor is manually weighed out and added to a closed mixing vessel in which it is diluted with water (40-60% liquor, the remainder water). During this blending operation the temperature will generally be about 40 to 50 °C, possibly up to 60 °C.

The leather to be treated with fat liquor is placed in a closed rotatable horizontal drum together with warm water and dyestuff and rotated at between 8 and 12 rpm. On completion of the dying stage the fat liquor is added to the drum by gravity via the hollow axle. The fat liquor is thereby effectively diluted with the water already in the drum at a ratio of about 5 of water to 1 of diluted fat liquor. The fat liquoring process takes place as the drum continues to rotate for a further 30-60 minutes during which time the temperature will be between 45 °C and ambient. Before the leather is removed from the drum a sample is taken for testing. When the quality is acceptable the leather is removed and mangled to remove surplus liquid. Finally drying will be undertaken either by vacuum drying at temperatures between 50 and 95 °C or by tumble drying at temperatures between 75 and 80 °C.

A single worker will look after six drums and will attend to the process from the initial weighing out of the MCCP through to the removal of the leather from the drum. Apart from weighing out the fat liquor it is only during sampling of the leather in the drum that the worker will come into contact with liquor. It is likely that each drum will complete two treatments per day. Thus the operator will take leather samples from the drums about 12 times per day. The worker would normally be expected to wear PPE comprising gloves, apron and wellington boots. It is not known how many workers are potentially exposed to MCCPs during the treatment of leather with fat liquor.

Modelled inhalation exposure data

Neither the HSE nor industry has made measurements of exposure to airborne MCCP during the manufacture and use in fat liquors containing it. Therefore the EASE model has been used to predict worker exposures during the manufacture of fat liquors.

As with previous scenarios the exposure predicted using EASE is 0-0.1 ppm, for processing temperatures up to 125 °C. As the mixing processes used to prepare fat liquors containing MCCP are carried out in closed vessels at ambient temperature, the predicted inhalation exposures to MCCP during its use in the production of paints will clearly be within the range 0-0.1 ppm. Moreover, as the saturated vapour concentration at ambient temperature is only 0.0027 ppm ($0.051 mg.m^{-3}$), the upper limit of the range of predicted exposures to MCCP vapour will be reduced to give an upper limit of 0.0027 ppm at 20 °C. The processing temperatures for fat liquor manufacture are such that the possibility of the creation of a mist resulting from the cooling of hot vapours can be discounted. In addition, the process will not produce mechanically induced spray formation to which workers could be exposed.

The fat liquoring process also takes place at temperatures at or below 45 °C. Thus exposures to MCCP vapour will again be in the range 0-0.0027 ppm ($0.051 mg.m^{-3}$) (upper end of the EASE predicted range corrected to the SVC). The processing temperatures for fat liquoring are such that the possibility of the creation of a mist resulting from the cooling of hot vapours can be discounted. In addition, the process will not produce mechanically induced spray formation to which workers could be exposed.

Finally in the drying process, even with temperatures up to 95 °C, the EASE exposure predictions will be still be within the range 0 to 0.0027 ppm (upper end of the EASE predicted range corrected to the SVC). The temperature achieved in drying the treated leather such that there is little possibility of the creation of a mist resulting from the cooling of hot vapours. In addition, the process will not produce mechanically induced spray to which workers could be exposed.

Modelled dermal exposure data

For workers involved in using MCCPs in manufacture of fat liquor the appropriate EASE scenario would be non-dispersive use with direct handling and incidental contact. For this the predicted dermal exposure for $420 cm^2$ is within the range 0-0.1 $mg/cm^2/day$.

In the case of the workers involved during the fat liquoring of the leather the scenario will be non-dispersive use with direct handling and intermittent contact yielding a predicted exposure to $840 cm^2$ in the range between 0.1 and 1 $mg/cm^2/day$. As only 10% of the fat liquor is MCCPs then the prediction is reduced to 0.01 – 0.1 $mg/cm^2/day$ over $840 cm^2$.

Finally for the workers involved in the leather drying process the scenario will be non-dispersive use with direct handling and incidental contact with a resultant prediction in the range 0-0.1 $mg/cm^2/day$ over $420 cm^2$. As only 10% of the fat liquor is MCCPs then the prediction is reduced to 0 – 0.01 $mg/cm^2/day$ over $420 cm^2$.

In practice dermal exposures will be reduced as the workers would normally be expected to wear PPE, in particular gloves, when handling any materials containing MCCPs.

4.1.1.1.9 Occupational exposure during the manufacture of carbonless copy paper

As indicated in Section 2.2.5, only 5% of the EU production of carbonless copy paper is manufactured using MCCPs as solvent for the colour former contained within the microcapsules. No further information on how MCCPs are added to the process is available. The microencapsulation process takes place within an enclosed vessel at ambient temperature. This is the only part of the process where there is the possibility of exposure to MCCP, as once the material is encapsulated, it is contained within the impervious microcapsule wall.

Modelled inhalation exposure data

Neither the HSE nor industry has made measurements of exposure to airborne MCCP during the of carbonless copy paper. Therefore the EASE model has been used to predict worker exposures during the manufacture of these materials.

As with previous scenarios the exposure predicted using EASE is 0-0.1 ppm, for processing temperatures up to 125 °C. As the process in which MCCP is microencapsulated is carried out in closed vessels at ambient temperature, the predicted inhalation exposures to MCCP during this process will clearly be within the range 0-0.1 ppm. Moreover, as the saturated vapour concentration at ambient temperature is only 0.0027 ppm, the upper limit of the range of predicted exposures to MCCP vapour will be reduced to give an upper limit of 0.0027 ppm (0.051mg.m^{-3}) at 20 °C. The processing temperatures for microencapsualtion of MCCP are such that the possibility of the creation of a mist resulting from the cooling of hot vapours can be discounted. In addition, the process will not produce mechanically induced spray formation to which workers could be exposed.

Modelled dermal exposure data

For workers involved in using MCCPs in microencapsulation of the solution of colour former in MCCP the appropriate EASE scenario would be non-dispersive use with direct handling and incidental contact. For this the predicted dermal exposure for 420cm^2 (assuming manual addition) is within the range 0-0.1 mg/cm^2/day. In practice dermal exposures will be reduced if the workers wear PPE, in particular gloves, when handling any material containing MCCPs.

4.1.1.1.10 Summary of inhalation exposure

HSE's National Exposure Database does not have any measurements of exposure to airborne C_{14} to C_{17} chlorinated paraffins (MCCPs) during their manufacture and use. Industry has provided exposure data for PVC compounding, extrusion, calendering, plastisol manufacture and use, and rubber manufacture. Individuals were sampled for the majority of the working shift and results are indicative of 8 hour time weighted averages (TWAs).

For all other scenarios the EASE model has been used to predict exposures of workers to airborne MCCP. Unfortunately the very low vapour pressure of MCCPs has meant that the EASE parameters are at the limits of the model's facility to predict exposure. Thus for the lowest exposure range the upper limit of 0-0.1 ppm is greatly in excess of the saturated vapour concentration for MCCPs at 20 °C (ambient temperature), namely, 0.0027 ppm (0.051mg.m^{-3}). It should be borne in mind that the saturated vapour concentration is the theoretical maximum achievable concentration in a steady state environment which will rarely, if ever, be achieved in practice in an industrial situation. In all the situations where MCCPs are used in the workplace *vapour* exposures are governed by this restriction, i.e. exposures to vapour will

be significantly below 0.0027 ppm (0.051mg.m^{-3}). Thus this upper limit to vapour exposure applies to all uses of MCCPs and materials containing them.

An added complication is that processes which operate in excess of 100 °C, in particular the hot processing of plasticised PVC formulations at up to temperatures of 200 °C, there is the possibility that as hot vapour laden air moves away from its source the MCCP will begin to condense to form a mist to which workers will be exposed in addition to the low concentration of vapour. EASE is not capable of dealing with this situation. It is therefore difficult to quantify the incremental effect that the mist will have on the assumed vapour concentration. However, good local exhaust ventilation at the PVC processes such as calendering will minimise the contribution of mist to the overall exposure to MCCPs.

Where the extraction is insufficient there is the potential for more significant release of mist into the workplace and therefore increased occupational exposure. The EASE predictions for vapour up to 200 °C are overestimates, since the actual working environment will be closer to ambient and the SVC is only 0.0027 ppm (0.051mg.m^{-3}). However, we can use the EASE predictions for vapour as a rough approximation for exposure to mist. If we assume that all the vapour condenses to form mist then the vapour range of 0.5-1.0 ppm becomes 9-18 mg.m^{-3} 8-hour TWA. These figures are likely to be overestimates and only representative of a poor standard of control of the vapour and mist. These scenarios where there is the possibility of exposure to mist where inadequate LEV or other such controls are in place, are:

- plastisol use
- calendering of plasticised PVC;
- compounding of plasticised PVC;
- extrusion and moulding of plasticised PVC; and
- rubber manufacture.

Sampling data, collected over 2 days were also provided by industry from plastisol use. Values ranged from <0.1 to 0.12 mg.m-3, with a median of 0.02 mg.m-3 and a 90th percentile of 0.12 mg.m-3. However, the results indicated that exposures were higher on day 1, ranging from <0.01 to 0.12 mg.m-3, than day 2 which ranged form <0.01 to 0.02 mg. m-3. This was attributed to a malfunctioning extraction system on one of the ovens on day 1 which was repaired by day 2. Most of the small number of measured data are below the EASE value of 0.05 mg/m3 and range from 0.02 to 0.08 mg/m3. The highest value of 0.08 mg/m3 will be taken forward to risk characterisation as the RWC.

Although originally no measured data were available for calendering of PVC a RWC of 0.1 mg.m^{-3} for this scenario was proposed by using analogous measured data and judgement. After new measured data were provided by industry this RWC value has now been revised to 1mg.m^{-3}. However, as it appears likely that calendering of MCCP-containing PVC will not be carried out every day at the workplaces that make these products it should be noted that the value of 1mg.m^{-3} will only apply to days when calendering of MCCP-containing PVC occurs. A range of <0.003 to 0.44 mg.m^{-3} MCCP exposures was found from 32 personal samples taken from 4 EU sites carrying out PVC compounding. The median of these exposures is 0.03 mg.m^{-3} and the 90th percentile is 0.15 mg.m^{-3}, which is the value taken forward as the RWC for this scenario.

Four samples were taken at a site carrying out the application of PVC insulation, by extrusion, to electrical cables. The values are <0.01, <0.01, 0.03 and 0.44 mg.m^{-3}. taking into account

the small amount of data, the similarities in process with other PVC processes and using judgement a value of 0.1 $mg.m^{-3}$ is taken forward as the RWC for extrusion.

A range of 0.01 to 0.07 $mg.m^{-3}$ MCCP exposures was found during rubber manufacture from 7 personal samples taken at one site. Taking into consideration the measured results and the similarities in process with PVC compounding and calendering it is proposed to take the highest measured value of 0.07 $mg.m^{-3}$ forward to the risk characterisation as the RWC.

Another exposure situation that EASE cannot readily handle is mechanically produced spray produced adventitiously by rapid mechanical agitation, "semi adventitiously" in the use of metal working fluids and purposely in the case of paint spraying. The difficulty is accentuated because of the very low vapour pressure of MCCPs. De Pater *et al.*, 1999 (Draft), provides a model for predicting exposure to non-volatile compounds during spray painting, which gave a result of 5 $mg.m^{-3}$ 8-hour TWA. Spray painting can be used as the worst case scenario for painting tasks and is likely to produce higher exposures. The de Pater model predicts that exposure for non-volatile compounds during spray painting would be 5 $mg.m^{-3}$ 8-hour TWA MCCPs. Although the task specific values produced by the sampling exercises are within the same order of magnitude of this, the comparable 8hr TWA values are not. Therefore it is proposed to take forward the highest 8hr TWA value (0.19 $mg.m^{-3}$) forward to risk characterisation. This value is preferred to the 90^{th} percentile of the sampling results to take into account the potential variability of exposures during paint spraying.

The exposure data from an HSE survey of premises using metal working fluids has provided some "real" exposure data which has been used to derive possible exposures to MCCP in the MWF spray generated by the rotation of the metal work piece. For the oil-based MWF the 95th percentile result was 3.4 $mg.m^{-3}$ 8-hour time weighted average (TWA) and for the water-based MWF the 95th percentile result was 1.6 $mg.m^{-3}$ 8-hour TWA. Assuming a maximum in-use concentration of 0.5% in and water-based MWFs this result corresponds to an 8-hour TWA exposure of 0.008 $mg.m^{-3}$ MCCP for for water-based MWFs. For oil-based MWFs, if it is assumed that the maximum in-use concentration of MCCP is 70% then the corresponding RWC 8-hr TWA is 2.4 $mg.m^{-3}$.

These results relate to exposure to liquid droplets containing MCCP, i.e. the MCCP is in liquid form. There will also be some exposure to MCCP vapour. However, as explained already the fact that the saturated vapour concentration of MCCP is 0.0027 ppm at 20 °C (equivalent to0.051 $mg.m^{-3}$) means that the contribution of the vapour to the total exposure to MCCP will be quite small.

The table below summarises the inhalation data to be taken forward for the risk characterisation (**Table 4.6**).

Table 4:6 Summary of occupational inhalation exposure data for risk characterisation

Industry		**Inhalation exposure**			
		vapour (ppm)	Mist (EASE) (mg/m^3)	Measured data (mg/m^3)	RWC (mg/m^3)
Manufacture of MCCPS		0.0027	neg		0.05
PVC formulating	**PVC plastisol manufacture**	0.0027	neg		0.08
	plastisol use	0.0027	neg		0.05
	calendering of plasticised PVC	0.0027	9 to 18	0.03 to 1.2 (0.01, 0.03)	1
	compounding of plasticised PVC	0.0027	9 to 18	<0.003 - 0.44	0.15
	extrusion and moulding of plasticised PVC	0.0027	9 to 18	<0.01 - 0.4	0.1
Manufacture of paints containing MCCPs		0.0027	neg		0.05
Use of paints containing MCCPs (spraying)		0.0027	5	0.002 – 0.19	0.19
Manufacture of sealants containing MCCPs		0.0027	neg		0.05
Rubber manufacture		0.0027	9 to 18	0.01 – 0.07	0.07
Manufacture of MWFs containing MCCPs		0.0027	neg		0.05
Use of water-based MWFs containing MCCPs		0.0027		0.008 (95^{th} percentile)	0.008
Use of oil-based MWFs containing MCCPs		0.0027		2.4 (95^{th} percentile)	2.4
Manufacture of fat liquor in leather treatment		0.0027	neg		0.05
Use of fat liquor in leather treatment		0.0027	neg		0.05
Manufacture of carbonless copy paper		0.0027	neg		0.05

Neg: negligible exposure. See text of respective sections.

4.1.1.1.11 Summary of dermal exposure

Table 4.7 below summarises the dermal data to be taken forward for the risk characterisation.

With the exception of the use of MWFs, EASE has been used to predict all dermal exposures values for risk characterisation. There are two types of MWFs; water-based and oil-based. These will be assessed separately as there are differences in the MCCP content of the two types of MWFs. Although EASE can be used to predict dermal exposures to MWFs, 112 real measured datapoints from Semple et al. (2005), have been used together with use concentration information to estimate dermal exposures to MCCP in MWFs. These data give RWC estimates of 180 mg/day MCCP for water-based MWFs and 25,000 mg/day MCCP for oil-based MWFs.

Table 4:7 Summary of occupational dermal exposure data for risk characterisation

Industry		Dermal exposure			
		Exposure (mg/cm²/day)	Area Exposed (cm²)	Source	RWC (mg/day)
Manufacture of MCCPS		0.1 – 1	210	EASE	210
PVC formulating	PVC plastisol manufacture	0.1 – 1	420	EASE	420
	plastisol use	0.03 – 0.3	420	EASE	126
	calendering of plasticised PVC	0.1 – 1	420	EASE	420
	compounding of plasticised PVC	0 – 0.1	840	EASE	84
	extrusion and moulding of plasticised PVC	0 – 0.1	210	EASE	21
Manufacture of paints containing MCCPs		0 – 0.1	420	EASE	42
Use of paints containing MCCPs (spraying)		0.015 – 0.15	840	EASE	126
Manufacture of sealants containing MCCPs		0 – 0.1	420	EASE	42
Rubber manufacture		0.1 – 1	420	EASE	420
Manufacture of MWFs containing MCCPs		0 – 0.1	420	EASE	42
Use of water-based MWFs containing MCCPs		36,000 mg MWF	both hands	Derived	180
Use of oil-based MWFs containing MCCPs		36,000 mg MWF	both hands	Derived	25,000
Manufacture of fat liquor in leather treatment		0 – 0.1	420	EASE	42
Use of fat liquor in leather treatment		0 – 0.1	840	EASE	84
Manufacture of carbonless copy paper		0 – 0.1	420	EASE	42

4.1.1.2 Consumer exposure

C_{14}-C_{17} chlorinated paraffins are not sold directly as consumer products (see section 2.2). They are found in the following materials to which consumers could be exposed:

- In fat liquors used in leather processing,
- As an additive to adhesive and sealants,
- Use in rubber and plastics,
- As a plasticiser in paints,

- As an extreme pressure additive in metal working fluids;

These are largely for industrial or commercial applications. However, there may be the potential for indirect consumer exposure and this is considered below. Investigations by the rapporteur indicate that exposure is negligible for some uses. However, exposure estimates are provided for the wearing of leather clothes and for the use of metal working fluids. The scenarios presented below are reasonable worst case exposures.

4.1.1.2.1 Leather clothes

There are varying reports regarding the use of MCCP usage in leather treatment. It has been reported that about 1048 tonnes of C_{14}-C_{17} chlorinated paraffins were used in the leather industry in 1997, showing a decline since 1994 when 1614 tonnes were used (CEFIC, 1999). Conversely, it has also been reported that there is no usage of MCCP in fat liquors in the leather producing industries (personal communication). However, from the available data, about 50% of the leather formulations are exported outside the EU. It is employed within the EU as a constituent of some fat liquors. MCCPs are used in conjunction with sulphated or sulphonated oils, chlorosulphonated paraffins, natural fats and oils. They improve surface sheen and help impart "wear and tear" and light fading resistance when used in some applications. These applications tend to occur in the top end quality range.

Inhalation exposure during the use of leather garments is considered to be negligible. The only potential realistic route of exposure is the dermal route, if such garments were worn next to the skin. It is possible to estimate a worst case dermal exposure scenario for leather garments which are worn regularly. An exposure scenario is presented below, for a consumer wearing leather coat and trousers.

Dermal exposure scenario for the use of chlorinated paraffins in leather coats and trousers

Around 3% of fat liquor is present in the formulation that is added to raw leather, of which approximately 10% is MCCPs. Around 2-2.5% of the added formulation is taken up by the leather. Therefore the amount of MCCPs present in the leather is up to about 0.0075% (information supplied by industry).

Assuming that a leather coat and trousers are worn next to the skin and weigh a total of 5 kg, there will be a maximum of 0.375 g of MCCPs in the clothing. Assuming that all of this migrates out of the leather over a period of one year, then the maximum daily exposure will be 0.375 g/365 = 1 mg/day.

This assumes that the leather clothing is worn continuously next to the skin, without a lining or other garments and that the migration rate is as high as suggested. However, if the garments are dry-cleaned, then most if not all of the chlorinated paraffins will be removed in this procedure (information from UK leather industry). Indeed, following dry-cleaning, oils (which are unlikely to contain chlorinated paraffins) are put back into the garments to maintain their suppleness.

A worst case daily exposure of 1 mg MCCPs/day will be taken forward to the risk characterisation. However, it should be noted that for the reasons given above, this is likely to significantly over-estimate actual exposure.

4.1.1.2.2 Adhesives and sealants

Chlorinated paraffins, including medium chain chlorinated paraffins (typically 55-65% chlorine content), are used as plasticisers/flame retardants in adhesive/sealants used for a variety of applications. Typical amounts are up to about 15 % by weight of the sealants (section 2.2.1.3). The sealants are likely to be applied by a caulking gun in larger applications which would lead to limited dermal exposure. Given the infrequency and short duration of use by a consumer (fitting a window frame for example), that they form a small proportion of the final product, and the physicochemical properties of very low volatility (around 2.2×10^{-3} Pa, see section 1.3), the inhalation exposure will be negligible, even assuming 100% absorption.

4.1.1.2.3 Use in rubber and plastics

Rubber goods

MCCP is used at up to 15% of the total weight of the rubber (Section 2.2.2.1). The treated rubber finds uses in conveyor belts (see section 4.1.1.1.6) and in building and automotive applications. Due to the nature of the products, consumer contact will be very unlikely. Exposure from the building and automotive applications of MCCPs are not applicable for the consumer because consumers do not come into contact with these products.

Plastic goods

MCCPs act as (secondary) plasticisers in PVC (typically 40-45% Cl) and other plastics, (section 2.2.1.3). They also have flame retardant applications but they are not specifically added for this purpose, instead being generally regarded as flame retardant plasticisers.

Door frame plastics for underground vehicles such as those used in mines, may be made from plastics with an MCCP content, due to its fire resistant property and there is no evidence to suggest there is any exposure to MCCPs (personal communication). Typical applications include garden hoses, floorings etc. These types of PVC products are not used for food contact purposes so exposure via the mouth to leaching plasticiser or flame retardant is not considered here. Additionally, leaching rates are likely to be minimal due to the amounts used and the physicochemical properties of the MCCPs, including low volatility and low solubility in water. Inhalation and dermal exposure to consumers from such products may also therefore be considered negligible.

Hence, there are no exposure values from this use to be taken forward to the risk characterisation.

4.1.1.2.4 Paints

Medium chain length chlorinated paraffins, with about 50-58 % chlorine content are used as plasticisers in some paints, varnishes and coatings. They are used at between 4-15 % w/w of the total paint. The main areas of application are mainly for industrial and commercial use and not in the kinds of paints or coatings commonly purchased by consumers. One exception is in the use of some paints used for coating swimming pools. The exposure from this source has not been measured but is thought to be negligible (personal communication).

Hence, there are no exposure values from this use to be taken forward to the risk characterisation.

4.1.1.2.5 Extreme pressure additives (metal cutting/working fluids)

Medium chain chlorinated paraffins are used in a wide variety of cooling and lubricating fluids used during metal cutting and metal working operations (section 2.2.3). These are industrial operations and no precise information is available about whether MCCPs are used in such fluids outside of the workplace. It is possible that metal working fluids containing these substances could be used in lathes for home or voluntary group use (e.g. car or engine restoring). However, there are no data to support this and such uses are likely to be infrequent and exposures will be for a short time period compared to an industrial worker. An individual working at home is unlikely to have the same degree of prolonged exposure that would arise over a full working day, nor would there be exposure to mists generated by a number of machines working simultaneously and/or continuously. In addition, systems used by consumers will have lower coolant capability than those used industrially, again reducing the potential exposure in comparison with workers. Therefore, both the level and duration of exposure would be much less than in an industrial setting and consequently dermal and inhalation exposure would be very much lower. Consequently, for consumers, the exposure information available for the workplace is likely to be an overestimate. The degree of overestimation is uncertain, but continuous exposure for 8 hours daily for a working week is unlikely. For the purposes of risk assessment, exposure will be considered as singular events averaged over a day rather than repeated exposures.

In section 4.1.1.1.7, exposure data indicated that a reasonable worst case daily inhalation intake of MCCP during the use of oil based metal working fluids is 5 mg/day (based on an 8-hour TWA of 0.5 $mg.m^{-3}$, 8-hour shift and a breathing rate of 1.25 $m^3.hour^{-1}$); during the use of water based metal working fluids, a reasonable worst case estimate is 0.9 mg/day.

To take account of the factors that are likely to lead to lower exposures for consumers, this worker daily inhalation intake will be reduced by a factor of 10 even taking into account that adequate ventilation is unlikely to be available in the consumer setting. It must be stressed that the use of this factor of 10 is judgemental to take account of the reduced duration and frequency of consumer exposure. It takes also account of the reduced airborne levels that inevitably would occur in the consumer scenario where there are not several machines working simultaneously and/or continuously. Thus, using the highest workplace daily inhalation intake of 5 mg/day, the equivalent intake for a consumer would be 0.5 mg/event .

Summary

Most applications of MCCP are not designed for consumer contact, and therefore exposures are clearly negligible. The only consumer exposure scenarios for which there may be exposure to MCCP are the use of metal working fluids and the wearing of leather clothes treated with MCCPs. For the use of metal working fluids, the estimated exposure is 0.5 mg/event, however, any such exposure from this scenario will be infrequent and should be considered as a single event, rather than repeated exposure. The wearing of leather clothes results in dermal exposure only (estimate of 1 mg/day); any such exposure from this scenario should be regarded as potentially a repeated exposure.

4.1.1.3 Indirect exposure via the environment

Medium-chain chlorinated paraffins have several uses that could result in releases to air and water. The uptake of medium-chain chlorinated paraffins from water by marine organisms, although it does occur, may be less than the very high log Kow values for this group of

substances would indicate. The potential for bioaccumulation in the environment appears to decrease with increasing chlorine in the group. This is discussed further in Section 3.1.0.5.

The EUSES model has been used to estimate various concentrations of medium-chain chlorinated paraffins in food, air and drinking water. Default calculations using the EUSES model identified uptake into root crops from soil as potentially a significant route for exposure of man through food. In order to refine the calculations for this source of exposure, a study investigating the actual accumulation of medium-chain chlorinated paraffins in roots of carrot (*Daucus carota*) has been carried out (Thompson *et al.*, 2005).

This study was carried out using a ^{14}C-labelled 52.5% wt. chlorinated n-pentadecane that was produced as a mixture with unlabelled C_{14-17} 52.5% wt. chlorinated paraffin. The mean bioaccumulation factor (defined as the concentration in root (mg/kg fresh weight)/concentration in soil (mg/kg wet weight)) was determined to be 0.045 over days 50 to 70 of the experiment. Overall the bioaccumulation factor based on the carrot study results is around 136 times smaller than the equivalent bioaccumulation determined for medium-chain chlorinated paraffins using the TGD/EUSES default methods. Using the methods outlined in the TGD, this bioaccumulation factor is equivalent to a value for the $K_{plant\text{-}water}$ of 330 m^3/m^3 (this is the partition coefficient between plant tissue and water). This value has been used in the EUSES 2.0.3 program in place of the default value to obtain a more reliable estimate of the resulting concentrations in root crops (and hence other parts of plants such as leaves) and so the likely exposure of man via the environment.

The resulting concentrations in the food chain for human exposure using this value for the $K_{plant\text{-}water}$ are summarised in **Table 4.8** and the estimated daily human intakes from environmental sources are summarised in **Table 4.9**. The calculations used regional concentrations based on measured data of 0.1 µg/l for surface water and 0.088 mg/kg wet wt. for agricultural soil (as used in the environmental parts of the risk assessment). The measured data are taken from representative industrial areas in the United Kingdom and the agricultural soil samples were from sites that were known to receive sewage sludge from treatment plants where chlorinated paraffins were known to be released (further details of these sites are given in EU (2005)).

In the EUSES model, a log Kow value of 7 has been used as being representative for the group as a whole. A fish bioconcentration factor of 1,087 l/kg (see Section 3.1.0.5) has been used in the model to estimate the concentration in wet fish (no biomagnification factor (BMF) has been used in the calculations). For other parts of the food chain, particularly leaf crops, meat and milk, EUSES estimates the concentrations in these using methods that rely on log Kow as no equivalent measured accumulation factors exist for medium-chain chlorinated paraffin. It is not known if these methods would be applicable to medium-chain chlorinated paraffins.

It should also be noted that the change to the K_{plant_water} coefficient value also affects the predicted concentrations in plant leaves and hence meat and milk.

Table 4:8 Estimated concentrations in food for human daily intake

Scenario	Step	Estimated concentration in human intake media[b]						
		Wet fish (mg/kg)	Root crops (mg/kg)	Leaf crops (mg/kg)	Drinking water (mg/l)	Meat (mg/kg)	Milk (mg/kg)	Air (mg/m^3)
Production	**Site A**	0.11	negligible[a]	negligible[a]	2.6×10^{-5}	negligible[a]	negligible[a]	negligible[a]
	Site B	0.19	negligible[a]	negligible[a]	4.4×10^{-5}	negligible[a]	negligible[a]	negligible[a]
	Site C	0.26	negligible[a]	negligible[a]	6.0×10^{-5}	negligible[a]	negligible[a]	negligible[a]
	Site D	0.11	negligible[a]	negligible[a]	2.5×10^{-5}	negligible[a]	negligible[a]	negligible[a]
Use in PVC – plastisol coating	**Compounding - O**	0.15	0.024	7.1×10^{-4}	5.0×10^{-5}	0.014	4.3×10^{-3}	negligible[a]
	Conversion – O	0.42	0.15	6.1×10^{-3}	3.2×10^{-4}	0.085	0.027	4.8×10^{-5}
	Compounding/conversion - O	0.46	0.17	6.1×10^{-3}	3.6×10^{-4}	0.092	0.029	4.8×10^{-5}
Use in PVC – extrusion/other	**Compounding - O**	0.26	0.076	2.3×10^{-3}	1.6×10^{-4}	0.04	0.013	1.8×10^{-5}
	Compounding – PO	0.94	0.40	9.4×10^{-3}	8.4×10^{-4}	0.19	0.059	7.4×10^{-5}
	Compounding – C	0.18	0.037	1.4×10^{-3}	7.9×10^{-5}	0.022	7.1×10^{-3}	1.1×10^{-5}
	Conversion – O	0.57	0.22	8.8×10^{-3}	4.7×10^{-4}	0.13	0.040	7.0×10^{-5}
	Conversion – PO	0.61	0.24	9.4×10^{-4}	5.1×10^{-4}	0.13	0.042	7.4×10^{-5}
	Conversion – C	0.53	0.20	8.1×10^{-3}	4.3×10^{-4}	0.11	0.036	6.4×10^{-5}
	Compounding/conversion – O	0.73	0.30	0.010	6.3×10^{-4}	0.16	0.050	8.2×10^{-5}
	Compounding/conversion - PO	1.4	0.63	0.018	1.3×10^{-3}	0.31	0.099	1.4×10^{-4}
	Compounding/conversion - C	0.60	0.24	8.8×10^{-3}	5.0×10^{-4}	0.13	0.041	7.0×10^{-5}
Use in plastics/rubber	**Compounding**	0.19	0.040	1.2×10^{-3}	8.6×10^{-5}	0.022	6.9×10^{-3}	9.2×10^{-6}
	Conversion	0.37	0.13	5.2×10^{-3}	2.7×10^{-4}	0.072	0.029	4.1×10^{-5}
	Compounding/conversion	0.44	0.16	5.6×10^{-3}	3.4×10^{-4}	0.087	0.028	4.5×10^{-5}

Table 4.8 continued

Scenario	Step	Estimated concentration in human intake media[b]						
		Wet fish (mg/kg)	Root crops (mg/kg)	Leaf crops (mg/kg)	Drinking water (mg/l)	Meat (mg/kg)	Milk (mg/kg)	Air (mg/m³)
Use in sealants	Formulation and use	negligible[a]	negligible[a]	negligible[a]	negligible[a]	negligible[a]	negligible[a]	negligible[a]
Use in paints	Formulation	0.36	0.12	2.2×10^{-3}	2.6×10^{-4}	0.054	0.017	1.7×10^{-5}
	Industrial application	0.21	0.050	7.1×10^{-4}	1.1×10^{-4}	0.023	7.2×10^{-3}	negligible[a]
	Domestic application	0.11	4.0×10^{-3}	7.1×10^{-4}	2.5×10^{-5}	7.2×10^{-3}	2.3×10^{-3}	negligible[a]
Use in metal cutting/working fluids	Formulation	1.5	0.65	7.3×10^{-4}	1.4×10^{-3}	0.23	0.071	negligible[a]
	Use in oil-based fluids (large)	0.66	0.26	7.2×10^{-4}	5.6×10^{-4}	0.094	0.030	negligible[a]
	Use in oil-based fluids (small)	0.61	0.24	7.2×10^{-4}	5.1×10^{-4}	0.086	0.027	negligible[a]
	Use in emulsifiable fluids	0.15	0.024	7.1×10^{-4}	5.0×10^{-5}	0.014	4.3×10^{-3}	negligible[a]
	Use in emulsifiable fluids – intermittent release	0.94[c]	2.1[c]	7.7×10^{-4} [c]	4.4×10^{-3} [c]	0.70[c]	0.22[c]	negligible[a]
Use in leather fat liquors	Formulation	0.28	0.083	0.011	1.8×10^{-4}	0.089	0.028	8.6×10^{-5}
	Use – complete processing of raw hides	1.6	0.71	7.3×10^{-4}	1.5×10^{-3}	0.24	0.077	negligible[a]
	Use – processing of wet blue	6.1	2.8	7.9×10^{-4}	6.0×10^{-3}	0.95	0.30	negligible[a]
Use in carbonless copy paper	Paper recycling	0.35	0.14	7.1×10^{-4}	3.0×10^{-4}	0.053	0.017	negligible[a]
Regional sources		0.11	4.0×10^{-3}	7.1×10^{-4}	2.5×10^{-5}	7.2×10^{-3}	3.3×10^{-3}	5.6×10^{-6}

Note: a) The process makes no significant contribution to the concentration in food/air. b) Figures are calculated based on the measured regional water and soil concentrations of 0.1 µg/l and 0.088 mg/kg wet wt. respectively. c) Assumes dilution of sewage sludge at wwtp before application to soil (see EU, 2005). O = Open systems; PO = Partially open systems; C = Closed systems.

Table 4:9 Estimated human daily intake of medium-chain chlorinated paraffins via environmental routes

Scenario	Step	Estimated human daily intake (mg/kg body weight/day)[c]							
		Wet fish	Root crops	Leaf crops	Drinking water	Meat	Milk	Air	Total
Production	Site A	1.8×10^{-4}	-	-	7.5×10^{-7}	-	-	-	1.8×10^{-4}
	Site B	$3.1\times10^{-}$	-	-	1.3×10^{-6}	-	-	-	3.1×10^{-4}
	Site C	4.3×10^{-4}	-	-	1.7×10^{-6}	-	-	-	4.3×10^{-4}
	Site D	1.8×10^{-4}	-	-	7.1×10^{-7}	-	-	-	1.8×10^{-4}
Use in PVC – plastisol coating	Compounding - O	2.5×10^{-4}	1.3×10^{-4}	1.2×10^{-5}	1.4×10^{-6}	5.9×10^{-5}	3.5×10^{-5}	1.6×10^{-6}	4.9×10^{-4}
	Conversion – O	6.8×10^{-4}	8.2×10^{-4}	1.0×10^{-4}	9.0×10^{-6}	3.7×10^{-4}	2.2×10^{-4}	1.4×10^{-5}	2.2×10^{-3}
	Compounding/conversion - O	7.5×10^{-4}	9.3×10^{-4}	1.0×10^{-4}	1.0×10^{-5}	3.9×10^{-4}	2.3×10^{-4}	1.4×10^{-5}	2.4×10^{-3}
Use in PVC – extrusion/other	Compounding - O	4.3×10^{-4}	4.2×10^{-4}	3.9×10^{-5}	4.6×10^{-6}	1.7×10^{-4}	1.0×10^{-4}	5.2×10^{-6}	1.2×10^{-3}
	Compounding – PO	1.5×10^{-3}	2.2×10^{-3}	1.6×10^{-4}	2.4×10^{-5}	8.0×10^{-4}	4.7×10^{-4}	2.1×10^{-5}	5.2×10^{-3}
	Compounding – C	2.9×10^{-4}	2.1×10^{-4}	2.5×10^{-5}	2.3×10^{-6}	9.6×10^{-5}	5.7×10^{-5}	3.3×10^{-6}	6.8×10^{-4}
	Conversion – O	9.4×10^{-4}	1.2×10^{-3}	1.5×10^{-4}	1.4×10^{-5}	5.4×10^{-4}	3.2×10^{-4}	2.0×10^{-5}	3.2×10^{-3}
	Conversion – PO	1.0×10^{-3}	1.3×10^{-3}	1.6×10^{-4}	1.5×10^{-5}	5.7×10^{-4}	3.4×10^{-4}	2.1×10^{-5}	3.4×10^{-3}
	Conversion – C	8.7×10^{-4}	1.1×10^{-3}	1.4×10^{-4}	1.2×10^{-5}	4.9×10^{-4}	2.9×10^{-4}	1.8×10^{-5}	2.9×10^{-3}
	Compounding/conversion – O	1.2×10^{-3}	1.6×10^{-3}	6.8×10^{-4}	1.8×10^{-5}	6.8×10^{-4}	4.0×10^{-4}	2.4×10^{-5}	4.1×10^{-3}
	Compounding/conversion - PO	2.4×10^{-3}	3.5×10^{-3}	3.1×10^{-4}	3.8×10^{-5}	1.3×10^{-3}	7.9×10^{-4}	4.1×10^{-5}	8.3×10^{-3}
	Compounding/conversion - C	9.9×10^{-4}	1.3×10^{-3}	1.5×10^{-4}	1.4×10^{-5}	5.6×10^{-4}	3.3×10^{-4}	2.0×10^{-5}	3.4×10^{-3}
Use in plastics/rubber	Compounding	3.1×10^{-4}	2.2×10^{-4}	2.0×10^{-5}	2.5×10^{-6}	9.4×10^{-5}	5.5×10^{-5}	2.6×10^{-6}	7.0×10^{-4}
	Conversion	6.0×10^{-4}	6.9×10^{-4}	8.9×10^{-5}	7.6×10^{-6}	3.1×10^{-4}	1.8×10^{-4}	1.2×10^{-5}	1.9×10^{-3}
	Compounding/conversion	7.3×10^{-4}	8.9×10^{-4}	9.7×10^{-5}	9.8×10^{-6}	3.8×10^{-4}	2.2×10^{-4}	1.3×10^{-5}	2.3×10^{-3}

Table 4.9 continued

Scenario	Step	Estimated human daily intake (mg/kg body weight/day)[c]							
		Wet fish	Root crops	Leaf crops	Drinking water	Meat	Milk	Air	Total
Use in sealants	Formulation and use	-	-	-	-	-	-	-	negligible[b]
Use in paints	Formulation	5.9×10^{-4}	6.7×10^{-4}	3.7×10^{-5}	7.4×10^{-6}	2.3×10^{-4}	1.4×10^{-4}	4.9×10^{-6}	1.7×10^{-3}
	Industrial application	3.4×10^{-4}	2.8×10^{-4}	1.2×10^{-5}	3.0×10^{-6}	9.7×10^{-5}	5.7×10^{-5}	1.6×10^{-6}	7.9×10^{-4}
	Domestic application	1.8×10^{-4}	2.2×10^{-5}	1.2×10^{-5}	7.1×10^{-7}	3.1×10^{-5}	1.8×10^{-5}	1.6×10^{-6}	2.6×10^{-4}
Use in metal cutting/working fluids	Formulation	2.4×10^{-3}	3.6×10^{-3}	1.3×10^{-5}	4.0×10^{-5}	9.7×10^{-4}	5.7×10^{-4}	1.6×10^{-6}	7.6×10^{-3}
	Use in oil-based fluids (large)	1.1×10^{-3}	1.4×10^{-3}	1.2×10^{-5}	1.6×10^{-5}	4.0×10^{-3}	2.4×10^{-4}	1.6×10^{-6}	3.2×10^{-3}
	Use in oil-based fluids (small)	1.0×10^{-3}	1.3×10^{-3}	1.2×10^{-5}	1.5×10^{-5}	3.7×10^{-4}	2.2×10^{-4}	1.6×10^{-6}	2.9×10^{-3}
	Use in emulsifiable fluids	2.5×10^{-4}	1.3×10^{-4}	1.2×10^{-5}	1.4×10^{-6}	5.9×10^{-5}	3.5×10^{-5}	1.6×10^{-6}	4.9×10^{-4}
	Use in emulsifiable fluids – intermittent release[a]	1.5×10^{-3}	0.011	1.3×10^{-5}	1.3×10^{-4}	3.0×10^{-3}	1.8×10^{-3}	1.6×10^{-6}	0.018
Use in leather fat liquors	Formulation	4.5×10^{-4}	4.5×10^{-4}	1.9×10^{-4}	5.0×10^{-6}	3.8×10^{-4}	2.3×10^{-4}	2.5×10^{-5}	1.7×10^{-3}
	Use – complete processing of raw hides	2.6×10^{-3}	3.9×10^{-3}	1.3×10^{-5}	4.3×10^{-5}	1.1×10^{-3}	6.2×10^{-4}	1.6×10^{-6}	8.2×10^{-3}
	Use – processing of wet blue	0.010	0.016	1.4×10^{-5}	1.7×10^{-4}	4.1×10^{-3}	2.4×10^{-3}	1.6×10^{-6}	0.032
Use in carbonless copy paper	Paper recycling	5.8×10^{-4}	7.8×10^{-4}	1.2×10^{-5}	8.6×10^{-6}	2.3×10^{-4}	1.4×10^{-4}	1.6×10^{-6}	1.8×10^{-3}
Regional sources		1.8×10^{-4}	2.2×10^{-5}	1.2×10^{-5}	7.1×10^{-7}	3.1×10^{-5}	1.8×10^{-5}	1.6×10^{-6}	2.6×10^{-4}

Note: a) Intermittent release – likely to occur 2-6 times/year only.

b) Process does not contribute significantly to estimated daily intake.

c) Figures are calculated using a measured regional surface water and soil concentration of 0.1 • g/l and 0.088 mg/kg wet weight respectively.

O = Open systems; PO = Partially open systems; C = Closed systems.

The exposure data from **Table 4.9** to be taken through to the risk characterisation (see section 4.1.3.3) are as follows:

Local exposure: 0.032 mg/kg/day (equivalent to an internal exposure of 0.016 mg/kg/day based on 50% oral and inhalation absorption): use in leather fat liquors.

Regional exposure: $2.6x10^{-4}$ mg/kg/day (equivalent to an internal exposure of $1.3x10^{-4}$ mg/kg/day based on 50% oral and inhalation absorption).

Few measured levels for C_{14-17} chlorinated paraffins in food exist. The available data are summarised in Section 3.1.4.2.

In one survey (Campbell and McConnell, 1980), the average levels of C_{10-20} chlorinated paraffins found in human foodstuffs were 0.3 mg/kg in dairy products, 0.15 mg/kg in vegetable oils and derivatives, 0.005 mg/kg in fruit and vegetables and not detected (<0.05 mg/l) in drinks. Levels of C_{10-20} chlorinated paraffins of up to 12 mg/kg have been measured in shell fish close to sources of discharge (Campbell and McConnell, 1980). As these measured levels represent the total C_{10-20} chlorinated paraffins, the medium-chain (C_{14-17}) will contribute to, but will not be the only source of, the level of chlorinated paraffin measured.

Levels of total (C_{10-24}) chlorinated paraffins in food and fish have also been reported by Greenpeace (1995). The mean levels reported (on a fat weight basis) were 271 µg/kg fat in mackerel, 62 µg/kg fat in fish oil (herring), 98 µg/kg fat in margarine containing fish oil, 69 µg/kg fat in pork, 74 µg/kg fat in cows milk and 45 µg/kg fat in human breast milk. Further information on the breast milk sampling was obtained from the author of the report. The mean level in human breast milk was derived from pooled samples of two groups of women, one of non-fish eaters (n=2) and one of fish eaters (n=6). The average chlorine content of the chlorinated paraffins detected was around 33%, although a value of 50% was assumed in the calculation of chlorinated paraffin content from the measured levels of n-alkanes. Medium chain length chlorinated paraffins were thought to make up between 6 and 29% of the total chlorinated paraffins found in biota samples as a whole. For the breast milk samples, an actual content of 10 and 22% can be deduced for the groups of non-fish eaters and fish eaters respectively. Taking an average value for MCCP content of about 17%, the concentrations of medium chain length chlorinated paraffins present can be estimated from the data as 46 µg/kg fat in mackerel, 12 µg/kg fat in fish oil, 28 µg/kg fat in margarine, 11 µg/kg fat in pork, 16 µg/kg fat in cows milk and 7 µg/kg fat in mothers milk. Alternatively, based on the highest MCCP content (29% for food and fish and 22% for human breast milk) as a worst case estimate, the concentrations of MCCPs present in food and fish would be 80 µg/kg fat in mackerel, 18 µg/kg fat in fish oil, 28 µg/kg fat in margarine, 10 µg/kg fat in pork, 21 µg/kg fat in cows milk and 9 µg/kg fat in mothers milk.

A recent Industry sponsored study has found medium-chain chlorinated paraffins to be present in human breast milk samples from the United Kingdom (Thomas and Jones, 2002). In all, 22 breast milk samples were analysed (8 from Lancaster and 14 from London, apparently randomly chosen) and medium-chain chlorinated paraffins were found in one sample from London at a concentration of 61 µg/kg fat but was below the limit of detection in the remaining 21 samples. The detection limit of the method varied with sample size but ranged from16 µg/kg fat to 740 µg/kg fat (mean level of 100 µg/kg fat). It is noted that these detection limits are higher than the measured levels in breast milk reported in the Greenpeace study. This suggests that the analytical method used in Thomas and Jones, 2002 was less sensitive than that used in the Greenpeace study. The fact that MCCPs were only found in

1/22 samples does not mean that it was not present in the other samples at levels below the detection limit.

Thomas et al (2003) have recently carried out a further investigation of the levels of medium-chain chlorinated paraffins in human breast milk samples from the United Kingdom. In this study, relatively large samples of human milk-fat were collected from the London (20 samples) and Lancaster (5 samples) areas of the United Kingdom between late 2001 and June 2002. It should be noted that some of London samples were taken from the same mother, such that 20 samples were from 13 mothers; five samples were provided from one mother over a three-day period, two samples were provided from another mother over a two-day period, a further two samples were provided by another mother over a five-day period, and a further two samples were provided by another mother over an unknown period. The analysis was carried out using high resolution gas chromatograph (HRGC) coupled with electrochemical negative ionisation (ECNI)-high resolution mass spectrometry (HRMS) detection. The analytical standard used was a commercial medium-chain chlorinated paraffin (C_{14-17}, 52% wt. Cl). In addition to total medium-chain chlorinated paraffins, twelve samples (four from Lancaster and eight from London) were also analysed in more detail to determine the various types of chlorinated paraffin (in terms of chlorine number and carbon chain length distributions) present in the samples.

Medium-chain chlorinated paraffins were found to be present in all 25 samples analysed. The median, 97.5th percentile value and range of concentrations found were 21 µg/kg lipid, 130.9 µg/kg lipid and 6.2-320 µg/kg lipid respectively. The levels found in the samples from Lancaster were not thought to be significantly different from the levels found in the samples from London. The more detailed analysis of the types of chlorinated paraffins present indicated that, in general, the pattern of medium-chain chlorinated paraffins found in the milk-fat samples was heavily skewed towards the C_{14}-chain length compared to the distribution found in the medium-chain chlorinated paraffin used as analytical standard. The C_{14-17}, 52% wt Cl substance used as an analytical standard was sourced from the United States. Thomas et al. (2003) indicated that discussions between European and US producers of medium-chain chlorinated paraffins had identified a possible difference in the carbon chain distribution of their products, with the products produced in Europe more likely to have a distribution skewed towards the shorter chain length components compared to a more Gaussian distribution in products in the United States. This is a possible explanation for the findings. Other explanations include different volatilities between the different components affecting transport from source uses to human exposure media and differences in human absorption efficiencies and in metabolism for the different components. It is not possible to determine which of these, or other, possibilities accounts for the findings.

Overall, given that of the three studies that are now available on levels of MCCPs in breast milk, the most recent one, Thomas et al., 2003 is a very well conducted study, a risk characterisation will be performed using the 97.5th percentile level of 130.9 µg/kg fat identified from this study.

In addition to human breast milk, Thomas and Jones (2002) also determined the levels of medium-chain chlorinated paraffins in a single sample of cow's milk from Lancaster and single butter samples from various regions of Europe (Denmark, Wales, Normandy, Bavaria, Ireland, and Southern and Northern Italy). Medium-chain chlorinated paraffins were present in the cow's milk sample at a concentration of 63 µg/kg fat and were found in the butter samples from Denmark at 11 µg/kg fat, Wales at 8.8 µg/kg fat and Ireland at 52 µg/kg fat. MCCPs were not detected in any other sample. The detection limit for the other butter

samples ranged between 8.0 and 11 µg/kg fat. Butter is regularly used as a convenient way of obtaining milk-fat samples and therefore the MCCPs levels measured in these butter samples can be considered equivalent to the levels present in cow's milk. For risk characterisation, the highest measured level of MCCPs in cow's milk/butter will be used. This value is 63µg/kg fat.

4.1.1.4 Combined exposure

For combined exposure, consideration should be given to a consumer exposed to MCCP and who is also exposed indirectly via the environment. However, consumer exposure is considered to be an infrequent event rather than repeated daily exposure. Therefore combined daily exposures are not relevant and will not be considered in this risk assessment.

4.1.2 Effects assessment: hazard identification and dose (concentration) - response (effect) assessment

Introduction

As indicated earlier (see Section 1), medium-chain chlorinated paraffins (MCCPs) are produced by the chlorination of straight-chain hydrocarbons of 14-17 carbon atoms in length. The degree of chlorination can vary generally from 20-70% by weight, although most commercially available products fall in the range 40-70%. Because of the variation in combinations of carbon chain length and degree of chlorination, a wide range of products are available with an average chain length usually being specified by the manufacturer and a chlorination degree being random but defined by weight. Some studies describe the use of a MCCP of defined carbon chain length (e.g. C_{15} or C_{16}). This seems unlikely as the paraffins produced during a 'cracking' process would be distilled off at temperature ranges that would lead to a mixed paraffin (e.g. C_{14-17}, perhaps predominantly C_{15}).

Owing to the wide range of combinations of chain length and chlorination available, it is not reasonable to expect there to be a full dataset of toxicology information that would cover each possibility. Hence, where data are not available on one particular MCCP product it may be possible to read across to information available from another MCCP product. Furthermore, short-chain chlorinated paraffins (SCCPs - C_{10-13}, 40-70% chlorination) are also closely related to MCCPs, and read-across from SCCP data may also be reasonable, particularly if the only difference is in the number of carbon atoms in the backbone of the molecule. MCCPs are produced by the chlorination of straight-chain hydrocarbons of 14-17 carbon atoms in length. The degree of chlorination can vary generally from 20-70% by weight, although most commercially available products fall in the range 40-70%. This compares to SCCPs which are produced in a similar way but differ inasmuch as they are composed of chlorinated straight-chain hydrocarbons of 10-13 carbon atoms also with 40-70% chlorination. Thus, other than a small number of carbon atoms in the main 'backbone' of the molecule, there is little structural difference between MCCPs and SCCPs.

SCCPs were reviewed recently as part of the EU ESR programme (SCCP ESR Risk Assessment Report, 2000). Typical physicochemical data for C_{10-13} SCCPs (SCCP ESR Risk Assessment Report, 2000) include: vapour pressure $2x10^{-2}$ Pa (50% chlorination, at 40 °C), measured log P_{ow} 4.4-6.9 (49% chlorination), 5.7-8.7 (70% chlorination), water solubility (59% chlorination) 0.15-0.47 mg/l (at 20 °C). This compares with MCCPs (see Section 1.3): vapour pressure $2.7x10^{-4}$ Pa (52% chlorination, at 20°C), measured log P_{ow} 5.5-8 (52% chlorination), water solubility ~0.027 mg/l. As the degree of chlorination increases so does the viscosity at any given temperature (concomitantly, vapour pressure decreases) giving the potential for considerable overlap in the range of vapour pressures of SCCPs and MCCPs (see Section 1.3). Typical relevant physicochemical data for C_{10-13} SCCPs and C_{14-17} MCCPs are tabulated below:

Physicochemical property	SCCPs	MCCPs
Physical state	Liquid	Liquid
Boiling point	> 200°C	> 200°C
Density (at 25°C)	1.2-1.6 g/cm^3	1.1-1.3 g/cm^3
Vapour pressure	2.1x10^{-2}Pa(50% chlorination, 40°C)	2.7x10^{-4}Pa(52% chlorination, 20°C)
Log Pow	4.4-6.9 (49% chlorination)	5.5-8.0 (45% chlorination)
Water solubility (at 20°C)	0.15-0.47mg/l (59% chlorination)	0.005-0.027 mg/l

Broadly, it can be seen that MCCPs have a lower vapour pressure but they seem to have generally similar physicochemical properties.

For many toxicological endpoints (where such data exist), there is a similarity, at least in qualitative terms in the profile of information obtained on MCCPs and SCCPs. Relevant toxicological data for C_{10-13} SCCPs and C_{14-17} MCCPs are tabulated below:

Toxicological property	SCCPs	MCCPs
Acute toxicity	Low oral and dermal toxicity	Low oral toxicity; no dermal data
Irritation	No skin and eye irritation	No skin and eye irritation
Sensitisation	Not a skin sensitiser	Not a skin sensitiser
Repeated dose toxicity	Target organs: liver, thyroid and kidney	Target organs: liver, thyroid and kidney
Mutagenicity	Not mutagenic	Not mutagenic
Carcinogenicity	Liver, thyroid and kidney tumours	No data
Reproductive toxicity - fertility	No effects on fertility	No effects on fertility
Reproductive toxicity - development	No effects on development	No effects on development
Reproductive toxicity – effects mediated via lactation	No data	Effects on the offspring mediated via lactation

Overall, it seems reasonable to suggest that a 'read-across' of toxicological data from SCCPs is valid where none exist for the MCCPs.

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

Inhalation

No studies are available.

Oral

<u>Studies in rats</u>

As part of a repeated-exposure study in which groups of 25 male and 25 female F344 rats received 0, 10 or 625 mg.kg^{-1}.day^{-1} of a mixed C_{14-17} chlorinated paraffin (52% chlorination)

in the diet for 13 weeks, there was an assessment of toxicokinetics (IRDC, 1984 - see also Section 4.1.2.6). At the end of the 13-week treatment period, 18 rats/group received a single oral gavage dose of either 10 or 625 $mg.kg^{-1}$ [8-^{14}C] chlorinated n-pentadecane mixed with corn oil (this marker substance is anticipated to have similar absorptive properties to the MCCPs used in the previous 13 weeks as it is itself a component of the MCCPs). From the original 25 animals per group, 7 animals per group were killed and discarded with no further investigations to leave 18 per group for the toxicokinetic studies. Animals were housed in groups of 3 in glass metabolism cages. During the first 12 hours after the single oral administration of radiolabelled material urine, faeces and CO_2 were collected from 3 rats per dose group. These animals were then killed and samples of whole blood, the contents of the alimentary tract, and samples of tissues (adipose, brain, gonads, heart, kidney and liver) taken for analysis of the distribution of radiolabelled material. At 24 and 48 hours post-administration, 3 animals per dose group were killed, with blood samples only being taken. A further 3 animals per dose group were also housed for 7 days for the continuous collection of urine, faeces and CO_2. These animals were killed on completion of the 7 days and samples of whole blood, the contents of the alimentary tract, and samples of tissues (adipose, brain, gonads, heart, kidney and liver) taken for analysis of the distribution of radiolabelled material. Additionally, 3 animals per dose group were killed after 28 and 90 days and samples of tissues (adipose, brain, gonads, heart, kidney and liver) taken for analysis of the distribution of radiolabelled material. Within this study, no attempts were made to identify potential metabolites.

The tissue distribution data of radiolabelled material was poorly presented; no units were provided for figures presented, although they were clearly not expressed as a percentage of the original dose administered. Hence, it is only possible to present a summary of distribution data in relative terms. There was no obvious dose-related pattern to the numbers presented, although as expected, the tissue concentrations recorded for animals receiving 625 $mg.kg^{-1}.day^{-1}$ were considerably greater (occasionally by an order of magnitude or more) than the concentrations at 10 $mg.kg^{-1}.day^{-1}$ The liver, kidneys and ovaries contained the highest initial (first 7 days) concentrations of radioactivity, followed by an increase in adipose tissue levels as the levels in the former tissues declined. This latter trend was less apparent in 'pretreated' compared to naive animals. Elimination of radioactivity from adipose tissue occurred more slowly than from the liver or the kidneys. No information on the half-life of elimination from adipose tissue was given.

In both 'pretreated' and naive animals, the faeces was the major route of elimination of radiolabelled material. The extent of faecal elimination was broadly similar in pre-treated and naive animals. About 40-48% of the total administered radioactivity was recovered in 7 days in males at 10 $mg.kg^{-1}.day^{-1}$ and around 53-61% over 7 days in males at 625 $mg.kg^{-1}.day^{-1}$. For females at 10 $mg.kg^{-1}.day^{-1}$ around 30% was recovered in the faeces during these first 7 days, and at 625 $mg.kg^{-1}.day^{-1}$ the recovery over the first 7 days was markedly greater at around 62-74%. For both males and females the majority of the radiolabel eliminated via the faeces occurred within the first 2 days after dosing. Recovery of radioactivity in urine and exhaled air within 7 days amounted to only 0.8-3% and 0.1-0.3% respectively for both naive and pre-treated males and females at 10 and 625 $mg.kg^{-1}.day^{-1}$.

The recovery data were poorly presented and it is unclear how recovery was calculated. It is presumed that the values given refer to the pooling of radiolabelled material from all of those tissues examined in the 90 days following the single oral administration; for males at 10 $mg.kg^{-1}.day^{-1}$, the total recovery of radiolabel amounted to around 67% of that administered, the remaining 33% being unaccounted for. For males at 625 $mg.kg^{-1}.day^{-1}$ total

recovery was about 85%; for females at 10 $mg.kg^{-1}.day^{-1}$, about 60%, and for females at 625 $mg.kg^{-1}.day^{-1}$, about 80%. Overall, at the higher exposure level a greater percentage of radiolabelled material was eliminated via the faeces, and the total recovery was also greater.

In summary, the results indicate that, in rats, the radiolabelled material from a C_{15} MCCP (52% chlorination) was absorbed by the oral route and widely distributed. The total recovery of radiolabelled material was incomplete (around 30-40% material at 10 $mg.kg^{-1}.day^{-1}$, and 15-20% at 625 $mg.kg^{-1}.day^{-1}$ was unaccounted for) making it difficult to draw many firm conclusions. A large proportion of the administered material was rapidly eliminated via the faeces and at the highest exposure level used, 625 $mg.kg^{-1}.day^{-1}$, there was evidence for increased faecal elimination. It is not clear if this was as the parent substance and/or metabolites. Furthermore, it is unclear whether faecal radioactivity represented material that was not absorbed or had been absorbed and then excreted via the biliary route. Of the material absorbed into the body, there was also evidence for uptake into fatty tissue.

In a study briefly summarised in a review by Birtley *et al* (1980), male Wistar rats were fed either 0.4 or 40 ppm [^{36}Cl]-mixed C_{14-17} chlorinated paraffin (52% chlorination, and presumably randomly radiolabelled) in the diet for 10 or 8 weeks respectively. Assuming a mean bodyweight for males of 250g, and 200g for females, and food consumption of $20g.day^{-1}$ for males and $16g.day^{-1}$ for females (using data from a repeated dose toxicity study presented in this review), these dietary inclusion levels correlate to approximately 0.03 and 3 $mg.kg^{-1}.day^{-1}$ for both males and females. Groups of 3 animals were killed at weekly intervals beginning at week 1 of treatment. On completion of the 10-week treatment period, surviving animals that had received 0.4 ppm only were returned to a control diet, and 3 animals were killed at various time points over an 8-week post-treatment period to assess the elimination half-life. Immediately after sacrifice, the level of radiolabelled material present in the liver, brain, adrenal glands and abdominal adipose tissue was assessed. For animals that received 40 ppm, samples of liver and adipose tissue were only taken during the first 8 weeks of the treatment period; there was no assessment of tissue retention and excretion on cessation of exposure.

At both 0.4 and 40 ppm, equilibrium levels of radioactivity were reached within 1 week for the liver and 7 weeks of treatment for adipose tissue. For each of the tissues examined (liver and adipose) the mean tissue concentration of radioactive material was approximately one hundred times as great in rats that had been administered 40 ppm ^{36}Cl MCCP compared to those adminstered 0.4 ppm. No radioactivity was found in the brain or the adrenals. The half-life for removal of radioactivity from the abdominal fat after treatment with 0.4 ppm was estimated as approximately 8 weeks, whilst in the liver, no radioactivity was detected at 1 week after the cessation of the radiolabelled dose. No attempts were made to identify potential metabolites or determine routes of elimination.

This study demonstrates absorption (via the oral route), and distribution of a mixed MCCP (52% chlorination) to the liver and adipose tissue. It also suggests that there is a relatively rapid elimination from the liver, but considerably slower release from adipose tissue, and at the concentrations used, an equilibrium between plasma levels and adipose levels of radiolabelled material is reached. However, in view of the dosing regime employed (dietary administration rather than gavage dosing), the reliability of the estimated equilibrium time is uncertain. Overall, given that an elimination half-life from adipose tissue of 8 weeks was measured, it can be concluded that MCCPs are sequestred for a protracted period in adipose tissue and therefore have the potential to accumulate in this tissue.

As part of a standard repeated-exposure study (Poon *et al*, 1995 see Section 4.1.2.6) samples of liver and adipose tissue were taken at termination from groups of 4 Sprague-Dawley rats that had received 0, 5, 50, 500, and 5000 ppm (approximately 0, 0.4, 4, 36, and 360 $mg.kg^{-1}.day^{-1}$ in males and 0, 0.4, 4, 42 and 420 $mg.kg^{-1}.day^{-1}$ in females) C_{14-17} MCCP (52% chlorination) by dietary administration for 13 weeks. There was a dose-dependent increase in the concentration of the parent compound in both of these tissues, with particularly high concentrations in adipose tissue. Data were not presented, although the authors stated that there was no bioconcentration (levels in adipose tissue did not rise to greater than the external concentration administered). Other tissues were not analysed.

In a recent QA-compliant study conducted to determine the elimination half-life of MCCPs in the rat following a single oral administration, 18 male F344 rats were given a single dose of [8-^{14}C]-labelled C_{15} chlorinated paraffin (52% chlorination) in corn oil at 525 mg/kg by gavage (day 1) (CXR, 2005a). Immediately after dosing, 3 animals were individually housed in metabolism cages for collection of urine and faeces once daily on days 2-5. The remaining 15 animals were housed together in normal cages. At 24 hours after dosing (day 2), 3 of these 15 animals were sacrificed and blood and tissues collected for analysis. The 3 rats individually housed in metabolism cages were sacrificed on day 5 and blood and tissues collected. On day 8 a second group of 3 rats were placed in metabolism cages and urine and faeces collected on days 9-12. The animals were then sacrificed on day 12 and blood and tissues collected. The same procedure was repeated with the remaining 3 sets of 3 rats each on days 22, 50 and 85 with animals being sacrificed on days 26, 54 and 89 respectively.

Twenty-four hours after dosing, the liver, kidney, fat and skin/fur contained the highest concentrations of radioactivity (1.6, 0.07 and 2.7% of the administered dose respectively). Thereafter, concentrations of radioactivity declined in all tissues except for the fat and the skin/fur. The amount of the administered dose recovered from body tissues including blood remained at approximately 7% until day 12, but it declined to approximately 2% by day 89. Although the amount of radioactivity (as % of the administered dose) recovered from the body was the same during the first 12 days, there was a re-distribution into fat (a maximum of 2.5% on day 12) and skin/fur (a maximum of 3.7% on day 12) over this time. At 24 hours after dosing (day 2), the liver contained 1.6% of the administered dose but this rapidly declined, and by day 5 only 0.3% of the administered dose was recovered from the liver. For well-perfused tissues such as the liver and kidney, the tissue:plasma distribution ratios of radioactivity remained constant throughout the study, indicating good equilibrium between the plasma and these tissues. For the fat and skin/fur, the tissue:plasma distribution ratios changed over time with radioactivity accumulating in these tissues over the first 12 days and thereafter slowly declining. Distribution into the liver and kidney was rapid, with the highest levels seen on day 2. Distribution into fat and skin/fur was slow with the highest levels seen on days 5 and 12. Elimination of radioactivity from body tissues occurred with an elimination half-life of approximately 2-5 days (tissues such as liver and kidney) or approximately 2 weeks (tissues such as white adipose).

Excretion via the faeces was the major route of elimination of radiolabelled material. Approximately 50% of the administered dose was rapidly eliminated in the faeces within the first 24 hours after dosing. It is reasonable to assume that this radioactivity represents material that was not absorbed by the gastro-intestinal (GI) tract. Therefore, it can be concluded that approximately 50% of the administered dose was absorbed from the GI tract following gavage administration of [8-14C]-labelled C15 chlorinated paraffin at 525 mg/kg. Approximately 70% of the dose was recovered in the faeces and approximately 5% in the urine by day 5. Over this time the total recovery of radiolabelled material was high (83.6%). On completion

of the study (day 89) approximately 2% of the administered radioactivity remained in the tissues, primarily in the skin/fur.

In summary, the results of this study indicate that, in the male rat, approximately 50% of a single dose of [8-^{14}C]-labelled C_{15} chlorinated paraffin was absorbed from the GI tract and this was widely distributed. The faeces were the major route of elimination of the radiolabelled material. The elimination half-life of a single dose of [8-^{14}C]-labelled C_{15} chlorinated paraffin and/or its metabolites in tissues such as liver and kidney was 2-5 days and in tissues such as white adipose was about 2 weeks. Since C_{15} chlorinated paraffin is itself a component of MCCPs, it is reasonable to assume that MCCPs will have similar kinetic properties to those shown in this study by C_{15} chlorinated paraffin.

The final report of a QA-compliant study investigating the bioaccumulation potential of MCCPs in the rat following repeated administration has recently become available (CXR, 2005b). Groups of 48 F344 rats/sex were administered MCCPs (52% chlorination) in the diet at a concentration of 3000 ppm (equivalent to 200/233 mg/kg/d in males/females) for 14 weeks, time at which steady state level of MCCPs in white adipose tissue was achieved. This was monitored by sacrificing groups of 8 animals (4 males and 4 females) at 3-week intervals. After 14 weeks exposure, the remaining rats were transferred to control diet. Groups of 8 rats (4 males and 4 females) were then sacrificed at weeks 15, 16, 18, 22, 30, 40 and 52 (weeks 1, 2, 4, 8, 16, 26 and 38 post-dosing) to determine the elimination of MCCPs from white adipose tissue, liver and kidney. The MCCPs content of these tissues was extracted in hexane and analysed by gas chromatography.

Recovery of MCCPs (in the hexane extract) from tissues was estimated using a limited number of samples collected from rats administered via gavage a single dose of 525 mg/kg ^{14}C-MCCP (CXR, 2005a; previous study) and stored at -70°C. Recovery was calculated as the fraction of radioactivity present in the hexane extract compared to the radioactivity present in the tissue homogenate. Mean recovery of MCCPs from adipose tissue was estimated to be approximately 55%, and ranged from 37% to 72%. Mean recovery of MCCPs from kideny and liver was estimated to be approximately 10% and 15%, respectively. It is not known why recovery from kidney and liver was lower than from adipose tissue, but one possible explanation is that the extraction of lipids into hexane might facilitate the excretion of MCCPs from adipose tissue.

The MCCPs content in white adipose tissue after correction for recovery increased with time until week 13, with females showing approximately twice the amount of MCCPs per gram of white adipose tissue than males (from 903 µg MCCPs/g tissue at 3 weeks up to 3110 µg MCCPs/g tissue at 13 weeks in females and from 826 µg MCCPs/g tissue at 3 weeks up to 1731 µg MCCPs/g tissue at 13 weeks in males). It should be noted that although steady state in the adipose tissue was reached at week 13, levels of MCCPs in this tissue were already close to the steady state levels by week 9 (2654 and 1621 µg MCCPs/g tissue in females and males respectively). Following exposure (with achievement of the steady state level), the elimination of MCCPs from adipose tissue appeared to be biphasic, with a rapid first phase of approximately 4-5 weeks (from wk 14 to wk 18) and a much slower second phase of approximately 34 weeks (from wk 18 to wk 52). Both male and female rats quickly eliminated MCCPs in the first phase with an initial half-life of 4.7 weeks (4.4 weeks in females and 5.0 weeks in males), followed by a markedly slower second phase. By week 22 (8 weeks into the wash-out phase), the concentration of MCCPs in adipose tissue of both sexes was similar (1198 and 984 µg MCCPs/g tissue in females and males respectively). The concentration of MCCPs in adipose tissue slowly decreased between weeks 22 and 52 (740

and 623 µg MCCPs/g tissue in females and males respectively). Analysis of the terminal elimination phase of MCCPs from white adipose tissue, using data from weeks 22 to 52 inclusive, elicited a second phase half-life of approximately 44 weeks for the females and approximately 42 weeks for the males.

It was not possible to quantify MCCPs in liver or kidney tissue. This was due to the poor recovery of MCCPs in the hexane extract and to the high background from endogeneous compounds.

Studies in mice

The distribution and excretion of a single dose of approximately 1 $mg.kg^{-1}$ of uniformly-labelled [^{14}C]- poly-chlorinated hexadecane (PCHD) was studied in female C57Bl mice treated via oral gavage administration (Biessmann *et al*, 1983). Expiration of $^{14}CO_2$ was monitored for 8 hours post-treatment and urine and faeces collected every 8 hours for 4 days for radioactivity determinations. A further group of mice received about 10 $mg.kg^{-1}$ via oral gavage and whole body autoradiography (WBA) was conducted on one animal at 4 hours, 1 day, 4 days, 12 days and 30 days post-administration.

WBA conducted at 4 hours, 1, 4, 12 and 30 days after the 10 $mg.kg^{-1}$ dose revealed that the administered radioactivity was concentrated mainly in the corpora lutea, liver, adrenal cortex and brown and white adipose tissue. Only a small number of sample autoradiographs were presented. These indicated a concentration of radiolabelled material (at 4 days) in the liver, brown adipose tissue, and corpora lutea. Thirty days post-administration, the corpora lutea and brown fat still showed high levels of radioactivity.

The major route of elimination was via the faeces; 66% of the administered radioactivity was eliminated via this route in 4 days, with a substantial proportion (57%) of the administered dose, being eliminated within the first 16 hours. With the 1 $mg.kg^{-1}$ dose, approximately 1% of the administered radioactivity was exhaled as $^{14}CO_2$. The remaining 34% of radiolabelled material was not directly accounted for, although the indication from WBA (see below) is that much was retained in the carcass (principally adipose tissue).

A similar study using i.v. administration was also conducted using the same experimental protocol as for oral dosing. Of the administered dose, again the major route of elimination was via the faeces with 43% of the administered dose being eliminated within 4 days of treatment; approximately 1% appeared in expired air as $^{14}CO_2$. This suggests that much of the faecal elimination following oral dosing represented excretion of material previously absorbed into the body, rather than the substance simply passing through the GI tract. However, in contrast to oral exposure, during the first 8 hours after treatment, faecal elimination following i.v. administration accounted for only 2% of the administered dose (compared to 22% by the oral route) indicating that excretion via the bile and faeces takes some time and perhaps that the early faecal levels are due to elimination rather than excretion. Urinary excretion accounted for 3% of the administered dose.

Overall, this study also indicates absorption, and widespread distribution via the oral route of a MCCP (69% chlorination) or metabolites. Substantial elimination of the parent substance and/or metabolites occurred via the faeces but there was limited excretion as exhaled CO_2 and via urine. Autoradiography studies demonstrated substantial retention of radiolabelled material in white adipose tissue, but also in corpora lutea, liver and adrenal cortex.

A group of 3 female C57Bl mice was given a single oral gavage dose of approximately 0.15 $mg.kg^{-1}$ [1-^{14}C]-radiolabelled PCHD via oral gavage (Darnerud and Brandt, 1982). One

animal was then sacrificed at each of 4 and 24 hours, and 4 days post-dose and sectioned for WBA. A further group of 5 pregnant females received a similar dose of [1-^{14}C]-radiolabelled PCHD by i.v. administration; animals were sacrificed on gestation day 10 and sectioned for WBA at each of 6 hours and 24 hours after the i.v. injection, and on gestation day 17 at each of 6 hours, 24 hours, and 2 days after the i.v. injection. In addition, one group of 8 females received a similar dose of [1-^{14}C]-radiolabelled PCHD by i.v. administration and one animal was sacrificed at each of the following timepoints after injection: 5 minutes, 20 minutes, 1 hour, 4 hours, 24 hours, 4 days, 12 days, and 30 days. Similarly, another group of two males received [1-^{14}C]-radiolabelled PCHD by i.v. administration with one animal sacrificed 24 hours post-administration and another at 30 days.

To determine tissue retention, 4 female mice were given a single oral gavage dose of around 0.01 mg.kg^{-1} [1-^{14}C]-radiolabelled PCHD. One group of 4 mice was sacrificed at each of 1 hour, 4 hours, 24 hours, 4 days, and 12 days after oral administration and samples taken of blood, liver, kidney, white and brown adipose tissue, and the brain for analysis of the tissue levels of radioactivity. Ether extracts of tissues taken at 1 hour were separated by thin-layer chromatography (TLC) and localised autoradiographically.

In addition, one group of 4 mice received a single oral gavage dose of approximately 0.02 mg.kg^{-1} [1-^{14}C]-radiolabelled PCHD. Pooled samples of exhaled air were collected between 15 minutes and 12 hours post-administration for analysis for $^{14}CO_2$. The total radioactivity was measured for pooled urine and faeces samples collected over this 12-hour period.

The WBA showed that at 4 hours following oral gavage administration, as expected, there was intense radioactivity in the stomach and GI tract. Twenty four hours post-administration, the most intense radioactivity was seen in brown adipose tissue, liver, kidney, adrenals, bone marrow, Harderian gland, salivary glands, pancreas, and intestinal mucosa.

At 12 days, following i.v. injection, high concentrations of the radiolabel were noted in the adrenal cortex, adipose tissue and gall bladder. It was stated that radioactivity was concentrated mainly in the brain and liver 30 days after i.v. administration (although no sample autoradiograph was presented to demonstrate this). The study in which pregnant mice received radiolabelled material by the i.v. route showed a broadly similar pattern of distribution, although the passage of radiolabelled material to the developing fetus was also observed.

The quantitative studies of tissue distribution did not present levels of radioactive material as a percentage of that administered. However, the data showed measurable levels of radiolabelled material in all tissues examined (blood, liver, kidney, white and brown adipose tissue, and brain). The peak plasma level was noted at 1 hour post-administration, gradually declining over the next 12 days. For liver and kidneys, peak levels were observed at 4 hours, with a subsequent decline. However, the highest levels were measured in brown adipose tissue, and to a lesser extent in white adipose tissue, and these tissue levels declined much more slowly. No quantitative data were presented for the brain.

TLC of samples taken from the liver, kidney, and brown adipose tissue 1 hour after the oral administration of radiolabelled material showed the presence of a radiolabelled substance that eluted in the same position as a referent sample of the parent compound (PCHD). There were no further attempts to quantify or identify these radiolabelled fractions but the implication is that these mixed MCCPs were distributed to these tissues without further metabolism.

In contrast with studies reviewed above, a substantial proportion (33%) of the administered radioactivity was eliminated as $^{14}CO_2$ in expired air within 12 hours of dosing. Approximately 6 and 14% of the administered dose appeared in the urine and faeces respectively. The remaining radiolabel was not accounted for in the balance study, although the qualitative (WBA) and quantitative studies indicate that much may have been distributed in other tissues around the body.

The study demonstrates extensive absorption from the GI tract following oral administration of this MCCP (34% chlorination). The WBA examinations showed widespread distribution although no meaningful quantitative data were presented. However, in common with other studies on MCCPs (of greater chlorination), the adipose tissue was seen to be a site of uptake of radiolabel. Transplacental passage of radiolabelled material was seen following i.v. administration, and given the similarities seen in the profile of distribution from oral and i.v. routes, it is presumed that this may also occur following oral administration of these MCCPs. There is evidence to suggest that, at least initially, this MCCP can reach the liver, kidneys and adipose tissue in an unmetabolised form. It is unclear what happens thereafter, although the production of radiolabelled CO_2 indicates that metabolism can and does occur. The relatively small degree of elimination via the faeces in this study differs markedly from that seen in the Biessmann *et al* (1983) study also conducted in mice, and the one available rat study exploring elimination (IRDC, 1984). The difference in elimination pattern may be attributable to the difference in the degree of chlorination for the MCCP used in this study, resulting in it being handled somewhat differently in the body.

Groups of 6 neonatal/pre-weaning NMRI mice (aged 3, 10 or 20 days old) received a single oral gavage dose of 1.1 $mg.kg^{-1}$ uniformly-labelled ^{14}C-PCHD (69% chlorination) (Eriksson and Darnerud, 1985). Animals were killed 1 and 7 days after treatment, and the only quantitative determinations of levels of radioactivity made were for the brain and liver. A further 2 mice (aged 3, 10 or 20 days old) received a single oral gavage dose of about 7 $mg.kg^{-1}$ uniformly-labelled ^{14}C-'PCHD' (69% chlorination) and following sacrifice (presumably also on days 1 and 7 after administration of the radiolabelled PHCD), sections were taken for WBA.

For mice that were 3 days old at the time of treatment, the level of radioactivity in the brain was around 3% of the dose administered, and for 20-day old mice, about 0.5% at the 24-hour time-point. Curiously, the level of radioactivity in the liver of 3-day old mice was stated to be around 150% of the dose administered, and for 10-day old mice was 100% at the 24-hour time point. For mice of each age (3 days, 10 days or 20 days) the level of radioactivity was lower at 7 days compared to 24 hours in both brain and liver samples.

WBA sections taken 7 days after the administration of radiolabelled material in 10-day old mice revealed high levels of radioactivity in adipose tissue, adrenals, and in myelinated areas of the brain. No data were presented for 3-day or 20-day old mice, but the results from these young animals seem to support other published autoradiography studies in more mature mice.

Dermal

No studies are available investigating dermal absorption of MCCPs *in vivo*.

In a briefly presented *in vitro* study, a ^{14}C-labelled $C_{14\text{-}17}$ MCCP (52% chlorination) was applied to a human epidermal membrane for 55 hours apparently using a static collection system (Scott, 1984). The source of human skin and position of radiolabel on the paraffin were not indicated. A range of different receptor fluids was used (100% ethanol, 50% aqueous

ethanol, 20% horse serum in saline, a non-ionic surfactant, and an emulsifying agent). No absorption of radiolabelled material was detected during the 56 hours of exposure.

In a recent *in vitro* skin absorption study conducted to GLP and OECD guidelines, [8-^{14}C]-labelled C_{15} chlorinated paraffin (52% chlorination; specific activity 1.33 mCi/ml) was applied to human skin membranes using a flow through apparatus (Johnson, unpublished, 2005). Discs of approximately 3.3 cm diameter of epidermal membranes from at least three subjects being checked for integrity were mounted in diffusion cells. Doses of 10 µl/cm^2 (equivalent to 12.6 mg/cm^2) and 100 µl/cm^2 (equivalent to 125.8 mg/cm^2) of the test substance were applied to the skin membranes for 24 hours. The cells dosed with 10 µl/cm^2 were left unoccluded while the cells dosed with 100 µl/cm^2 were occluded. At 2, 4, 8, 12, 16, 20 and 24 hours after dosing, 0.5 ml samples of the receptor fluid (6% polyoxyethylene 20 oleyl ether in water) were taken for analysis. At the end of the exposure period, the epidermal surface was decontaminated by gently swabbing the application site and the surface of the skin was allowed to dry naturally. To assess penetration through the stratum corneum, successive layers of the stratum corneum were removed by the repeated application of adhesive tape to a maximum of 5 strips and analysed. The remaining epidermis was removed from the receptor chamber, digested and analysed.

The mass balance recovery for both dose levels was excellent, in the range 90.1-113% of the applied dose, with the vast majority of the applied dose (97%) being removed by the washing procedure, 0.702% being found in the epidermis and 2.15% being recovered from the stratum corneum. For the unoccluded dose of 10 µl/cm^2 and the occluded dose of 100 µl/cm^2 respectively, 0.002% and 0.001% of the applied dose was recovered in the receptor fluid by 24 hours. By assuming that the material absorbed is made of the fraction present in the receptor fluid and of that found in the epidermis, the maximal dermal absorption of a C_{15} chlorinated paraffin through human skin after 24 hours was approximately 0.704% (0.002+0.702) of the dose applied. Since C_{15} chlorinated paraffin is itself a component of MCCPs, it is reasonable to assume that MCCPs will have a similar dermal absorption to that shown in this study by C_{15} chlorinated paraffin. It is noted that this percentage is likely to be an overestimate as this study was specifically designed to measure skin penetration under the most conservative conditions. Epidermal membranes were used (not whole skin); a solubilising receptor phase containing surfactant was used (not saline) to ensure free partitioning of the test substance; and a worst case continuous exposure for 24 hours under occluded conditions was studied. It is also deemed that under the condistions of this study the fraction present in the stratum corneum represents unabsorbable material that would be lost by desquamation in vivo. This is supported by evidence showing that the test substance had not moved beyond this outer layer in 24 hours and by the lack of a significant lag phase (based on the absorption profile between 2 and 24 hours).

Other studies

In a limited assessment of the formation of potential metabolites, a group of 4 bile-duct cannulated female Sprague-Dawley rats received 5-6 mg.kg^{-1} uniformly labelled PCHD (65% chlorination) by i.v. injection (Ahlman *et al*, 1986). Bile was collected for up to 3 days and potential metabolites analysed chromatographically. Urine and faeces were collected over a 2-day period. Animals were killed on completion of these collections and radioactivity was measured in liver, kidneys, adipose tissue, muscle, adrenals and ovaries.

A total of around 20-30% of the administered radiolabel was eliminated via the bile in 3 days, with around 10% eliminated within 24 hours of treatment. Unchanged parent compound accounted for up to a maximum of 3% of the radiolabelled material present in the bile. Very

low levels of radioactivity were found in the urine and faeces samples collected over 2 days (less than 0.5% in each case). Radioactivity was also detected in each of the tissues removed at sacrifice, with the highest levels being observed in liver, adrenals and ovaries. However, the data were not quantified as a percentage of the amount administered. There was no quantitation of the proportion of the dose administered represented by these metabolites.

The TLC analysis of urine samples indicated metabolites that were tentatively identified as mercapturic acids and methylated mercapturic acids of the MCCP, indicating conjugation of the MCCPs with glutathione. Similarly, analysis of the biliary metabolites suggested the presence of a mercapturic acid of the MCCPs.

Overall, this study is limited, but it does demonstrate metabolism of a MCCP (65% chlorination) probably involving conjugation with glutathione.

4.1.2.1.2 Studies in humans

The only human data available relates to the presence of chlorinated paraffins in human breast milk, indicating that excretion via this route can occur. Greenpeace (1995) reported a mean level of 45 µg/kg (on a fat weight basis) chlorinated paraffins in human breast milk. Further information on the breast milk sampling was obtained from the author of the report. The breast milk analysis was based on pooled samples of two groups of women, one of non-fish eaters (n=2) and one of fish eaters (n=6). The average chlorine content of the chlorinated paraffins detected was around 33%, although a value of 50% was assumed in the calculation of chlorinated paraffin content from the measured levels of n-alkanes. Medium chain length chlorinated paraffins were thought to make up between 6 and 29% of the total chlorinated paraffins found in the biota sampleas as a whole, although an actual content in breast milk of 10 and 22% can be deduced for the groups of non-fish eaters and fish eaters respectively. Taking an average value for MCCPs of about 17%, this is equivalent to an estimated MCCP concentration of 7 µg/kg in breast milk; alternatively, based on the highest MCCP content (22%) as a worst case estimate, this is equivalent to a concentration of about 9.0 µg/kg in breast milk. The pattern of carbon chain length alkanes reported does not reflect that of a typical C_{14-17} chlorinated paraffin.

A recent Industry sponsored study has found medium-chain chlorinated paraffins to be present in human breast milk samples from the United Kingdom (Thomas and Jones, 2002). In all, 22 breast milk samples were analysed (8 from Lancaster and 14 from London, apparently randomly chosen) and medium-chain chlorinated paraffins were found in one sample from London at a concentration of 61 µg/kg fat but was below the limit of detection in the remaining 21 samples. The detection limit of the method varied with sample size but ranged from 16 µg/kg fat to 740 µg/kg fat (mean level of 100 µg/kg fat). It is noted that these detection limits are higher than the measured levels in breast milk reported in the Greenpeace study. This suggests that the analytical method used in Thomas and Jones, 2002 was less sensitive than that used in the Greenpeace study. The fact that MCCPs were only found in 1/22 samples does not mean that it was not present in the other samples at levels below the detection limit.

Thomas et al (2003) have recently carried out a further investigation of the levels of medium-chain chlorinated paraffins in human breast milk samples from the United Kingdom. In this study, relatively large samples of human milk-fat were collected from the London (20 samples) and Lancaster (5 samples) areas of the United Kingdom between late 2001 and June 2002. It should be noted that some of the London samples were taken from the same mother,

such that 20 samples were from 13 mothers; five samples were provided from one mother over a three-day period, two samples were provided from another mother over a two-day period, a further two samples were provided by another mother over a five-day period, and a further two samples were provided by another mother over an unknown period. The analysis was carried out using high resolution gas chromatograph (HRGC) coupled with electrochemical negative ionisation (ECNI)-high resolution mass spectrometry (HRMS) detection. The analytical standard used was a commercial medium-chain chlorinated paraffin (C_{14-17}, 52% wt. Cl). In addition to total medium-chain chlorinated paraffins, twelve samples (four from Lancaster and eight from London) were also analysed in more detail to determine the various types of chlorinated paraffin (in terms of chlorine number and carbon chain length distributions) present in the samples.

Medium-chain chlorinated paraffins were found to be present in all 25 samples analysed. The median, 97.5th percentile value and range of concentrations found were 21 µg/kg lipid, 130.9 µg/kg lipid and 6.2-320 µg/kg lipid respectively. The levels found in the samples from Lancaster were not thought to be significantly different from the levels found in the samples from London.

4.1.2.1.3 Summary of toxicokinetics

The only human data relates to information on the presence of chlorinated paraffins in human breast milk, indicating the potential for excretion via this route. No studies have been undertaken to investigate the toxicokinetics of MCCPs following exposure of animals via the inhalation or dermal routes. A recent GLP- and OECD-compliant *in vitro* study using human skin showed that after 24 hours, approximately 0.7% of a C_{15} chlorinated paraffin was absorbed. A dermal absorption value of 1% is therefore taken forward to the risk characterisation.

Absorption following oral exposure in animals has been demonstrated to be significant (probably at least 50% of the total administered dose). Overall, therefore, 50% absorption by this route will be assumed for risk characterisation purposes. There is no specific information for the inhalation route of exposure; however, given that the data indicate 50% absorption by the oral route and only 1% by the dermal route, and in view of the very high log Pow and the very low water solubility of MCCPs, it reasonable to assume that inhalation absorption is also unlikely to be higher than 50%. This figure will therefore be taken forward to the risk characterisation in relation to absorption via the inhalation route of exposure. The data available do not allow any conclusions to be drawn regarding the way in which the degree of chlorination of these substances may affect the extent of absorption following oral administration (or any other route).

Following absorption of radiolabelled material via the oral route, as with SCCPs, there is an initial preferential distribution of radiolabel to tissues of high metabolic turnover/cellular proliferation. Subsequently, there is a re-distribution of radiolabelled material to fatty tissue. Following single gavage dosing in the rat, an elimination half-life of approximately 2-5 days was estimated for tissues such as the liver and kidney and of about 2 weeks for tissues such as white adipose. Following repeated dietary administration, retention in fatty tissue occurs, with one study in rats revealing a half-life for elimination from the abdominal fat of 8 weeks. Results of a very recent study in the rat have shown that steady state in adipose tissue is reached at approximately 13 weeks and that elimination of MCCPs from this tissue appears to be biphasic, with an initial half-life of approximately 4 weeks, followed by a markedly slower second phase with a terminal half-life of approximately 43 weeks. For most studies, it is

unclear whether the distributed material is the parent compound and/or metabolites. However, two studies clearly indicate that it is the parent compound that is sequestered in adipose tissue and liver. In a later section (see Section 4.1.2.9), there is evidence to suggest that MCCPs or metabolites might be transferred to offspring via breast milk; MCCPs have also been measured in human breast milk. Transmission of MCCPs (34% chlorination) or metabolites via the mother to the developing fetus *in utero* was evident although it is not clear if this occurs with all forms of MCCPs. There are no parallel data from SCCPs in terms of transmission of the substance or its metabolites via maternal milk or to the developing foetus.

In relation to metabolism, one study with a 65% chlorinated MCCP indicated conjugation with glutathione. The production of CO_2 from MCCPs has also been demonstrated; metabolism to CO_2 was quite extensive with MCCPs of lower chlorination, but appeared to be much more limited with more heavily chlorinated MCCPs (e.g. 69% chlorination). CO_2 was also produced following oral administration of SCCPs in rodents, and the degree of chlorination had a similar influence on the extent of CO_2 production. Elimination of MCCPs and/or their metabolites occurs via the faeces, via exhaled CO_2 with lower chlorinated MCCPs (e.g. 34% chlorination), and to a limited extent in the urine.

Although limited data are available on short-chain chlorinated paraffins, there are many parallels in the overall toxicokinetic profile which would tend to support the validity of read-across of toxicological data when these are lacking for MCCPs (SCCP ESR Risk Assessment Report, 2000).

4.1.2.2 Acute toxicity

It is noted that some of the MCCPs for which toxicity test data are available have had a low concentration of an ‘epoxy stabiliser’ added. However close inspection of data (some studies having been conducted without any ‘stabiliser’ added) indicates that the presence of the stabiliser at the levels used had no effect on the toxicological profile.

4.1.2.2.1 Studies in animals

Inhalation

No animal studies are available on MCCPs. However, the limited data on structurally-related SCCPs (C_{11-13}, 59% chlorination) demonstrate low toxicity by single inhalation exposure; there was no evidence of toxicity in rats following a 1-hour exposure to a vapour or aerosol of 3300 $mg.m^{-3}$ (cited in SCCP ESR Risk Assessment Report, 2000). Hence, in view of the similarities in structure and physicochemical properties (see Introduction to Section 4.1.2) it is predicted that MCCPs would also be of low toxicity by single inhalation exposure. This is supported by the observation of low toxicity of MCCPs by oral and dermal routes (see below) and the generally unreactive nature of these substances.

Oral

A number of unpublished studies are available in which rats received single oral gavage doses of up to 15 000 $mg.kg^{-1}$ MCCPs (40-52% chlorination; containing 0.2-1% epoxy stabiliser) (Kuhnert,1986a; Kuhnert,1986b; Chater,1978). No deaths occurred in any of these studies and clinical signs of toxicity were confined to urinary incontinence or "oily/moist pelt around the anal-genital region" during the first 24-48 hours following administration.

The results of eight single exposure studies in which Alderley Park (Wistar-derived) rats received oral gavage doses of 500-10 000 $mg.kg^{-1}$ C_{14-17} MCCPs (51-60% chlorination; with or without 0.2% epoxy stabiliser) were cited by Birtley *et al* (1980). This review also reported the results of two single exposure studies using SCCPs. However, it was not possible to clearly delineate the results of work on SCCPs and MCCPs. Nonetheless, no mortalities were observed. It is reported that clinical signs included piloerection, incoordination and urinary incontinence. Histopathologically, hepatocellular vacuolation and focal necrosis were seen in the liver, and cloudy swelling of inner cortical cells was seen in the kidney. The limitations in reporting make it impossible to ascertain which observations were attributable to treatment with MCCPs or SCCPs; if the results applied to both, or the dose levels at which the reported effects occurred.

Dermal

No animal studies are available in relation to MCCPs. However, data are available on SCCPs which indicate that no signs of local or systemic toxicity were seen in rats following dermal administration of 2800 $mg.kg^{-1}$ of a 52% chlorinated SCCP (cited in SCCP ESR Risk Assessment Report, 2000). This review also cited a dermal LD_{50} value of approximately 13000 $mg.kg^{-1}$ in rabbits for a 59% chlorinated SCCP (SCCP ESR Risk Assessment Report, 2000).

Overall, there are no experimental data specifically in relation to the acute dermal toxicity of MCCPs. SCCPs have been demonstrated to be of low toxicity by this route, and in consideration of the structural and physicochemical similarities, together with the low acute oral toxicity of MCCPs, it can be predicted that MCCPs are likely to be of low acute toxicity by the dermal route of exposure.

4.1.2.2.2 Human data

There are no data available.

4.1.2.2.3 Summary of single exposure studies

No information is available on the effects of single exposure to MCCPs in humans. There are no single inhalation exposure studies available in animals. However, based upon inhalation data for SCCPs and oral data for MCCPs it is predicted that the MCCPs are also likely to be of low acute inhalation toxicity.

MCCPs are of low acute oral toxicity with no deaths and only limited, non-specific clinical signs of toxicity resulting from exposure of rats to very high doses (up to 15000 $mg.kg^{-1}$). No data are available relating to single exposure via the dermal route. However, SCCPs are of low toxicity via the dermal route and MCCPs are of low toxicity via the oral route. Hence, it is predicted that the MCCPs are of low acute dermal toxicity. Although no information is available relating to the degree of chlorination, it is predicted that given the low acute toxicity of the MCCPs studied, this is unlikely to be of significance for this endpoint.

4.1.2.3 Irritation

4.1.2.3.1 Studies in animals

Skin

Rabbits

Two unpublished studies are available which were performed according to contemporary OECD test guidelines (Kuhnert, 1986c; Kuhnert, 1986d). Both studies involved application of 0.5 ml of undiluted liquid mixed C_{14-17} MCCPs (40% and 52% chlorination respectively; containing 1% epoxy stabiliser) to the shaved skin of 6 rabbits under occlusive conditions for 4 hours. Observation of the skin was continued for up to 14 days after application. Mean 24-72 hour scores for erythema and oedema were 1.5 and 0.6 and 1.3 and 0.3 respectively for the two studies. Scales were also seen from the 6th to 10th day following exposure, and in the case of the first study, drying and hardness (at 72 hours) and “peeling” (observed on days 6-8) presumably of the outermost layers of the skin were seen.

The skin irritation potential of two types of C14-17 40% or 45% chlorinated paraffins was investigated in briefly reported, unpublished studies conducted in rabbits (Chater, 1978). An unspecified amount of undiluted liquid material was applied to the skin for 24 hours under an occlusive dressing and signs of irritation scored at 24 and 72 hours post-treatment. No signs of skin irritation were seen with the C14-17 45% chlorinated paraffin tested, and only "slight" erythema was reported in one animal at 24 hours using the 40% chlorinated paraffin.

Rats

In a briefly reported, unpublished study, groups of 6 Alderley Park (Wistar-derived) rats received single application of an unstated, but presumably undiluted, volume of C_{14-17} MCCP (45% chlorination, containing 0.2% epoxy stabiliser) or at least 5 repeated applications of the same material (Moses, 1980). The report did not indicate if occlusive conditions were used, or what the duration of exposure was. Following single exposure, slight desquamation was noted in 3 of these animals “at some stage during the test”. By repeated exposure, one of the six test animals developed slight desquamation after the 4th and 5th applications. Other animals were stated to be unaffected.

In a briefly reported, unpublished study a group of 3 female Alderley Park (Wistar-derived) rats received 6 daily applications of 0.1 ml undiluted, C_{14-17} 40% chlorinated paraffin under occlusive conditions (Chater, 1978). "Slight" (not further defined) erythema and/or desquamation were noted after 3-5 applications, progressing to cracking and thickening of the skin.

The results of 9 unpublished skin irritation studies using C_{14-17} chlorinated paraffins (51-60% chlorination, some of which contained 0.2% epoxidised vegetable oil stabiliser) are cited (Birtley *et al,* 1980). Groups of 3 rats received, under occlusive conditions, up to 6 repeated applications of 0.1ml undiluted MCCPs or MCCPs in an unspecified vehicle for 24 hours. Twenty-four hour treatment-free periods separated each application. "A mild skin irritancy response" was produced. No further details were given.

Overall, all of these studies, although having some limitations in reporting, are consistent and indicate that MCCPs have only slight skin irritation potential. However, there was some

potential for cracking of the skin following repeated dermal application of liquid MCCPs, probably because of defatting.

Eye

In two unpublished studies conducted according to contemporary OECD testing guidelines, C_{14-17} chlorinated paraffins (40 or 52% chlorination; containing 1% epoxy stabiliser) were tested for their potential to cause eye irritation in rabbits (Kuhnert, 1986e; Kuhnert, 1986f). Undiluted material (0.1ml) was instilled into the conjunctival sac of one eye of each of 3 rabbits.

No iridial or corneal effects were noted in either study. Conjunctival redness (score 1) was noted in all 3 animals at 1 hour in the second study and 1 animal at 24 hours (both studies) and 48 hours (first study only). Discharge was noted in 1-2 animals at 1 hour in both studies and also at 48 hours in the second study. Overall, the samples tested were judged to be of low irritant potential.

Two types of undiluted C_{14-17} chlorinated paraffins (40 and 45% chlorination respectively; containing 0.2% epoxy stabiliser) were instilled into the conjunctival sac of each of 3 rabbits (Chater, 1978). A "slight" initial pain response (2 on a 0-5 point scale) was seen for both samples, and what was described as "slight transient conjunctivitis" (score of 3 out of 8 for conjunctival effects) within 1-2 hours of instillation. No effects were seen at 24, 48 or 72 hours.

The results of 6 unpublished eye irritation studies are briefly reported (Birtley *et al*, 1980): no ocular irritation was noted following a single application of different types of C_{14-17} MCCPs (51-60% chlorination) into the eyes of groups of 3 rabbits.

Overall, these studies indicate that MCCPs have low eye irritation potential.

Respiratory tract

There are no data in relation to respiratory irritation in humans or animals. However the lack of any reports relating to this endpoint given the widespread use of these substances, suggests that they lack the potential to cause such an effect. The low skin and eye irritation potential and generally unreactive nature of this group of substances lends further support to this view.

4.1.2.3.2 Human data

No studies are available.

4.1.2.3.3 Summary of irritation

No data are available in humans relating to skin or eye irritation. However, based upon two standard animal studies, C_{14-17} chlorinated paraffins have been shown to cause only slight skin irritation on single exposure. The observation of somewhat more pronounced irritation following repeated application to the skin is considered to be due to a defatting action. Studies conducted in rabbits indicate that C_{14-17} chlorinated paraffins produce only slight eye irritation. Similar findings arising from repeated exposures of the eyes have been seen with SCCPs. There are no data specifically in relation to respiratory tract irritation, but on the basis of the low skin and eye irritation potential and generally unreactive nature, and the lack of human reports, it is anticipated that MCCPs are unlikely to cause such an effect.

Although there is only limited information the degree of chlorination does not appear to be of significance for these endpoints.

4.1.2.4 Corrosivity

There are no human data available. However, based on the animal data for the skin and eyes (Section 4.1.2.3), it can be concluded that MCCPs do not have corrosive effects.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

An unpublished report of a guinea pig maximisation test conducted to current regulatory guidelines is available (Murmann, 1988). Twenty and 10 animals were utilised in the treated and control groups respectively. For intradermal induction, a 20% $C_{14\text{-}17}$ chlorinated paraffin (40% chlorination, containing 1% epoxy stabiliser) in maize oil was used. At topical induction, undiluted material was applied producing "intense, sometimes haemorrhagic, purulent inflammation" (given that MCCPs do not have any significant irritation potential, this reaction is most likely to be related to pre-treatment with Freund's Adjuvant). An initial challenge using the undiluted $C_{14\text{-}17}$ chlorinated paraffin was conducted. Following the observation in one test and one control animal of a reaction at 48 hours (scores of 1 and 3 respectively) a second challenge was conducted using 50% material in maize oil. No skin responses were seen. Overall, these results indicate a negative response in this test system.

The outcome of two other guinea pig maximisation tests conducted on samples of $C_{14\text{-}17}$ chlorinated paraffins (40-45% chlorination, containing 0.2% epoxy stabiliser) is reported within an unpublished paper (Chater, 1978). These studies are only briefly summarised, but were stated to have been performed using the Magnusson and Kligman method. A 5% concentration of sample material in olive oil was given intradermally followed by topical application at 20%. Challenge was also conducted with 20% preparations. No skin reactions were produced either in test or control animals with any of the samples. No further details were provided such as numbers of test and control animals used and whether any signs of irritation were seen at topical induction.

4.1.2.5.2 Human data

No studies are available.

Respiratory tract

There are no data relating to this endpoint in humans or animals. However, the generally unreactive nature of this group of substances and lack of skin sensitisation potential suggests that they do not possess the potential to causerespiratory sensitisation.

4.1.2.5.3 Summary of sensitisation

No data are available on skin sensitisation potential in humans. No evidence of skin sensitisation was produced in guinea pig maximisation tests using C_{14-17} MCCPs (40 or 45% chlorination). Overall, the available data and generally unreactive nature of MCCPs (and data on SCCPs) indicate an absence of skin sensitisation potential.

Although there are no data relating to respiratory sensitisation in humans or animals, the generally unreactive nature of this group of substances and the lack of skin sensitisation potential suggests that they do not possess the potential to cause such an effect.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

Inhalation

No studies are available.

Oral

A number of studies are available which have all investigated the repeated dose toxicity of a commercially available C_{14-17} MCCP (52% chlorination). This section reports studies of a more conventional design. Further, detailed investigations exploring the mechanisms underlying some of the observed effects and their relevance to human health are reported in another section (see Mechanisms of Toxicity below).

Studies in rats

In a recent study conducted to GLP standards and QA assessment, groups of 10 male and 10 female Fischer 344 rats received 30, 100, 300 or 3000 ppm C_{14-17} MCCP (52% chlorination) by dietary administration for 90 days (CXR, 2005c). The resultant dose levels were: 2.38, 9.34, 23.0 and 222 $mg.kg^{-1}.day^{-1}$ for males and 2.51, 9.70, 24.6 and 242 $mg.kg^{-1}.day^{-1}$ for females. A control group of 20 male and 20 female animals received powdered diet *ad libitum* for the duration of the study. Investigations included clinical observations, body weight and food consumption analysis, clinical chemistry and extensive, GLP-compliant histopathological examinations of liver, thyroid and kidney. Further, detailed investigations exploring parameters related to MCCPs-induced liver, thyroid and kidney toxicity (hepatic T4-UDPGA glucuronyl transferase activity, hepatic peroxisome proliferation, free and total plasma T4, T3 and TSH levels and renal and hepatic α2u globulin levels) were also performed at the end of the study.

No treatment-related deaths or clinical signs were observed and there were no adverse effects on terminal bodyweight, bodyweight gain or food consumption. Small but statistically significant decreases in plasma triglycerides (by 28-39%) and cholesterol (by 14-23%) were observed in the top dose animals only. In the 3000 ppm animals liver and kidney weights were significantly increased by 13-31% and 9-13% of the control values respectively. No effects on liver or kidney weights were observed at the lower dose levels. In males, small but statistically significant decreases in plasma free T3 levels were seen at the two highest dose levels (by 26 and 22% at 300 and 3000 ppm respectively). However, there were no effects on total T3 levels or on free and total T4 levels. In males, there was also a slight increase in

plasma TSH levels (by 17%) but at the top dose only. In females, there were no effects on plasma free or total T3 levels, or on plasma total T4 levels, but a statistically significant increase (by 41%) in plasma free T4 levels was seen at the top dose. The biological significance of this increase (rather than a decrease) is unclear and it is considered likely to be a chance finding. A dose-related increase in plasma TSH levels was observed in female animals of the two highest dose levels (by 20 and 39% at 300 and 3000 ppm respectively).

Hepatic microsomal T4-UDPGA glucuronyl transferase activity was increased in the top dose males (by 82%) and in the 100, 300 and 3000 ppm females (by 30, 30 and 252% respectively). There was no effect of MCCPs administration on hepatic peroxisome proliferation as determined by palmitoyl CoA oxidation. Alfa2u globulin levels (determined by Western blotting) from kidney or liver homogenates were also unaffected by treatment in males. As expected, α2u globulin was not detected in female kidney or liver homogenates. No treatment-related histopathology was observed in the kidney or thyroid of the treated animals, but minimal centrilobular hepatocyte hypertrophy was noted in 9/10 top dose males.

The effects on the liver (the increased liver weight observed in the top dose animals and the minimal centrilobular hepatocyte hypertrophy reported in the top dose males) are likely to be related to increased metabolic activity associated with xenobiotic metabolism, and hence, are considered to be an adaptive response of no toxicological significance. This is confirmed by the observation of significant liver enzyme induction (increased levels of hepatic microsomal T4-UDPGA glucuronyl transferase activity) at the top dose. The effects on thyroid hormones (decreases in free T3 levels in the 300 and 3000 ppm males and increases in TSH levels in the top dose males and in the 300 and 3000 ppm females) appear to be slight, inconsistent changes likely to be related to altered liver metabolic activity. In view of this and given that no concurrent thyroid histopathology was observed, these effects are not considered to be adverse. However, decreases in plasma triglycerides and cholesterol and increased kidney weights were observed at the top dose. Therefore, overall, there were no adverse effects in this 90-day study in F344 rats at exposure levels up to 300 ppm (23.0 and 24.6 mg/kg/day in males and females respectively) MCCPs.

Groups of 10 male and 10 female Sprague-Dawley rats received 0, 5, 50, 500 or 5000 ppm C_{14-17} MCCP (52% chlorination) by dietary admixture for 90 days (Poon *et al*, 1995). These dietary inclusion levels equated to dose levels of approximately 0, 0.4, 4, 36, and 360 $mg.kg^{-1}.day^{-1}$ in males and 0, 0.4, 4, 42 and 420 $mg.kg^{-1}.day^{-1}$ in females. Investigations included urinalysis at 4 and 12 weeks, and haematological and blood biochemistry determinations at study termination. Extensive histopathological examinations were also performed at the end of the study.

No treatment-related deaths or clinical signs were observed and there were no adverse effects on bodyweight gain or food consumption. Increased serum cholesterol was observed on completion of 13-weeks administration of MCCP amongst females only, attaining statistical significance at 50 ppm (4 mg/kg/day) and above. At 5 (0.4 mg/kg/day), 50 (4 mg/kg/day), 500 (36/42 mg/kg/day males/females) and 5000 ppm (360/420 mg/kg/day males/females) respectively, increases were 7%, 18%, 18% and 28% above the mean control value. No similar trend was observed in males. Individual values varied by up to 50% of the means for each group of females. Hence, it is likely that this apparent increase in serum cholesterol has arisen fortuitously rather than as a result of MCCP administration. In addition, in males at 5000 ppm (360 mg/kg/day), there was a slight increase in aspartate aminotransferase (ASAT) activity (about 20% higher than control) indicative of minimal liver damage and inorganic phosphate (about 13% higher than control), which may be indicative of kidney damage.

Changes seen in some of the haematology parameters were minor in degree and likely to have arisen fortuitously.

At 5000 ppm (360/420 mg/kg/day males/females) significant increases in absolute and relative liver weights were seen in males and females (28% and 48% greater than control respectively for absolute weights). Absolute and relative kidney weight was increased (by 11%) in both sexes at 5000 ppm (360/420 mg/kg/day males/females). Histopathologically, in the liver, minimal to mild anisokaryosis and vesiculation of the nuclei was seen in males and females at 500 (36/42 mg/kg/day males/females) and 5000 ppm (360/420 mg/kg/day males/females) (7-10 animals affected). In addition, in the 5000 ppm males (360 mg/kg/day) and in the 500 (42 mg/kg/day) and 5000 ppm (420 mg/kg/day) females there was an increase in 'perivenous homogeneity' of the liver (an increase in cellular volume involving the mid-zonal hepatocytes, or centrilobular hypertrophy). Single cell necrosis was also reported in the liver of males and females at 5000 ppm (360/420 mg/kg/day males/females) although the incidence was not stated. There were no histological changes in the liver at 50 ppm (4 mg/kg/day) or less. Dose-related morphological changes were observed in the thyroid glands of both males and females, affecting both the architecture (reduced follicle sizes and collapsed angularity) and the epithelium (increased height, cytoplasmic vacuolation and nuclear vesiculation). The changes were generally minimal to mild in nature and were observed in the males at 500 (36 mg/kg/day) and 5000 ppm (360 mg/kg/day) and in the females starting at 50 ppm (4 mg/kg/day).

Changes in the kidney included increased hyaline-droplet like cytoplasmic inclusions (considered further in 'Mechanisms of Toxicity') in males of all doses. The severity of this effect was rated as minimal to mild, and significant accumulation of hyaline droplets was observed only at 5000 ppm (360 mg/kg/day). These changes were not observed in females. Also in the kidney, a dose-related inner medullary tubular dilation (of minimal severity) was recorded in females and was seen in 0/10, 0/10, 1/10, 4/10, 8/10 animals respectively at 0, 5 (0.4 mg/kg/day), 50 (4 mg/kg/day), 500 (42 mg/kg/day) or 5000 ppm (420 mg/kg/day) dietary levels of MCCP, but was not seen in any treated groups of males.

The toxicological significance of the effects observed in the liver is unclear and may be related to increased metabolic activity associated with xenobiotic metabolism. This is discussed in more detail in 'Mechanisms of Toxicity'. There is also some concern with the observation of single cell necrosis at 5000 ppm (360/420 mg/kg/day males/females) (this effect was not seen at lower exposure levels). The slight effects seen in the thyroid starting from 50 ppm (4 mg/kg/day) (females only) are likely to be related to altered liver metabolic activity; however, since in this same study, induction of liver enzyme activity was not measurable at doses below 5000 ppm (360/420 mg/kg/day males/females) and hepatic morphological changes were not seen at doses below 500 ppm (36/42 mg/kg/day males/females) (see Mechanisms of Toxicity), it cannot be completely ruled out that the thyroid changes represent primary adverse effects. The increased hyaline-droplet like cytoplasmic inclusions in the kidney can be considered as of doubtful relevance to human health. However, inner medullary tubular dilation (seen in females at 4 $mg.kg^{-1}.day^{-1}$ or more) remains as an indicator of renal damage that may be of importance to human health. Questions have been raised over the validity and reliability of this study's findings, in particular in relation to the scoring system used for classifying the histopathological findings. It is noted that the effects on female kidney reported in this study starting from the relatively low dose of 4 mg/kg/day have not been seen in other rat 90-day studies even at higher dose levels. It is also noted that although histopathological findings of the thyroid have been described in other rat 90-day studies, only this study has reported them from the relatively low

dose of 4 mg/kg/day. It is clearly apparent that this study is unrepresentative of the repeated dose toxicity profile of MCCPs and hence, it should not be used for risk characterisation purposes. It could possibly be argued that these differences in findings in the different studies are due to the different strain of rats used by Poon and colleagues (Sprague-Dawley) compared to that (F344) employed in the other 90-day studies. However, at present, there is no evidence indicating that Sprague-Dawley rats differ from F344 rats in any kinetic or dynamic factor.

In an unpublished study, groups of 15 male and 15 female F344 rats were administered C_{14-17} MCCP (52% chlorination) in the diet at levels corresponding to 0, 10, 100 or 625 $mg.kg^{-1}.day^{-1}$ for 90 days (IRDC, 1984; see also Section 4.1.2.1). Observations included haematology, blood biochemistry and urinalysis at various timepoints throughout the study, and an ophthalmoscopic examination pre-terminally. A comprehensive histopathological examination was also performed.

There were no treatment-related mortalities although one control female and one female at 100 $mg.kg^{-1}.day^{-1}$ died during the study. These deaths were apparently the result of blood collection and not related to treatment. No treatment-related clinical signs of toxicity were noted amongst any animals. There were no treatment-related ophthalmoscopic findings. At the top dose, slightly reduced body weight gain relative to controls in both sexes was associated with a similar reduction in food consumption. In females, a dose-related decrease in water consumption was seen (by up to approximately 20% at 625 $mg.kg^{-1}.day^{-1}$). There were no haematological changes that could be considered toxicologically significant. Slight, but statistically significant blood biochemistry changes were noted in both sexes (blood urea nitrogen increased by 35% at 625 $mg.kg^{-1}.day^{-1}$, and total protein increased by 13% at 625 $mg.kg^{-1}.day^{-1}$). A statistically significant increase (25%) in serum cholesterol was also noted in females at the top dose. At 625 $mg.kg^{-1}.day^{-1}$ there were marked decreases in urinary volume noted at each of weeks 5, 8, and 13 (males, 52-72% lower than controls, females 58-74% lower than controls), with concommitant increases in specific gravity and osmolality. Animals in other groups were not adversely affected. In addition, there were slight increases in the concentration of urinary protein, ketones, bilirubin and urobilinogen at 625 $mg.kg^{-1}.day^{-1}$, which were probably a consequence of the reduction in urinary volume.

Absolute and relative liver weights were statistically significantly increased in males and females at 100 and 625 $mg.kg^{-1}.day^{-1}$ with the increases in absolute values being 22-26% and 64-92% greater than control values respectively. Absolute and relative kidney weights were statistically significantly increased in males and females at 625 $mg.kg^{-1}.day^{-1}$ only (18% greater than controls). There was also a significant increase in absolute thyroid weights in males only at the top dose (50% greater than controls) and adrenal weights in both sexes (25% greater than controls).

Histopathology revealed hepatocellular hypertrophy of ‘trace’ severity in 13/15 males and 13/15 females at 625 $mg.kg^{-1}.day^{-1}$ with 1/15 males at 100 $mg.kg^{-1}.day^{-1}$ also affected. Mild to moderate thyroid hypertrophy was seen in almost all control and treated male animals although there was a trend towards increasing severity with increasing dose. Females were unaffected. A similar pattern was observed for thyroid hyperplasia, being of trace to mild severity in almost all males, but with a general trend towards increasing severity with increasing dose. The effects seen in the liver and thyroid are discussed further in the section on Mechanisms of Toxicity, and overall, given the underlying mechanism(s), are considered to be of no relevance to human health.

A significant increase above controls in the incidence of 'chronic nephritis' was seen in the top dose males (10/15 vs 1/15 in controls), although the effect was graded only as 'mild'. 'Chronic nephritis' was also reported in 3/15 and 4/15 animals at 10 and 100 $mg.kg^{-1}.day^{-1}$ respectively. However, at 10 and 100 $mg.kg^{-1}.day^{-1}$ the severity of these changes was graded as 'trace'. Overall, given the low incidence observed at the low- and mid-dose levels and the mildness of the effect reported at all dose levels, although kidney changes were observed from 10 $mg.kg^{-1}.day^{-1}$, a lesion considered to be of toxicological significance only occurred at the top dose of 625 $mg.kg^{-1}.day^{-1}$. Chronic nephritis (although not dose-related) was also present in some females. Renal tubular pigmentation (yellow-brown granular pigment in the cytoplasm of renal tubular epithelial cells) was seen in females only at 625 $mg.kg^{-1}.day^{-1}$ (9/14 animals). The terminology 'chronic nephritis' seems somewhat misleading (given that this is a 90-day study rather than 'life-time') and possibly reflects the age of the report. The 'chronic nephritis' is described in further detail: 'a mixed population of interstitial inflammatory cells, tubular regeneration and minimal degenerative changes in the tubular epithelium occurring alone or in combination.' These lesions are indicative of renal toxicity that, given the age of rats in this study, could not be described as 'progressive glomerular nephropathy' that is commonly seen in some strains of aging rats (such as Sprague-Dawley), nor, by the nature of the description, are they similar to hyaline droplet nephropathy. Overall, there is some cause for concluding that the renal changes observed at the top dose represent a toxicological significant lesion that is not attributable to hyaline droplet nephropathy. Supporting evidence of renal pathology comes from the observation of increases in urinary protein, bilirubin and urobilinogen, and reduced water consumption at the top dose.

With kidney changes observed at 625 $mg.kg^{-1}.day^{-1}$, a NOAEL of 100 $mg.kg^{-1}.day^{-1}$ is identified from this 90-day study in F344 rats.

A 90-day repeated oral exposure study in rats was briefly summarised in a review by Birtley *et al* (1980); no original study report was available. Groups of 24 male and 24 female Wistar-derived rats were fed diets containing 0, 500, 2500 or 5000 ppm C_{14-17} MCCP (52% chlorination, containing epoxidised vegetable oil as a stabilizer). Assuming a mean bodyweight of 300g for males and 250g for females, and a food consumption of $20g.day^{-1}$ for males and $16g.day^{-1}$ for females, the mean intakes of test substance were approximately 0, 33, 167, 333 $mg.kg^{-1}.day^{-1}$ (males) and 0, 32, 160, 320 $mg.kg^{-1}.day^{-1}$ (females). Haematological and clinical chemistry analyses were performed pre-study, at 6 weeks and again at study termination. An extensive histopathological examination (including liver, kidney and thyroid) was conducted at 90 days. At 6 weeks, further groups of 24 male and 24 female rats fed a diet containing 250 ppm MCCP (approximately equivalent to 16 $mg.kg^{-1}.day^{-1}$) were introduced into the experiment together with an additional control group of 12 male and 12 female rats. These rats were treated in an identical manner to those on the main study.

No deaths or clinical signs of toxicity were noted. Bodyweight gain of males receiving 2500 ppm and 5000 ppm was statistically significantly reduced (17% and 25% lower than controls respectively). The weight gain of males at 500 ppm, and all groups of treated females, was not adversely affected. A statistically significant decrease in food consumption was noted amongst all treated groups of males. However, when presented on an individual basis, the consumption in males receiving 5000 ppm was less than 10% lower than that of controls. Food consumption of females was not adversely affected.

A statistically significant increase in relative liver weight was seen amongst males at 2500 and 5000 ppm (15% and 22% greater than controls, respectively), and amongst females at 500, 2500 and 5000 ppm (11%, 21%, 48%). Relative kidney weight was also affected, being increased by 15% at 5000 ppm in both sexes. Gross examination revealed a dose-related

congestion of the kidney, the incidence and severity of which was not given. However, it was stated that no histological abnormalities were observed in any tissues by light microscopy. At 500 ppm and above, a dose-related proliferation of liver smooth endoplasmic reticulum (SER) was observed using electron microscopy.

The observed increases in liver weight and SER proliferation are indicative of an adaptive response occurring as a result of enzyme induction in this organ. In view of the brevity of reporting in this study, it is not possible to draw firm conclusions on the toxicological profile of this MCCP (52% chlorination).

In a study primarily of liver function, groups of 5 male and 5 female F344 rats received 0, 150, 500, 1500, 5000 or 15000 ppm C_{14-17} MCCPs (52% chlorination) by dietary administration for 14 days (Spicer, 1981). Based on the food consumption and bodyweight values, these dietary inclusion levels were equivalent to approximately 0, 18, 58, 170, 550, and 1540 $mg.kg^{-1}.day^{-1}$ in males and 0, 18, 58, 180, 580, and 1290 $mg.kg^{-1}.day^{-1}$ in females. At study termination, hepatic microsomal protein, aminopyrine demethylase, and cytochrome P450 levels were determined. Histopathology examinations were limited to liver, kidneys, spleen, and ovaries. There were no further investigations.

No deaths or clinical signs of toxicity were observed. At 15000 ppm, statistically significant decreases in food consumption (by up to 31% in females) were noted, probably related to dietary unpalatability. At 5000 and 15000 ppm, a statistically significant elevation (up to 80%) in both absolute and relative liver weights was seen in all animals. Also, absolute and relative ovary weights were significantly decreased (by 38%) in top dose females compared to the controls.

Histopathologically, diffuse mild hypertrophy was noted in the liver of all animals at 5000 and 15,000 ppm; no changes were noted in the liver of animals at 1500 ppm or below. There were no histopathological findings in the ovary, indicating that the decrease in weight of this organ was of doubtful toxicological importance.

In summary, the liver hypertrophy produced at dose levels of 550-580 $mg.kg^{-1}.day^{-1}$ and above is considered to be indicative of an adaptive response of this organ to an increase in metabolic demand and/or a reflection of peroxisome proliferation (see section on Mechanisms of Toxicity).

In a range-finding study, C_{14-17} MCCP (52% chlorination) were administered by oral gavage to rats for 5 days at doses of 0, 1000, 2500 or 5000 $mg.kg^{-1}.day^{-1}$ in corn oil (IRDC, 1982b). No deaths or clinical signs of toxicity occurred. All the animals were sacrificed at the end of the 5-day treatment period and subjected to a gross pathological examination. There were no macroscopic findings following examination of the contents of the abdominal, thoracic and cranial cavities. No further investigations were made, and overall this study is of very limited value.

Studies in dogs

An unpublished 90-day repeated exposure dietary study in dogs was reviewed by Birtley *et al* (1980); the original study report was not available. Groups of 4 male and 4 female beagles received 0, 10, 30, or 100 $mg.kg^{-1}.day^{-1}$ MCCP (52% chlorination) for 90 days. After 42 and 90 days of treatment haematological and clinical chemistry determinations were performed. Urinalysis and extensive histopathology were carried out at study termination.

As the full study report was not available, it is difficult to draw firm conclusions. However, the only findings apparently observed related to the liver. There was reported to be a statistically significant increase in the activity of serum alkaline phosphatase and in relative liver weight at 100 $mg.kg^{-1}.day^{-1}$, both of which were unquantified in the review. It was also stated that cloudy, pale and enlarged hepatocytes and an increase in SER in these cells were seen in "some" dogs at 30 and 100 $mg.kg^{-1}.day^{-1}$. It is considered that these liver changes are reflective of a physiological response due to increased metabolic demand. No more information from this study is available.

Dermal

No studies are available.

4.1.2.6.2 Human data

No studies are available.

4.1.2.6.3 Mechanisms of toxicity

A number of studies have been conducted to investigate the possible underlying mechanistic events leading to the observed spectrum of toxicity in animals, with the view to assessing their relevance to humans. In general, studies in rats have looked at the underlying mechanism of effects in the liver, thyroid and kidneys. Studies in mice and guinea pigs have focused mainly on the liver.

Liver and thyroid

Studies in rats

Groups of 10 male and 10 female F344 rats received 0, 312 or 625 $mg.kg^{-1}.day^{-1}$ of a C_{14-17} MCCP (40% chlorination) via oral gavage for 15, 29, 57 or 91 days (Wyatt *et al*, 1997). Blood samples were collected on day 8 and at termination on days 15, 29, 57 and 91, for analysis of T_3, T_4 and TSH. Replicative DNA synthesis at a number of different organ sites was assessed using bromodeoxyuridine incorporation seven days before sacrifice on days 29 and 91. Liver and thyroid sections were examined histopathologically and hepatic microsomes prepared for determination of UDPG-transferase activity (UDPG-T; an enzyme playing a key role in the excretion of thyroxine - T_4) and peroxisomal fatty acid β-oxidation.

There was a statistically significant increase in relative liver weight at 312 and 625 $mg.kg^{-1}.day^{-1}$ at all sacrifice timepoints (both sexes) by up to 37% and 72% respectively. Absolute liver weights and data on bodyweights were not presented. Dose-dependent centrilobular hypertrophy was apparently observed, but no details on the incidence or severity of this finding were reported. A dose-related and statistically significant increase in hepatic peroxisomal β-oxidation was noted at 312 and 625 $mg.kg^{-1}.day^{-1}$ from day 29 onwards (about 2.7-fold and 3.3-fold respectively at study termination). Also, a dose-related and statistically significant increase of at least 100% was seen in UDPG-transferase activity at 312 and 625 $mg.kg^{-1}.day^{-1}$ from day 15. It should be noted that UDPG-transferase activity was not measured at day 8.

Levels of free and total plasma T_3 were reduced relative to controls at both doses and in both sexes, but only attained statistical significance on days 15 and 57. Levels of TSH were

significantly increased at both doses (up to a 2-fold increase) on day 8 only (males only). By day 91, in females only, levels of free T_3 had recovered such that in both dose groups the values were significantly above control levels. Significant reductions (by up to 25%) in total plasma T_4 were measured in treated females only, on day 57 of the study. Thyroid follicular cell hypertrophy was reportedly apparent at both doses throughout the study, and was said to be accompanied by follicular cell hyperplasia on days 55 and 91. However, no information on the incidence and severity of these changes was presented. Thyroid cell replicative DNA synthesis was significantly increased on day 29 at both dose levels, but not at day 91.

The pattern of these results fits a general hypothesis that an increase in liver UDPG-transferase activity leads to decreased plasma T_3/T_4, leading to increased TSH and thyroid stimulation.

In an investigation primarily of the liver and thyroid, groups of 5 F344 rats, received 0, 10, 50, 100, 250, 500 or 1000 $mg.kg^{-1}.day^{-1}$ mixed C_{14-17} MCCP (40% chlorination) by oral gavage for 14 days (Wyatt *et al*, 1993). Liver weights were determined and peroxisomal fatty acid β-oxidation assessed as a potential marker for peroxisomal proliferation. In relation to thyroid effects, blood levels of thyroid stimulating hormone (TSH), T_3 and T_4 (both free and total forms of each) were measured in samples obtained only from the top dose and control animals. The activity of UDPG-transferase was also determined in liver microsomes only at 1000 $mg.kg^{-1}.day^{-1}$ and in the controls.

At 100, 250, 500 and 1000 $mg.kg^{-1}.day^{-1}$ increases (generally statistically significant, although the increase at 250 $mg.kg^{-1}.day^{-1}$ did not follow the generally dose-related pattern) in absolute and relative liver weights were observed (18, 2, 29 and 32% respectively for absolute weights). There were no adverse effects on liver weight at 10 and 50 $mg.kg^{-1}.day^{-1}$. A significant increase in peroxisomal fatty acid β-oxidation activity occurred at 500 and 1000 $mg.kg^{-1}.day^{-1}$ (around 102 and 170% greater than the control activity, respectively) although no significant effects were seen at 250 $mg.kg^{-1}.day^{-1}$ and below. Significant reductions in both free and total plasma T_4 levels (by 44 and 53% respectively) and an almost 2-fold increase in UDPG-transferase activity was noted at 1000 $mg.kg^{-1}.day^{-1}$. T_3 levels remained unaffected, whilst TSH levels showed an approximate 1.5-fold increase at 1000 $mg.kg^{-1}.day^{-1}$ (notably other exposure levels were not investigated). No other significant changes were identified.

These results show that peroxisome proliferation is a factor in the effects on the liver of MCCPs, and that thyroid stimulation could arise from increased TSH, consequent to increased clearance of T_3/T_4 via an increase in hepatic UDPG-transferase.

As part of a 90-day dietary study in which Sprague-Dawley rats received 0, 5, 50, 500 or 5000 ppm C_{14-17} MCCP by dietary admixture (reported in Section 4.1.2.6), a number of parameters were measured in relation to liver function (Poon *et al*, 1995). These included measurements of UDPG-transferase, urinary ascorbic acid (a metabolite of glucuronic acid, hence a possible indicator of increased UDPG-transferase activity) and liver vitamin A levels (vitamin A levels were measured as exposure to, and subsequent tissue accumulation of TCDD or PCBs, can lead to decreased levels in the liver).

At termination, in females at 5000 ppm (approximately 400 $mg.kg^{-1}.day^{-1}$), hepatic UDPG-transferase and N-acetylglucosaminidase were significantly elevated (by 70 and 50% respectively). No effects on UDPG-transferase or N-acetylglucosaminidase were observed in animals receiving 500 ppm or less. At 12 weeks, an approximately 6-fold increase in urinary ascorbic acid was measured at 500 ppm (approximately 40 $mg.kg^{-1}.day^{-1}$) and 5000 ppm

(females) and 5000 ppm (males) only; other groups were not affected. Concentrations of liver vitamin A were significantly reduced in males and females (by up to 59%) at 5000 ppm and in females only at 500 ppm (by 23%). As indicated above, the observation of the decreased hepatic vitamin A may be interpreted as circumstantial evidence of uptake of this MCCP.

In an investigation primarily of liver function, groups of 4-5 male and female F344 rats received 0 or 1000 $mg.kg^{-1}.day^{-1}$ C_{14-17} MCCP (40% chlorination) in corn oil by oral gavage for 14 days (Elcombe *et al*, 1997). Following sacrifice, livers were removed and microscopically examined and a number of biochemical determinations (including studies of peroxisomal β-oxidation and cytochrome P450 levels) conducted on prepared microsomes. UDPG-transferase activity was not measured.

Hepatocellular hypertrophy and proliferation of peroxisomes and smooth endoplasmic reticulum was observed in the MCCP-treated rats. The hepatic peroxisome proliferation was confirmed by morphometric analysis and described as "marked". Increases (at least 1.5-fold) in relative liver weights (absolute values not presented) and levels of cytochrome P450 were measured in comparison with the controls and peroxisomal β-oxidation showed up to a 3.5-fold increase, with the degree of effect in males being almost double that produced in females.

Groups of 4 male rats received 1000 $mg.kg^{-1}.day^{-1}$ C_{14-17} MCCP (50% chlorination) by i.p. administration for 4 days (Nilsen *et al*, 1981). Following sacrifice on the 5th day, a number of liver microsomal enzyme activities were determined. There was a statistically significant increase in relative liver weight (12% greater than control), but changes in absolute liver weight did not achieve statistical significance. In relation to liver microsomal cytochrome P450 enzyme activity, an approximately 1.5-fold increase in benzo(a)pyrene hydroxylase activity was demonstrated as measured by the formation of the 4,5-diol metabolite of benzo(a)pyrene *in vitro*.

Studies in mice

In a study to investigate hepatic effects, groups of 5 male Alderley Park CD-1 mice received 0, 10, 50, 100, 250, 500 or 1000 $mg.kg^{-1}.day^{-1}$ mixed C_{14-17} MCCPs (40% chlorination) by oral gavage for 14 days (Wyatt *et al*, 1993). Liver weight determinations were performed and peroxisomal fatty acid β-oxidation was assessed as a marker for peroxisome proliferation.

Absolute liver weight was significantly increased (by 22%) at 1000 $mg.kg^{-1}.day^{-1}$. There were no changes in liver weight at 500 $mg.kg^{-1}.day^{-1}$ and below. Significant increases in peroxisomal fatty acid β-oxidation activity were noted at 500 and 1000 $mg.kg^{-1}.day^{-1}$ only (272% and 168% respectively); there were no adverse effects at 250 $mg.kg^{-1}.day^{-1}$ and below.

Groups of 4-5 male and female $B6C3F_1$ mice received 0 or 1000 $mg.kg^{-1}.day^{-1}$ mixed C_{14-17} MCCPs (40% chlorination) in corn oil via oral gavage for 14 days (Elcombe *et al*, 1997). Following sacrifice, livers were removed for microscopic examination and following the preparation of microsomes, a number of biochemical determinations (including peroxisomal β-oxidation and cytochrome P450 levels) conducted.

At microscopy, liver hypertrophy together with smooth endoplasmic reticulum and peroxisome proliferation were seen in the MCCP-treated group. Morphometric analysis confirmed the peroxisomal proliferation as "marked". A 20% increase in relative liver weight was seen in females compared to the controls, although there was no effect on male relative liver weights. No data were provided on absolute liver weights. Elevations in cytochrome P450 levels of 15-27% occurred and β-oxidation was increased approximately 2- to 4-fold.

Male mice received 0 or 400 $mg.kg^{-1}.day^{-1}$ C_{14-17} MCCP (70% chlorination) in corn oil for 5 days by i.p. administration (Meijer *et al* 1981, Meijer and DePierre, 1987). Liver microsomal enzyme activities were measured. Significant increases (28%) in relative liver weight were observed compared to the controls, and a 1.5 to 3-fold elevation in epoxide hydrolase activity was noted together with a 50% increase in microsomal cytochrome P450 content.

Studies in guinea pigs

Groups of 4-5 male guinea pigs received 0 or 1000 $mg.kg^{-1}.day^{-1}$ C_{14-17} MCCPs (40% chlorination) in corn oil by oral gavage for 14 days (Elcombe *et al*, 1997). Following sacrifice, livers were removed and microscopically examined and a number of biochemical determinations (including peroxisomal β-oxidation as a marker for peroxisome proliferation) and cytochrome P450 levels conducted on prepared microsomes.

Electron microscopy revealed no treatment-related changes in the liver and no evidence of peroxisome proliferation was found upon morphometric analysis. However, a 35% elevation in β-oxidation was obtained compared to the controls. Relative liver weight was increased by 35% with absolute values not being reported. Treatment produced virtually no effect in liver cytochrome P450 levels.

Kidney

As reported previously, groups of 10 male and 10 female F344 rats received 0, 312 or 625 $mg.kg^{-1}.day^{-1}$ of a 40% chlorinated paraffin via oral gavage for 15, 29, 57 or 91 days (Wyatt *et al*, 1997). Replicative DNA synthesis in the kidney was assessed using bromodeoxyuridine incorporation seven days before sacrifice on days 29 and 91, and at termination kidney sections were examined histopathologically.

In male rats, renal tubular eosinophilia was noted in males at 312 and 625 $mg.kg^{-1}.day^{-1}$ from day 15 onwards, and the incidence and severity of this effect increased with time, and in a dose-related manner; from day 29 onwards, this was accompanied by focal, followed by multifocal, areas of basophilia. The kidneys of female rats remained unaffected by treatment. Significant increases in replicative DNA synthesis in the kidney were seen in males on days 29 and 91, with no effect seen in females. Immunocytochemical staining demonstrated the presence of a statistically significant increase (by 15%) in the amount of α2u-globulin in the proximal convoluted tubules of male rats. This was not restricted to hyaline droplets and was seen dispersed throughout the cytoplasm; this is not typical of light hydrocarbon nephropathy, and is consistent with other repeated-exposure studies in which renal effects were noted as being not typical of male rat-specific nephropathy (see Section 4.1.2.6.1).

As part of a 90-day dietary study in Sprague-Dawley rats (reported in Section 4.1.2.6.1), urinary β_2u globulin was measured in relation to kidney function (Poon *et al*, 1995). Levels of β_2u globulin were determined since an increase in this protein is usually associated with kidney proximal tubular damage and hyaline-droplet nephropathy. Reduced levels of urinary β_2u globulin were seen in treated males (59%, 60%, 47%, and 56% lower than controls respectively at 5, 50, 500, and 5000 $mg.kg^{-1}.day^{-1}$). A similar reduction was seen in females (13%, 40%, 26%, and 49% respectively). The profile of results does not show a clear dose-response relationship, and the apparent reduction in urinary β_2u globulin observed in this study cannot be readily explained. It is plausible that the apparent changes in relation to concurrent controls may be due to unusually high control values although the lack of

historical control dat amakes this difficult to clarify. The significance of the reduction in urinary β_2u globulin is unclear.

Additional research into the mechanisms of nephrotoxicity and carcinogenicity

The following series of investigations has been conducted to help elucidate the mechanism underlying the formation of kidney tumours that have been seen in carcinogenicity studies on SCCPs (SCCP ESR Risk Assessment Report, 2000). It is proposed that these will inform discussions on the hazard identification of SCCPs. However, as there is extensive read-across of toxicological data to MCCPs, these data will also provide information for the hazard identification and risk assessment of MCCPs.

As part of a series of mechanistic studies, groups of 3-4 male and 4 female Fischer 344 rats received 0 or 1000 $mg.kg^{-1}.day^{-1}$ of a mixed C_{10-12} paraffin (58% chlorinated) in corn oil by oral gavage 7 days/week for 28 days (Elcombe, 1999). Investigations were focused on the liver and kidney and included: light microscopy with immunocytochemical staining for α2u globulin, two-dimensional polyacrylamide gel electrophoresis of kidney homogenates and subsequent immunochemical staining for α2u, quantification of renal bromodeoxyuridine (BrdU) incorporation (to assess S-phase DNA synthesis) using osmotic pumps installed 7 days before terminal sacrifice, and an assay of cyanide-insensitive palmitoyl CoA oxidation (as a marker of peroxisomal β-oxidation activity) from kidney and liver homogenates.

At termination, no histological abnormalities were observed in the kidneys of control males. Moderate proximal tubular hypertrophy/eosinophilia was seen in all males receiving 1000 $mg.kg^{-1}.day^{-1}$ SCCP. Minimal to moderate cortico-medullary calculi were seen in all control females, slight to minimal tubular basophilia in 2/4, and moderate proximal tubular hypertrophy/eosinophilia in one control female. Slight to moderate cortico-medullary calculi and moderate proximal tubular hypertrophy/eosinophilia were seen in all females at 1000 $mg.kg^{-1}.day^{-1}$. No information was presented in relation to histological investigations that were stated to have been conducted on the liver.

On completion of 28 days, control males were judged to have a 'normal' content (assessed semi-quantitatively) of α2u globulin as determined by immunochemical staining of 2-D PAGE and histologically. Localised high concentrations were found in the pars convoluta (the expected region of high peroxisomal activity), and with less dense, and diffuse amounts being found in the pars recta, the straight portion of the proximal tubules. In this first study, a decreased amount of α2u globulin immunostaining in the pars convoluta was observed in SCCP-treated males. There was little or no change in the extent of immunostaining in the pars recta region. For females, there was no α2u globulin observed in the pars recta of control or treated animals, and little or no staining in the pars convoluta.

At 28 days, there was a statistically significant decrease in BrdU incorporation in two regions of the kidney (pars convoluta and pars recta) of male rats treated with the SCCP compared to controls. The decrease was more marked in the pars convoluta than the pars recta. In females, there was essentially no effect on BrdU incorporation in the pars recta, but a statistically significant decrease in the pars convoluta.

In the kidney homogenates taken from rats at 28 days, the rate of peroxisomal β-oxidation was increased approximately 2.5-fold in both male and females receiving SCCP compared to controls. No data were presented for the enzyme activity in liver homogenates that were taken.

Overall, this investigation showed histologically-observable kidney lesions (hypertrophy and increased eosinophilia in the proximal convoluted tubules) related to treatment with this SCCP, with a concommitant decrease in α2u globulin formation and a decrease in cell replication in the proximal convoluted tubules. Increased peroxisomal activity was noted in kidney of both males and females. No conclusions can be drawn in relation to effects on the liver as no data were presented in this report, despite the indication that investigations had been performed.

In another 28-day study by the same author, groups of 4 male and 4 female Fischer 344 rats received 0 or 625 $mg.kg^{-1}.day^{-1}$ of a C_{12} paraffin (59% chlorinated) in corn oil by oral gavage 7 days/week. This study also included groups of 4 animals that received 300 $mg.kg^{-1}.day^{-1}$ 1,4-dichlorobenzene (as a 'positive control' for α2u globulin renal deposition). As with the previous study, kidneys and liver were examined by light microscopy, immuno-stained for assessment of α2u globulin deposition (kidneys only), and renal BrdU incorporation quantified. In addition, an assay of cyanide-insensitive palmitoyl CoA oxidation was performed from kidney and liver homogenates.

There were no abnormalities observed histologically in the liver or kidneys of control males and females (with the exception of slight renal tubular basophilia in one female). Marked proximal tubular hypertrophy/eosinophilia was observed in the kidneys of all SCCP-exposed males. Marked panlobular or centrilobular eosinophilia/hypertrophy, moderate periportal hyperplasia and loss of glycogen were seen in the liver of all SCCP-exposed males. The lesions seen in DCB-exposed animals were moderate hyaline droplet nephropathy in the kidneys of 3/4 males receiving DCB. In addition, slight renal tubular eosinophilia or proximal tubular eosinophilia, and slight, increased intratubular protein in the pars recta were observed incidentally. In the liver, slight to moderate centrilobular eosinophilia/hypertrophy was seen in all DCB-treated males. In females, slight to moderate proximal tubular hypertrophy/eosinophilia was seen in the kidney of all SCCP-exposed animals, with the additional observation of tubular basophilia in 1/4 females. Moderate or marked panlobular eosinophilia/hypertrophy, moderate or marked periportal hyperplasia were seen in the liver of all SCCP-treated females. No abnormalities were seen in the kidneys of DCB-treated females, although slight hepatic centrilobular eosinophilia and moderate periportal hyperplasia were observed in all or most animals.

On completion of 28 days, slight α2u globulin formation was noted in the pars convoluta of control males and in the pars recta, little or no α2u globulin was detected. The same pattern of distribution was maintained in SCCP-exposed animals although staining was increased (slight to moderate in the pars convoluta) compared to the controls. For DCB-exposed animals, staining was more intensive still (moderate to severe). And in the case of SCCP- and DCB-treated animals, the staining was more intense in the pars convoluta than the pars recta. These results contradict those of the first study in this series in which a decreased amount of α2u globulin immunostaining in the pars convoluta was observed in SCCP-treated males and little or no change in the extent of immunostaining in the pars recta region upon treatment with SCCP. For females in this second study, there was no staining of α2u globulin observed in the pars recta of controls, SCCP- or DCB-treated animals, and little or none in the pars convoluta.

Again in contrast to the first 28-day study, SCCP caused an increase in BrdU incorporation in males and females with the effect being more pronounced in males than females. For males receiving DCB, the incorporation was even more pronounced although females were unaffected. It is plausible that the contrasting results may be due to the different exposure levels used.

No details were provided on renal peroxisomal β-oxidation activity and as with the first 28 day study, no data were presented on any of the liver investigations that were documented as having been performed (with the exception of light microscopy).

This second 28-day study seems to indicate that SCCP exposure does lead to a preferential increase in α2u globulin deposition in the pars convoluta of male rats (which is typical of the pattern documented for other agents implicated as causing 'male rat specific light hydrocarbon nephropathy'), and that this is associated with changes seen histopathologically in the kidneys. The increase in BrdU incorporation suggests an increase in cell proliferation that, given the lack of genotoxic activity of SCCPs, would most likely be associated with the postulated cytotoxicity resulting from α2u accumulation.

The report also presented summary data of the quantification of α2u globulin in kidney samples taken at days 15, 29, 57, and 91 from groups of 5 or 10 male of female rats that had received 0, 312, or 625 $mg.kg^{-1}.day^{-1}$ of a C_{12} paraffin (59% chlorinated) in corn oil. At the highest exposure level an increase in the formation of α2u globulin was demonstrated in male rats only.

More recent, further investigations have been conducted at the same laboratories:

Investigation 1: Groups of 20 male and female F344 rats received 0 or 625 $mg.kg^{-1}.day^{-1}$ of a SCCP (Chlorowax 500C, C_{12}: 60%Cl) in corn oil, by oral gavage daily for 28 days (Warnasuriya *et al*, 2001). In addition, groups of 10 rats received 300 $mg.kg^{-1}.day^{-1}$ 1,4-Dichlorobenzene (DCB) and 150 $mg.kg^{-1}.day^{-1}$ *d*-limonene (DL) as positive controls for α2u deposition. For these mechanistic studies, investigations were restricted to the liver and kidney, and all animals were 10-12 weeks old at the start of each investigation. Seven days before termination osmotic mini-pumps were implanted to assess bromodeoxyuridine (BrdU) incorporation in kidney cells (as a measure of cell proliferation). At termination, kidney samples were evaluated for α2u formation using immunohistochemical techniques. Liver (where α2u is synthesised) and kidney α2u levels were also assessed using immunoblotting after 2-D polyacrylamide gel electrophoresis (PAGE) using isoelectric focussing and molecular weight as separation parameters. Palmitoyl CoA activity (a marker of peroxisome proliferation) was determined in liver samples. In addition, liver mRNA levels and α2u gene transcription products (using a reverse-transcriptase polymerase chain reaction) were measured spectrophotometrically.

The immunohistochemical technique (not quantitative) demonstrated the presence of α2u in the renal cortex of control and SCCP-treated male rats, with hyaline droplet formation and more intense staining in DCB- and DL-treated males. Immunoblotting for α2u of 2-D PAGE resolved proteins from kidney homogenates revealed similar migration patterns for control, SCCP, DCB and DL-treated male rats. The intensity of staining for α2u was similar in controls and SCCP-treated rats and greater in the DCB and DL-treted animals. This was further supported by the semi-quantitative assessment of band intensity; levels of α2u were broadly similar to controls.

For the liver, immunoblotting for α2u of 2-D PAGE revealed levels that were similar between control, DCB- and DL-treated males. However, there was a marked decrease in hepatic α2u for SCCP-treated animals. This was also seen in the semi-quantitative intensity assessment.

Cell proliferation, assessed using BrdU incorporation, was similar in SCCP-animals compared to controls (mean percentage of proliferating cells 1.2 and 1.6% respectively). The mean

percentage of proliferating cells was higher and attained statistical significance in DCB- and DL-treated rats (4.5% and 7.3% respectively).

An increase in the marker of hepatic peroxisome proliferation (palmitoyl CoA activity) was seen in SCCP-treated animals compared to controls (enzyme activity increased approximately 2-fold). DCB and DL did not affect palmitoyl CoA activity.

The reverse-transcriptase polymerase chain reaction of liver mRNA showed that α2u synthesis was inhibited in SCCP-treated animals, compared with controls, whereas DCB- and DL-exposure led to increased α2u mRNA synthesis.

Investigation 2: In another experiment, groups of 2-4 male and female F344 rats received 0 or 625 $mg.kg^{-1}.day^{-1}$ of a radiolabelled SCCP, ^{14}C tridecane (C_{13}:55% Cl) in corn oil, by oral gavage daily for 4 days. The qualitative assessment of binding of this to kidney proteins was then assessed by 2-dimensional PAGE of kidney homogenates and visualising bound radiolabel using X-ray film; binding of radiolabelled material to 3 isoforms of α2u was seen to occur in males but not females. The result indicates male rat-specific binding of SCCP to renal α2u.

Investigation 3: In the final stage, groups of 2 male F344 rats received 0 or 625 $mg.kg^{-1}.day^{-1}$ of a radiolabelled SCCP (^{14}C-tridecane, C_{13}: 55%Cl) in corn oil, by oral gavage daily for 4 days. Other groups of 1-2 rats received a single oral gavage dose of 0 or 625 $mg.kg^{-1}$ ^{14}C-tridecane (C_{13}:55%Cl) in corn oil, or 300 $mg.kg^{-1}$ ^{14}C-DCB. After the exposure period, the kidneys were removed and homogenised. Quantitative assessment of the binding of radiolabelled substance to protein was performed using liquid scintillation counting of chromatographically size-separated samples. Kidney α2u levels were also assessed using immunoblotting of samples from the chromatography columns.

Single-exposure of ^{14}C-DCB showed a clear peak of radioactivity corresponding to the elution time of α2u. A smaller peak was seen with a single dose of ^{14}C-tridecane (55%Cl), although there was an additional peak of radiolabelled material that corresponded to albumin. Upon repeated exposure of ^{14}C-tridecane (55%Cl), the peak of α2u-related radioactivity was even smaller. The binding of the radioactive material corresponded with α2u detected by immunoblotting of the collection fraction.

The immunohistochemistry and cell proliferation studies in Investigation 1 indicated that, in contrast to DCB and DL, there was no increase in renal α2u or cell proliferation associated with SCCP.

Increased hepatic peroxisome proliferation activity was observed with SCCP (but not DCB and DL), and this effect is associated with a decrease in hepatic α2u and down-regulation of α2u transcription. A similar response has been seen in the liver of animals exposed to ciprofibrate (a well-documented peroxisome proliferator). Again, the SCCP differs in the hepatic responses usually associated with agents such as DCB and DL that produce kidney tumours by the α2u mechanism; with SCCP there was a reduced synthesis of α2u. However, that which was produced seems to be accumulating in the kidney. In fact, although there was virtually no α2u expression in the liver of male rats administered SCCP, the level of α2u in the kidney was not significantly different to that of control animals. This suggests that even though very little α2u was synthesised in the livers of SCCP-treated male rats, the small quantity of protein that was expressed was indeed accumulating in the kidney.

The second investigation demonstrated the specific in vivo binding of SCCP to renal α2u. This binding was only observed in male rats, suggesting that this phenomenon is male rat specific. Further evidence for binding was provided by gel filtration chromatography of kidney cytosol from male rats treated with a single dose of either DCB or SCCP in the third investigation. The peak of α2u-associated radioactivity was smaller in the SCCP-treated rats and even smaller in the rats treated with SCCP for 4 days, but this was as expected since SCCPs cause down-regulation of α2u synthesis in the liver.

Overall, these data suggest that α2u-binding is probably the primary mechanism for renal toxicity (and ultimately tumour formation) induced by SCCPs in male rats. There is clearly a down-regulation in hepatic α2u production (at the transcription level) induced by SCCPs, which is consistent with other known peroxisome proliferators. However, that α2u which is produced clearly binds to SCCPs as shown by size-exclusion gel chromatography and immunoblotting. Thus when transported to the kidney the α2u is deposited and retained; this is evidenced by the large increase in the ratio of renal to hepatic α2u seen in SCCP-treated rats compared to controls upon repeated exposure for 28 days. Therefore, it may be postulated that the SCCP-α2u complex accumulates at a slower rate, however, over a more prolonged period of exposure, continued α2u deposition would result in the delayed onset of an α2u globulin nephropathy.

Overall assessment of mechanistic studies

The findings of these mechanistic studies demonstrate that MCCPs are capable of eliciting hepatic enzyme induction and proliferation of smooth endoplasmic reticulum indicative of increased metabolic demand arising from xenobiotic metabolism. These effects are considered to be indicative of physiological adaptation rather than a toxicological response.

In addition, hepatic peroxisome proliferation is induced in rats and mice at higher dose levels as evidenced by microscopy, morphometric analysis and enzyme marker activity. Peroxisome proliferation was not observed in guinea pigs (this species has been demonstrated to be relatively insensitive to the effect) although there was a small elevation in β-oxidation activity (much less than in rats or mice). It is clear that humans are also relatively insensitive to the induction of hepatic peroxisome proliferation (Bentley *et al*, 1993; Ashby *et al*, 1994). Thus the changes seen in rats and mice are considered to be of limited relevance to human health.

Similar conclusions in relation to hepatic effects (i.e. the significance of changes related to xenobiotic metabolism and peroxisome proliferation) were agreed for SCCPs (SCCP ESR Risk Assessment Report, 2000).

Exposure to a MCCP (40% chlorination) has been shown to lead to thyroid effects (follicular cell hypertrophy and hyperplasia) in two studies in rats. Effects in this organ have not been investigated in mice or guinea pigs. The first study (Wyatt et al, 1993) provides evidence in support of the thyroid effects being attributable to stimulation of this organ arising from a negative feedback control. Initially an increase in the liver enzyme UDPG-transferase is stimulated by treatment with MCCPs resulting in increased glucuronidation and consequent excretion of T4, with a resultant reduction in plasma T4 levels. The pituitary responds to the decreased levels of T4 by releasing more TSH, which in turn leads to increased production of T4 by the thyroid. The continuous stimulation of the thyroid in response to the increased excretion of plasma T4 (seen in this 14-day study) is predicted to ultimately give rise to hypertrophy and hyperplasia in this organ.

The second study (Wyatt et al, 1997) is more difficult to interpret since although there was an increase in UDPG-transferase activity together with an expected increase in the release of TSH, plasma T4 levels remained generally unaffected with significant reductions only being seen in females at one timepoint in this 90-day study. Plasma T3 levels were reduced at two timepoints, in both sexes. The thyroid follicular cell hypertrophy and hyperplasia observed in this study are considered to have arisen as a result of continued stimulation by TSH. It may well have been the case in this study the homeostatic balance had been reset such that increased TSH levels resulted in "normal" T4 levels and therefore, no detectable decrease in this hormone upon measurement.

No toxicologically significant effects on thyroid hormones and TSH levels were observed up to the top dose of 222/242 mg/kg/day (males/females) in a recent, well-conducted 90-day study in rats.

It has been demonstrated that decreases in T4 or T3 levels in humans produced by altered hepatic clearance are typically insufficient to increase TSH levels. The decreased sensitivity of the human thyroid-pituitary axis to increased hepatic clearance of thyroxin is not fully understood, but appears to be influenced by several important quantitative differences between rats and humans. These quantitative differences include: A) The half-life of T4 in rats is approximately 12 h, whereas in humans, the half-life is 5-9 days (Dohler et al, 1979). The shorter half-life of T4 in rats is likely related to a high-affinity binding globulin for thyroxin (TBG) that is present in humans (75% of T4 is bound to TBG, 15% to TTR and the remainder to albumin) but absent in rodents Although other binding proteins are present in the plasma in rodents such as TTR, their binding efficiency is considerably less than human TBG. In the absence of TBG, more free T_4 is available for metabolism and hence excretion from the body in rodents, compared to humans. On the contrary, in humans, binding of T_4 to TBG accounts for slower metabolic degradation and clearance. B) Increased turnover and heapatic clearance of T_4 and T_3 renders the basal activity of the thyroid gland markedly more active in rats than in humans. In the absence of a functional thyroid gland, a rat requires approximately 10 times more T_4 than and adult human for full reconstitution (Dohler *et al*, 1979). C) Constitutive TSH levels are nearly 25 times higher in rats than in humans, reflecting the increased activity of the thyroid-pituitary axis in rats.Based upon these considerations humans are predicted to be less susceptible than rodents to fluctuations in levels of free plasma T_4 and hence any subsequent thyroid stimulation arising from a reduction in free T_4 levels. Again, similar effects on thyroid activity were observed for SCCPs (SCCP ESR Risk Assessment Report, 2000).

Overall, considering the probable mechanisms outlined above, and the apparent association with the observed liver effects, together with the highlighted differences in T_4 binding capacity between humans and rats, it is considered that the thyroid effects produced in rats would be of little relevance to human health at relevant levels of exposure.

Changes seen in the kidneys (increased weight, 'chronic nephritis' and tubular pigmentation) are considered as being potentially relevant to human health. Mechanistic studies indicated some deposition of α2u globulin in proximal convoluted tubules of male rats only at higher dose levels. However, this was unrelated to the pathological findings described above. Thus, these changes are not considered to be a male rat-specific phenomenon. From the data that are available, no adverse effects were seen at 23 $mg.kg^{-1}.day^{-1}$ in a recent and well-conducted 90-day study.

4.1.2.6.4 Summary of repeated exposure studies

No information is available on the effects of repeated exposure in humans. In animals there are no data relating to repeated inhalation or dermal exposure. A number of oral studies in several rodent species are available which have investigated the repeated dose toxicity of C_{14-17}, 40% or 52% chlorinated paraffins. In the absence of any information on MCCPs outside this range it is not possible to assess whether or not the degree of chlorination would have an effect upon the resulting toxicity.

The liver, thyroid and kidney are the target organs for repeated dose toxicity of MCCPs. For the liver, increases in weight were seen in rats and dogs at exposure levels of 100 $mg.kg^{-1}.day^{-1}$ and above. In addition, enzyme induction and histopathological changes (centrilobular hepatocyte hypertrophy) were seen in rats starting from 222 $mg.kg^{-1}.day^{-1}$, and, from a limited study in dogs, at 30 $mg.kg^{-1}.day^{-1}$ and above. These changes are likely to be related to an increase in metabolic demand as an adaptive response, possibly combined with peroxisome proliferation in the rat at higher dose levels. Both of these hepatic effects are considered of no or limited toxicological significance to human health. However, in rats, at higher exposure levels (around 360 $mg.kg^{-1}.day^{-1}$) single cell necrosis was observed; this effect is not thought to be related to increased metabolic demand or to peroxisome proliferation and therefore is considered to be of relevance to human health.

For the thyroid, clear pathology (follicular hypertrophy and hyperplasia) was seen at relatively high dose levels (312 mg/kg/day and above). Increased TSH levels and decreased T4 levels were also seen at similar dose levels. However, no toxicologically significant effects on thyroid hormones and TSH were observed up to top dose of 222/242 mg/kg/day (males/females) in a recent, well-conducted 90-day study in rats. The thyroid pathology observed at relatively high doses of MCCPs is likely to have occurred due to repeated stimulation of this organ because of a negative feedback control effect arising from plasma T_4 depletion following increased excretion of this hormone. This depletion results from an increase in the activity of hepatic UDPG-transferase. Humans, unlike rodents, possess T_4-globulin binding protein and are therefore less susceptible to plasma T_4 depletion and hence any resultant thyroid stimulation. Overall based on these considerations, the thyroid effects observed in rats should be considered not to be of relevance to human health at relevant levels of exposure.

From the data that are available, no adverse renal effects were seen in males and females at 23 $mg.kg^{-1}.day^{-1}$ in a recent and well-conducted rat 90-day study. Changes seen in the kidneys at 222 $mg.kg^{-1}.day^{-1}$and above (increased weight, 'chronic nephritis' and tubular pigmentation) are considered as being potentially relevant to human health. Mechanistic studies indicated some deposition of α2u globulin in proximal convoluted tubules of male rats only at higher dose levels. However, this was unrelated to the pathological findings described above. Thus, these changes are not considered to be a male rat-specific phenomenon. In terms of severity, an increase in kidney weight of 9-13% was observed at the top dose of 222 $mg.kg^{-1}.day^{-1}$ in one study and of 18% at the top dose of 625 $mg.kg^{-1}.day^{-1}$ in another study. The increase above controls in the incidence and severity of what has been misleadingly termed 'chronic nephritis' ('a mixed population of interstitial inflammatory cells, tubular regeneration and minimal degenerative changes in the tubular epithelium occurring alone or in combination') was seen in treated males at 10 $mg.kg^{-1}.day^{-1}$ and above. At 10 $mg.kg^{-1}.day^{-1}$ the severity of these changes was graded as 'trace', and even at the highest exposure level, 625 $mg.kg^{-1}.day^{-1}$, was only 'mild'. Furthermore, a significant increase above controls in the incidence of this lesion (10/15 vs 1/15) was only seen at the top dose of 625 $mg.kg^{-1}.day^{-1}$ with 3/15 and 4/15

animals affected at 10 and 100 $mg.kg^{-1}.day^{-1}$ respectively. It is therefore concluded that, although kidney changes were observed from 10 $mg.kg^{-1}.day^{-1}$, a lesion considered to be of toxicological significance only occurred at the top dose of 625 $mg.kg^{-1}.day^{-1}$. Tubular pigmentation was also seen in females at the top dose of 625 $mg.kg^{-1}.day^{-1}$.

Overall, a NOAEL of 23 $mg.kg^{-1}.day^{-1}$is identified for repeated dose toxicity based upon effects seen in rat kidney (increased weight at the next dose level of 222 $mg.kg^{-1}.day^{-1}$ and 'chronic nephritis' and tubular pigmentation at 625 $mg.kg^{-1}.day^{-1}$). It is noted that at 222 $mg.kg^{-1}.day^{-1}$ there were also slight decreases in plasma triglycerides and cholesterol levels.

4.1.2.7 Mutagenicity

4.1.2.7.1 *In vitro* studies

Bacterial studies

A C_{14-17} MCCP (40% chlorination) when tested in a standard Ames test up to a maximum concentration of 5000 mg/plate produced negative results in *S. typhimurium* tester strains, TA 98, 100, 1535, 1537 and 1538 (Wiegand, 1989). Testing was conducted in the presence and absence of metabolic activation, although no data were presented relating to positive controls.

In an unpublished study reviewed by Birtley *et al* (1980), two C_{14-17} MCCPs (52% chlorination, with and without the addition of a 0.2% epoxidised vegetable oil stabilizer) were tested in duplicate in *S. typhimurium* strains TA 98, 100, 1535, and 1538 at concentrations between 4 and 2500 mg/plate with and without Aroclor-induced rat liver S9. There did not appear to be a separate, replicate assay. No cytotoxicity was observed. In TA 1538, a greater than 2-fold increase in the number of revertants was observed at 4 and 20 mg/plate MCCP (without stabilizer) compared to the vehicle control. However, these were isolated increases, with no dose-related pattern. No increases were seen under any other test conditions. Overall, therefore, the assay is considered to have yielded negative results.

Two other studies cited in an IPCS EHC Document (IPCS, 1996) have tested two different MCCPs using a range of *S. typhimurium* tester strains. The first study (Conz and Fumero, 1988a; the rapporteur was unable to trace the original unpublished study report), tested a C_{14-17} chlorinated paraffin (42% chlorination) whilst the second test (Elliott, 1989a; only summary data were available) was conducted using a C_{14-17}, 45% chlorinated paraffin. Testing was performed using a standard protocol up to a maximum concentration of 5000 mg/plate both in the presence and absence of S9 (source not stated). In both tests negative results were apparently obtained. No further details were given.

Similarly, negative results were obtained in Ames tests that have been conducted with SCCPs (SCCP ESR Risk Assessment Report, 2000)

Mammalian cell studies

No *in vitro* cytogenetic or gene mutation studies are available. For SCCPs (56% chlorination) a negative result was obtained in a well-conducted gene mutation assay conducted up to cytotoxic concentrations; a similar negative result could, therefore, be anticipated for MCCPs. There were no *in vitro* cytogenetics data from SCCPs.

4.1.2.7.2 *In vivo* studies

In an unpublished report of an *in vivo* bone marrow chromosomal aberration test, groups of 8 male rats received 0 (corn oil/saline), 500, 1500 or 5000 $mg.kg^{-1}.day^{-1}$ C_{14-17} MCCP (52% chlorination) for 5 days via oral gavage (Spicer, 1983). Animals were sacrificed on the day after the final treatment, and 100 metaphases/animal were evaluated. No deaths occurred and no treatment-related signs of general systemic toxicity were observed. The frequency of chromosomal aberrations (including and excluding gaps) in MCCP-treated animals was not increased; the positive control produced a clear positive result. Although cytotoxicity in the bone marrow was not assessed, the available toxicokinetic data demonstrate that MCCPs undergo significant absorption following oral administration, with one study (Darnerud and Brandt, 1982), showing distribution to the bone marrow. As such, it is concluded that the target organ was exposed in this study and that the negative result is a reliable one.

Two mouse bone marrow micronucleus studies have been reviewed in brief detail within the IPCS EHC Document 181 (IPCS, 1996) although the rapporteur has been unable to trace the original unpublished study report. A C_{14-17} MCCP (42% chlorination) was investigated in the first study (Conz and Fumero, 1988b cited in IPCS, 1996) with groups of 5 males and 5 females receiving a single oral gavage dose of 5000 $mg.kg^{-1}$ in corn oil. Sampling times of 18, 43 and 66 hours were employed. No increase in the frequency of micronuclei occurred in MCCP-treated animals. The positive control substances produced a clear response. No further details were available.

In the second bone marrow micronucleus study a C_{14-17}, 45% chlorinated paraffin was evaluated (Elliott, 1989b, summary data only available). Groups of 5 male and 5 female mice received a single oral gavage dose of 0, 3125, or 5000 $mg.kg^{-1}$ in corn oil. Three sampling times were employed at 5000 $mg.kg^{-1}$ (ie. 24, 48 and 72 hours), and only one sampling time of 24 hours was used for the lower dose. There were no increases in micronucleus formation in any of the MCCP-treated groups. Clear responses were obtained with the positive control substance. No further details were available.

Similarly, for SCCPs, negative results were obtained in a rat bone marrow chromosomal aberration test, and in a dominant lethal assay (SCCP ESR Risk Assessment Report, 2000).

4.1.2.7.3 Human data

No information is available.

4.1.2.7.4 Summary of mutagenicity

Relatively few data are available on the genotoxicity of MCCPs, and in particular in relation to the consequences for mutagenic potential of variation in the degree of chlorination of the different compounds included within this family.

MCCPs (40-52% chlorination) are not mutagenic to bacteria. No *in vitro* cytogenetic or gene mutation studies are available but negative results were obtained for SCCPs in a gene mutation assay. Three *in vivo* bone marrow studies demonstrate that MCCPs are not mutagenic towards this target tissue. Negative results for *in vivo* genotoxicity tests in somatic and germ cells have been obtained for SCCPs.

Overall, the available data on MCCPs and SCCPs indicate that MCCPs do not possess genotoxic activity.

4.1.2.8 Carcinogenicity

No information is available on the carcinogenicity of SCCPs and MCCPs from studies in human populations. However, from animal cancer bioassays only conducted with SCCPs, an increased incidence of liver and thyroid tumours was observed in mice, and an increase in kidney tumours was seen in male rats. From the available evidence, clear modes of action were indicated for the liver and thyroid tumours, namely chronic tissue damage caused by peroxisome proliferation in the case of the liver, and for the thyroid, long-term hormonal stimulation. For the male rat kidney tumours, the evidence available at that time was insufficient to clearly identify a plausible mode of action. Although it had been noted that binding to and consequent accumulation of α2u globulin leading to hyaline droplet nephropathy might be the underlying mechanism for these tumours, there was no convincing evidence for accumulation of α2u. Recently however, work has been conducted to explore this further as a plausible mode of action in SCCPs kidney carcinogenesis. In view of this new information, the mode of action for the kidney tumours induced in male rats by SCCPs is reviewed again. In order to bring transparency to this analysis, and, thereby, promote confidence in the conclusions reached, a structured approach as defined in the IPCS framework for evaluating a mode of action in chemical carcinogenesis has been used (Sonich-Mullin et al., 2001). This provides a defined procedure, which mandates a clear and consistent documentation of the facts and reasoning including inconsistencies and uncertainties in the available data.

In addition, since SCCPs are structurally related to MCCPs, and have generally similar physicochemical and toxicological properties where comparative data are available, it is considered prudent to assume that the carcinogenic potential of MCCPs would be comparable to that of SCCPs. Thus, this analysis is deemed to be applicable to both SCCPs and MCCPs, and relevant data from both groups of chlorinated paraffins are considered in this evaluation.

IPCS conceptual framework for evaluating a mode of action in SCCPs [and by analogy, MCCPs] male rat kidney carcinogenesis

Postulated Mode of Action

The mode of action considered is binding of SCCPs to the male rat-specific protein, α2u globulin which results in the formation of digestion-resistant complexes within secondary lysosomes of the renal proximal tubule epithelium after reabsorption from the urinary ultrafiltrate. The resulting accumulation of the α2u globulin complex causes cell death and sustained regenerative cell proliferation which, in turn, leads to compensatory hyperplasia and ultimately tumour formation. However, since SCCPs also cause peroxisome proliferation which, in turn, leads to a down-regulation at the transcriptional level of α2u globulin synthesis in the male rat liver, α2u globulin accumulates at a slower rate in the kidney, and the typical α2u n*ephropathy takes longer to appear.*

Key Events

The key events considered with respect to SCCPs kidney tumorigenesis in male rats include:

- binding of SCCPs to α2u globulin;

- accumulation of α2u globulin in the renal proximal tubule epithelium;
- induction of hyaline droplet nephropathy;
- induction of regenerative renal tubule cell proliferation;
- induction of kidney tubular cell hyperplasia.

Binding of SCCPs to α2u globulin

The *in vivo* binding of SCCPs to α2μ globulin has been clearly and consistently measured in investigations 2 and 3 by Warnasuriya et al., 2001. These studies showed that SCCPs specifically bind *in vivo* to α2u globulin. SCCPs-α2u globulin complexes were found in male rat kidneys following either a single or a repeated (4 days) oral exposure to 625 mg/kg SCCPs.

Accumulation of α2u globulin in the renal proximal tubule epithelium

Accumulation of α2u globulin in the renal proximal tubule epithelium has been demonstrated in some, but not all of the available studies which have investigated this phenomenon. However, the apparent inconsistencies may be explained by the fact that the peroxisome proliferation-mediated down-regulation of α2u makes less α2u available for accumulation in the kidney over the relatively short periods of time over which investigations have been conducted. A marked decrease in hepatic α2u levels was observed in investigation 1 by Warnasuriya et al., 2001 in which rats were dosed orally with 625 mg/kg/d SCCPs for 28 days. This decrease was in association with undetectable levels of α2u mRNA which indicates that the down-regulation of α2u synthesis occurs at the transcriptional level.

There are two 90-day studies and three 28-day studies which have adequately investigated α2u globulin levels in the kidney. In one 90-day study (Wyatt et al., 1997), a statistically significant increase (by 15%) in the amount of α2u globulin was demonstrated by immunocytochemical staining in the proximal convoluted tubules of male rats orally given 625 mg/kg/day MCCPs, but not at 312 mg/kg/day. Although in the other 90-day study (CXR, 2005b), no increase in α2u globulin levels determined by Western blotting were seen in kidney homogenates of male rats given in the diet up to 242 mg/kg/day MCCPs, this is not inconsistent with the findings by Wyatt et al (1997), which indicate that α2u globulin accumulation only occurs at relatively high levels of MCCPs exposure. Of the three 28-day studies, two have shown some evidence of α2u globulin accumulation, while a third one (Elcombe, 1999a) has shown a decrease in α2u levels. Increased α2u globulin immunostaining was seen in the proximal tubules of male rats orally dosed with 625 mg/kg/day C_{12}:59%Cl for 28 days by Elcombe (1999b). Renal α2u globulin levels were the same in controls and male rats orally administered 625 mg/kg/day C_{12}:60%Cl for 28 days by Warnasuriya et al (2001, investigation 1). However, a significant down-regulation of α2u was seen in the liver of the treated male rats in this study. Hence, although there was virtually no α2u expression in the liver of treated male rats, the level of α2u in the kidney was not significantly different to that of control animals. This suggests that even though very little α2u was synthesised in the liver of the treated male rats, the small quantity of protein that was expressed, was indeed accumulating in the kidney. Decreased α2u globulin immunostaining was seen in male rats orally dosed with 1000 mg/kg/day C_{10-12}:58%Cl for 28 days by Elcombe (1999a). This decrease, although in apparent conflict with the findings of the other two 28-day studies, is not inconsistent with the hypothesis of the peroxisome proliferation-mediated down-regulation of α2u. It is possible that the higher dose (1000 mg/kg/day) employed by Elcombe (1999a) might have produced higher levels of peroxisome

proliferation, leading to greater down-regulation of α2u and therefore to a decrease in the renal α2u levels. (Expression of α2u in the liver was not assessed in this study).

Induction of hyaline droplet nephropathy

The evidence for the induction of a hyaline droplet nephropathy is limited. However, again, the peroxisome proliferation-mediated down-regulation of α2u will lead to a slower accumulation of α2u in the kidney and, consequently would result in a delayed onset of the typical hyaline droplet nephropathy. Unfortunately, there are no chronic studies available either for SCCPs or for MCCPs and the majority of the subchronic studies that have investigated kidney pathology either have not found hyaline droplets or have not confirmed hyaline droplet formation by immunocytochemical techniques.

- In the case of SCCPs, the histopathology investigations showed renal tubular eosinophilia, increasing in intensity with time, from day 15 in male rats treated with 313 and 625 mg/kg for up to 91 days in the study by Elcombe et al. (1994; SCCPs EU RAR). From day 29 increasing numbers of males also showed initially focal and then multifocal areas of basophilia at both dose levels. It is unclear from the study report whether or not these effects showed a dose-response relationship. Although no typical hyaline droplets were observed and no investigations of α2u levels performed, the authors claimed that this response was indicative of an atypical hyaline droplet nephropathy since the increased eosinophilia was an expression of smooth endoplasmic reticulum (SER) accumulation in association with peroxisome proliferation, and the areas of basophilia represented evidence of proximal tubular regeneration.

Mild nephritis was reported in male rats, but not females, orally dosed (either in the diet or via gavage) with 100 or 625 mg/kg/day SCCPs for 90 days by Serrone et al. (1987; SCCPs EU RAR). No further description of this lesion was provided, and it is not clear if this was indicative of hyaline droplet nephropathy.

There two studies which repeat a form of nephropathy occurring in both males and females. These studies are iincluded here for completeness, but given that the kidney effects are seen in females as well as males, it is considered that these effects are not indicative of hyaline droplet nephropathy.

Nephropathy was reported in all male rats given by gavage 5000 mg/kg/day SCCPs 5 days/week for 13 weeks, but not in animals dosed with ≤ 2500 mg/kg/day (NTP, 1986; SCCPs EU RAR). No further description of this finding was provided, but, since it was also seen in 3 females at 5000 mg/kg, it is presumed not to be related to α2u nephropathy, and, as female rats do not develop kidney tumours, it is therefore unlikely to be relevant to SCCPs kidney carcinogenesis.

A dose-related increase in the incidence and severity of tubular damage and interstitial inflammation was observed in male and female rats given by gavage 312 or 625 mg/kg/day SCCPs 5 days/week for either 6 or 12 months (the two interim sacrifices of the 2-year cancer bioassay by NTP, 1986). However, again, since these lesions were also seen in females, they are presumed not to be related to α2u nephropathy, and therefore are unlikely to be relevant to SCCPs kidney carcinogenesis.

- In the case of MCCPs, renal tubular eosinophilia was noted from day 15 onwards in male rats, but not females, treated with 312 and 625 mg/kg for up to 91 days by Wyatt et al. (1997). Multifocal areas of basophilia were also observed from day 29 onwards at both dose levels, again in males, but not females. The incidence and the severity of these effects increased with

time and in a dose-related manner. In addition, an increased staining for α2u globulin was seen throughout the cytoplasm at termination in males, but not females, at 625 mg/kg. The authors suggested that, since no obvious increase in hyaline droplets was determined but increased α2u globulin levels were measured, the response seen represented an atypical form of light hydrocarbon nephropathy.

A significant increased incidence of chronic nephritis (a mixed population of interstitial inflammatory cells, tubular regeneration and minimal degenerative changes in the tubular epithelium) of mild severity was reported by IRDC (1984) in male rats orally dosed with 625 mg/kg/day MCCPs for 90 days. It seems that these lesions were not consistent with either a form of nephropathy commonly seen in some strains of ageing rats or a hyaline droplet nephropathy. However, since they were also present in some females (although no dose-response observed), they are unlikely to be related to α2u nephropathy, and therefore are unlikely to be relevant to kidney carcinogenesis.

No treatment-related histopathology was observed in the kidney of rats given in the diet up to 242 mg/kg/day MCCPs for 90 days (CXR, 2005b).

Overall, there is no histopathological evidence of a clear form of hyaline droplet nephropathy either with SCCPs or MCCPs. However, an atypical form of light hydrocarbon nephropathy (renal tubular eosinophilia with multifocal areas of basophilia) was observed in males only in subchronic studies both with SCCPs and MCCPs. In those studies where renal toxicity occurred in both males and females (the chronic nephritis reported for MCCPs by IRDC, 1984, the nephropathy reported for SCCPs in the 13-week NTP, 1986 study and the tubular damage accompanied by interstitial inflammation reported for SCCPs at the 6 and 12 months interim sacrifices of the 2-year NTP, 1986 cancer study), the effects seen are presumed not to be related to α2u nephropathy; however, since female rats do not develop kidney tumours, it is also presumed that this nephropathy does not lead to tumour formation and it is therefore irrelevant to SCCPs kidney carcinogenesis.

Induction of regenerative renal tubule cell proliferation

More recently, a number of mechanistic studies have performed subtler kidney histopathological investigations looking at early biomarkers of non-genotoxic kidney carcinogenicity. Although the classical signs of hyaline droplet nephropathy have not been investigated in these studies, they provide clear evidence that the accumulation of α2u is associated with sustained regenerative cell proliferation.

An increase in replicative DNA synthesis (assessed by BrdU incorporation) in the renal tubules was seen in male rats orally dosed with 625 mg/kg/day C_{12}:59%Cl for 28 days by Elcombe (1999b). This increase, which is an expression of tubular regeneration, was seen in association with a parallel increase in male proximal tubule α2u globulin immunostaining.

In contrast to this 28-day study, a statistically significant decrease in BrdU incorporation in the renal tubules was seen in male rats orally dosed with 1000 mg/kg/day C_{10-12}:58%Cl for 28 days by Elcombe (1999a). This decrease was seen in association with a parallel decrease in male proximal tubule α2u globulin immunostaining, and hence, although in apparent conflict with the findings of the other 28-day study, is not inconsistent with the hypothesis of the peroxisome proliferation-mediated down-regulation of α2u. It is possible that the higher dose (1000 mg/kg/day) employed by Elcombe (1999a) might have produced higher levels of

peroxisome proliferation, leading to greater down-regulation of α2u and therefore to a decrease in the renal α2u levels and, in turn, to a decrease in replicative DNA synthesis.

No increase above controls in renal tubule cell proliferation (assessed by BrdU incorporation) was seen in male rats orally dosed with 625 mg/kg/day C_{12}:60%Cl for 28 days by Warnasuriya et al. (2001, investigation 1). However, in consistency with this finding, no increase above controls in renal α2u globulin levels was also noted in this study. These observations seem to indicate that in the absence of α2u accumulation, no regenerative cell proliferation is induced.

Significant increases in renal tubule replicative DNA synthesis were seen on days 29 and 91 in male rats, but not females, orally given 625 mg/kg/day MCCPs for up to 91 days by Wyatt et al. (1997). No effect was seen at the lower dose of 312 mg/kg/day. As with SCCPs, these increases, which are expression of tubular regeneration, were seen in association with a parallel increase in male proximal tubule α2u globulin immunostaining (also observed at the top dose of 625 mg/kg/day), therefore providing clear evidence that α2u accumulation leads to sustained regenerative cell proliferation.

Induction of kidney tubular cell hyperplasia

A dose-related increase in the incidence of kidney tubular cell hyperplasia was seen in male rats, but not female rats, orally administered 312 or 625 mg/kg/day SCCPs 5 days/week for 104 weeks (NTP, 1986; SCCP EU RAR). This study is the only cancer bioassay available in the rat.

Dose-Response Relationship

In vivo binding of SCCPs to α2u globulin

In vivo binding of SCCPs to α2u globulin was demonstrated by Warnasuriya et al., 2001, investigations 2 and 3 in male rat kidneys following either a single or a repeated (4 days) oral exposure to 625 mg/kg SCCPs. These mechanistic studies were conducted at only one high dose, and hence correlations with dose level are not observable.

Accumulation of α2u globulin

Accumulation (or relative accumulation) of α2u globulin was observed by two different studies (Elcombe, 1999b and Warnasuriya et al., 2001, investigation 1) in male rats orally administered 625 mg/kg/day SCCPs for 28 days. Since only one high dose was used in these two studies, correlations with dose level are not possible. Accumulation of α2u was also seen after 91 days of treatment with 625 mg/kg/day MCCPs, but not with 312 mg/kg/day MCCPs (Wyatt et al., 1997) or with 242 mg/kg/day MCCPs and below (CXR, 2005b).

Hyaline droplet nephropathy

There is no histopathological evidence of a clear form of hyaline droplet nephropathy either with SCCPs or MCCPs. However, an atypical form of light hydrocarbon nephropathy (renal tubular eosinophilia with multifocal areas of basophilia) was observed in male rats, but not females, treated with 312 and 625 mg/kg MCCPs for up to 91 days by Wyatt et al. (1997) and with 313 and 625 mg/kg SCCPs for up to 91 days in the study by Elcombe et al. (1994). The incidence and the severity of these effects increased with time and in a dose-related manner.

Regenerative renal tubule cell proliferation

An increase in replicative DNA synthesis (assessed by BrdU incorporation) in the renal tubules was seen in male rats orally dosed with 625 mg/kg/day C_{12}:59%Cl for 28 days by Elcombe (1999b). Since only one high dose was used in this study, correlations with dose level are not possible. Increases in renal tubule BrdU incorporation were also seen after 29 and 91 days of treatment with 625 mg/kg/day MCCPs, but not 312 mg/kg/day MCCPs (Wyatt et al., 1997).

Kidney tubular cell hyperplasia

A dose-related increase in the incidence of kidney tubular cell hyperplasia was seen in male rats treated with 312 and 625 mg/kg/day SCCPs 5 days/week for 104 weeks (NTP, 1986). In the same study, the 312 mg/kg/day males showed a statistically significant increase in kidney tubular cell adenomas. No increase was seen in the high dose (625 mg/kg/day) males, although, the absence of any increase is likely to be due to the very low survival rates achieved at the end of the study. Kidney tubular cell adenocarcinomas were also noted in the low dose males but not in the high dose or control animals. It should be noted that the low survival rates achieved at the end of the study in the high dose group could also explain why, in contrast to the tumour response, a dose relationship was noted for the hyperplasia. It is likely that the high dose animals dying before scheduled termination had already developed hyperplasia, but not yet the tumour.

Overall, except for the hyaline droplet-like cytoplasmic inclusions and the kidney hyperplasia, limitations in the database mean that no clear dose-response relationships could be identified for the other key events and the tumour response itself. It is therefore difficult to establish whether or not the dose-response relationship for any key event parallels the dose-response relationship for the male kidney tumours. However, it is worth noting that all the key events including the tumours showed a response in the dose range of approximately 300-625 mg/kg/day. Furthermore, changes in renal tubule relicative DNA synthesis were always seen in clear association with parallel changes in proximal tubule α2u globulin immunostaining.

Temporal Association

Although no stop/recovery experiments have been conducted for either SCCPs or MCCPs, the findings of the available studies (mechanistic, subchronic and the 2-year cancer bioassay all previously described) provide some evidence that events occurred in the following sequence: (1) binding of SCCPs to α2u globulin (seen 1-4 days after dosing); (2) accumulation of α2u globulin in the renal proximal tubule epithelium (seen at slight levels after 28 days, and at significant levels after 91 days of dosing); (3) induction of an atypical form of light hydrocarbon nephropathy (seen after 90 days of dosing); (4) sustained regenerative tubular cell proliferation (seen at the earliest after 28-29 days of dosing, but also after 91 days); (5) induction of kidney tubular cell hyperplasia (seen after 104 weeks); (6) induction of kidney tubular cell tumours (seen after 104 weeks).

Strength, Consistency, and Specificity of Association of Tumour Response with Key Events

Ideally, stop/recovery studies could provide the strongest evidence linking the key events with the tumour response. However, in the absence of such studies for either SCCPs or MCCPs, there are a number of other elements in the database which seem to indicate a relationship between the key events and the tumour response. Each of the key events for the postulated mode of action has been observed in at least one study. Some key events, i.e. binding of SCCPs to α2u globulin, α2u accumulation and regenerative cell proliferation have been

observed in more than one study. The available studies showed that there is a temporal relationship or sequence of events since, at similar dose levels, the in vivo binding of SCCPs to α2u globulin observed after either a single treatment or 4 days of treatment seemed to progress in time to the α2u accumulation seen after 28 and 90 days of treatment, and this in turn to the appearance of an atypical form of light hydrocarbon nephropathy after 90 days of treatment and ultimately to the kidney hyperplasia and kidney tumours seen in the 2-year cancer bioassay. In addition, mechanistic studies which have investigated early biomarkers of non-genotoxic kidney carcinogenicity, have shown a clear association between α2u accumulation and renal tubule replicative DNA synthesis, providing clear evidence that α2u accumulation leads to sustained regenerative cell proliferation.

In relation to consistency and repeatability of events, some inconsistencies have been observed in the induction of hyaline droplet nephropathy. One study (Serrone et al., 1987) reported a form of mild nephritis the relationship of which to hyaline droplet nephropathy is unclear, and two more recent studies reported areas of tubular eosinophilia and basophilia which are suggested to represent an atypical expression of hyaline droplet nephropathy. For the other key events in the postulated mode of action, a resonable degree of consistency and repeatability has been observed.

In relation to specificity, the available evidence has clearly demonstrated that the key events in the postulated mode of action are sex-specific and tissue-specific, and the tumours produced are only seen in the rat and not in the mouse. Each of the key events including the tumours was observed in males, but not in females. The key events also occurred in the renal tubule with no other areas of the kidney being affected. Three studies have also reported some renal pathology in female rats (chronic nephritis after 90 days of treatment with MCCPs by IRDC, 1984, nephropathy after 13 weeks of treatment with SCCPs by NTP, 1986, and tubular damage accompanied by interstitial inflammation after 6 and 12 months of treatment with SCCPs by NTP, 1986) that is obviously not attributable to α2u globulin and therefore is relevant for repeated exposure risk assessment; however, since no kidney tumours were observed in females, it is implied that this female renal pathology does not lead to tumour formation and it is therefore irrelevant for the mode of action of SCCPs kidney carcinogenesis.

Biological Plausibility and Coherence

The postulated mode of action for the kidney tumours induced by SCCPs and the key events that are considered in this analysis appear to be generally consistent with what is known about α2u globulin-associated nephropathy and neoplasia and with the general current understanding of cancer biology. It is widely accepted that toxicity and mitogenesis are of critical importance in the expression of non-genotoxic carcinogenicity, and these events have been clearly detected in SCCPs-induced kidney carcinogenesis (i.e. nephropathy and biomarkers of tubular regeneration for both SCCPs and MCCPs and kidney hyperplasia for SCCPs).

In addition, it seems that tumours induced by chemicals that cause indirect cytotoxicity resulting from the impairment of a physiological process, which is the proposed mode of action for α2u globulin nephropathy and associated renal carcinogenesis, tend to occur with a low incidence (less than 30%) and a long latency, and may exhibit species- and sex-specificity (IARC Sci. Publ. 147, 1992). These characteristics have also been observed with the kidney tumours induced by SCCPs in the 2-year rat cancer bioassay. Incidence rates of 14% and 6% were reported for the tubular cell adenomas at the low and high dose levels respectively, and an incidence rate of 4% was recorded for the adenocarcinomas in the low dose males.

Additional groups of animals terminated after 6 and 12 months of treatment presented no kidney tumours. Males, but not females were affected, and no kidney tumours were observed in the 2-year cancer bioassay conducted with SCCPs in mice (NTP, 1986; SCCPs EU RAR).

α2u globulin-associated nephropathy and renal neoplasia in the male rat have been observed with exposure to a number of other aliphatic hydrocarbons. These positive structure-activity relationships therefore give further support to the plausibility of the postulated mode of action.

Finally, the available databases on SCCPs and MCCPs indicate a lack of genotoxicity for these chemicals. The lack of genotoxicity is obviously one of the essential criteria to be met when considering a non-genotoxic mode of action. These data therefore further support the coherence of the postulated mode of action.

Other Modes of Action

In view of the available data, no alternative modes of action for SCCPs-induced kidney carcinogenesis that logically present themselves can be supported by as significant a body of evidence as the one presented in this assessment. However, there is one form of kidney toxicity exclusively observed in males and not females, which may or may not be associated with α2u globulin nephropathy. Mild nephritis was reported in male rats, but not females, orally dosed (either in the diet or via gavage) with 100 or 625 mg/kg/day SCCPs for 90 days by Serrone et al. (1987). It is important to note that since this finding occurred at the same dose levels at which the tumours were seen or at lower doses, greater relevance can be attached to its potential toxicological significance in relation to the SCCPs-induced kidney carcinogenesis. In addition, there are still some uncertainties in relation to the significance of the areas of tubular eosinophilia and basophilia observed in two 90-day studies and their role in hyaline droplet nephropathy.

Assessment of Postulated Mode of Action

Overall, the weight of evidence appears to indicate that α2u globulin-associated nephropathy is the most likely the underlying mechanism for the kidney tumours induced by SCCPs. Although the evidence for a classical hyaline droplet nephropathy is limited, mechanistic studies which have investigated early biomarkers of non-genotoxic kidney carcinogenicity, have shown an association between α2u accumulation and renal tubule replicative DNA synthesis, providing clear evidence that α2u accumulation leads to sustained regenerative cell proliferation. The association between these two key events should be considered to be far stronger evidence in support of the postulated mode of action than a clear observation of a hyaline droplet nephropathy, which is only the histopathological expression of α2u accumulation. In view of this, it is felt that the level of confidence in the postulated mode of action can be reasonably high.

Uncertainties, Inconsistencies, and Data Gaps

The main uncertainty in the postulated mode of action relates to the observation of mild nephritis in male rats, but not females, orally dosed (either in the diet or via gavage) with 100 or 625 mg/kg/day SCCPs for 90 days (Serrone et al., 1987). It cannot be completely ruled out that this is a form of male renal toxicity other than α2u globulin nephropathy, and therefore its possible role in tumour formation in male rats is unclear. However, it is important to point out that this study is relatively old and hence might have limitations with regard to the stringency of the histopathological investigations conducted. Certainly, the descriptions of the

lesions are brief and somewhat unclear, and similar findings have not been observed as an exclusively male rat phenomenon in other more recent, well conducted studies.

It is also noted that the evidence for a classical hyaline droplet nephropathy is rather limited. The significance of the areas of tubular eosinophilia and basophilia observed in two 90-day studies (one with SCCPs and one with MCCPs) and their role in hyaline droplet nephropathy is unclear. However, it should be noted that this atypical picture might simply be due to the overlap of two concomitant and interdependent processes, the induction of peroxisome proliferation and the induction of α2u globulin-associated nephropathy. Furthermore, in spite of the limited evidence in support of a classical hyaline droplet nephropathy, mechanistic studies which have investigated early biomarkers of non-genotoxic kidney carcinogenicity, have shown a clear association between α2u accumulation and renal tubule replicative DNA synthesis, providing clear evidence that α2u accumulation leads to sustained regenerative cell proliferation.

Other studies

$C_{14\text{-}17}$ MCCPs (52% chlorination, with and without the addition of a 0.2% epoxidised vegetable oil stabilizer) were tested in cell transformation assays using baby hamster kidney cells up to cytotoxic concentrations (Birtley *et al*, 1980). Negative responses were obtained.

Summary of carcinogenicity

No carcinogenicity studies in human populations with potential exposure to MCCPs are available, and similarly no investigations in animals have been conducted. Although no direct information is available, MCCPs are are generally unreactive and not mutagenic. In the absence of experimental carcinogenicity data on MCCPs, given the similarities between MCCPs and SCCPs in physicochemical properties and in the results obtained in relation to other toxicological endpoints, particularly the effects seen on the liver, thyroid and kidneys on repeated exposure, it seems reasonable to presume that the carcinogenic potential of MCCPs will be similar, at least in qualitative terms, to that of SCCPs. SCCPs have been investigated in animal studies and found to induce liver, thyroid and kidney tubular cell adenomas and carcinomas. On mechanistic considerations, the liver and thyroid tumours were considered to be of little or no relevance to human health. The underlying mechanism for the kidney tumours has not been fully elucidated. However, there is recent mechanistic evidence to show that α2u-binding is probably the primary mechanism for kidney tumour formation induced by SCCPs in male rats. The available evidence strongly suggests that the underlying mechanism would not be relevant to humans. Therefore, overall, SCCPs, and by analogy MCCPs, should be considered not to pose a carcinogenic hazard to humans.

In discussions with Member States, uncertainties about this mechanism for the kidney tumours have been highlighted. Hence, in January 2004, this issue was referred to the EC Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity.

The Specialised Experts agreed that there were still data gaps leading to uncertainty about the relevance of these tumours for humans. Some experts argued that there were inconsistencies and contradictions in the mechanistic studies which might indicate that alternative mechanisms could not be excluded. The relation between α2u mechanism and the kidney tumours was not adequately established in this case. These data gaps led the Experts to conclude that the criteria for no classification for SCCPs were not met, and hence, they recommended that the current classification of SCCPs with Carc Cat 3 be retained.

However, the Specialised Experts agreed that a read-across from SCCPs to MCCPs was not justified for carcinogenicity, and consequently MCCPs could not be classified for this endpoint. They noted the absence of animal tumour data for MCCPs, the toxicological differences seen between SCCPs and LCCPs, and the heterogenous nature of all these compounds.

Hence, based on the opinion of the Specialised Experts read-across from SCCPs to MCCPs for this endpoint is not appropriate in terms of classification. However, in terms of hazard and risk, the carcinogenic potential of MCCPs still needs to be addressed. Taking into account all the other existing data on MCCPs, specifically the genotoxicity and the repeated dose toxicity data, it is noted that MCCPs lack genotoxicity activity, but produce kidney toxicity in male and female rats (increased weight at 222 $mg.kg^{-1}.day^{-1}$ and 'chronic nephritis' and tubular pigmentation at 625 $mg.kg^{-1}.day^{-1}$). Based on this evidence, it cannot be completely ruled out that this form of kidney toxicity might lead to cancer in male and female rats through a non-genotoxic mode of action, even though with SCCPs kidney tumours were seen in male rats only. Therefore, a risk characterisation for the carcinogenicity endpoint will be conducted using the same NOAEL of 23 mg/kg/day identified for repeated dose effects on the kidney.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

The majority of the available studies have been conducted using a C_{14-17}, 52% chlorinated paraffin.

Effects on fertility

The only data available are those contained in an one-generation study (CXR, 2006) and in an unpublished range-finding study performed with the aim of identifying dose levels for a 2-generation reproduction study; however, the full study was not then conducted (IRDC, 1985).

In the IRDC (1985) study, groups of Wistar rats (5 males and 10 females) were administered 0, 100, 1000 or 6250 ppm C_{14-17} MCCP (52% chlorination) in the diet for 28 days prior to mating, during mating and up to post-natal day 21 (females only). These animals constituted the F_0 (parental) generation. The average doses of test substance received were 0, 6, 62 or 384 mg/kg/day for males and 0, 8, 74 or 463 mg/kg/day for females. Five male and 10 female F_1 pups were selected at random from each group, and were retained (receiving the same diet as their parents from weaning) up to 70 days of age. One F_1 litter/group was killed on lactation days 6 and 7 at the high dose and in the controls, respectively. The remaining F_1 animals were sacrificed on lactation day 21 and the F_0 females after weaning of their offspring. Necropsy examination was performed (on kidneys, lungs, ureter, and urinary bladder only) on F_0 females but not males. A number of reproductive and litter parameter assessments were conducted following sacrifice. Blood samples were collected for haematological analysis from F_1 pups at various timepoints.

No deaths occurred amongst the F_0 (parental) generation, and there were no abnormalities noted in the histology examinations of females. The only finding of any note was a statistically significant decrease (by 12%) in food consumption in females at 6250 ppm during week 5. No treatment-related effects on fertility indices were observed. At birth, F_1 pup survival in all dose groups was equivalent to that of the control group F_1 pups. However,

amongst the F_1 generation, a marked and statistically significant decrease in pup survival was noted during lactation at 6250 ppm, such that none of the pups survived until weaning. Reduced pup survival (by 11%) was also evident at 1000 ppm and, although not statistically significant, is considered to be of toxicological importance. The effect on survival was further investigated in a study (Hart *et al*, 1985) summarised in the developmental toxicity section.

Decreased activity and swollen and dark or black eye(s) were observed in a few F_1 pups in 1 or 2 mid- and high-dose litters. Haematological analyses revealed "reductions" (quantified data not presented) in erythrocyte counts, haemoglobin concentration and haematocrit among a single litter of F_1 pups at the top dose on lactation day 6 compared to the controls on lactation day 7; however, the small sample size involved precludes the drawing of any firm conclusions on the basis of these findings.

Necropsy of the pups revealed dose-related, but not statistically significant, increases amongst F_1 pups at 1000 and 6250 ppm in the occurrence and severity of subcutaneous haematoma, pallor, blood around the orifices, pale liver, kidneys, lungs and spleen and blood in the cranial cavity and brain. Haematoma was noted in all of the litters at 6250 ppm.

In summary, it is difficult to draw firm conclusions in relation to fertility from this study due to the small numbers of animals used and limitations in design (although it was only intended as a range-finding study). Although this is a limited study, the administration of a C_{14-17} MCCP (52% chlorination) to rats in the diet at up to approximately 400 mg/kg/day had no apparent effect upon fertility. However, significant effects were seen in the developing offspring prior to them having been weaned; a concentration of 1000 ppm in the diet (~74 mg/kg/day) resulted in a number of necropsy findings in the offspring indicative of internal haemorrhaging. All pups born to dams receiving 6250 ppm (equivalent to approximately 460 mg/kg/day) died before weaning, probably as a result of the internal haemorrhaging. This would indicate that the pups had either died as a result of receiving the test substance or metabolites through breast milk, or that the milk that was produced by dams was deficient in factors essential for pup survival, or both. Further studies (see below) confirmed that this was mediated via the breast milk. From this study, however, no adverse effects were seen in offspring at approximately 8 $mg.kg^{-1}.day^{-1}$ (pre- or post-natally).

In a recent one-generation study (CXR, 2006) conducted to refine the NOAEL for effects in the offspring and to further explore the mechanisms of the haemorrhagic effects, groups of 12-17 nine-ten weeks old male and female Sprague-Dawley rats were administered 0 (17 animals/sex), 300 (12 animals/sex), 600 (12 animals/sex) or 1200 (17 animals/sex) ppm C_{14-17} MCCPs (52% chlorination) via the diet for 4 weeks before pairing, throughout pairing, gestation and lactation until termination. The males were terminated after 9 weeks of treatment (day 4 of lactation) and the females were allowed to litter and rear their offspring until PND 21 and were killed on day 21 of lactation (approximately 11-12 weeks of treatment). The offspring were terminated on PND 21. The study was performed in accordance with the general principles of the OECD testing guideline 421, although a larger number of animals and a longer treatment duration before pairing and during lactation were employed. The study was also conducted in compliance with GLP and QA standards. Five females and their litters from the control and 1200 ppm group were classed as satellite animals and used for additional investigations of blood, liver and milk samples. During the study, clinical condition, bodyweight, food consumption, gestation length and parturition observations, liver weights and macroscopic pathology investigations were undertaken on the F0 females. The F0 males were assessed for clinical condition, bodyweight, food consumption and macropathology. Mating performance and fertility were also evaluated. Clinical condition, litter size and survival, sex ratio and bodyweight of all offspring were

assessed before pathology investigations were undertaken at necropsy. Milk, blood and liver samples were obtained from dams and blood and liver samples were obtained from selected offspring at specific time points between the birth of litters and day 21 of lactation. The analysis of these samples is still underway and will be reported as part of a separate study.

Mean achieved dosages for males prior to pairing were 21, 44 and 84 mg/kg/day in the 300, 600 and 1200 ppm groups respectively. For females, mean achieved dosages prior to pairing were 23, 47 and 99 mg/kg/day in the 300, 600 and 1200 ppm groups respectively. There were no adverse effects of treatment on clinical condition, bodyweight, bodyweight gain or food intake of the F0 males and females prior to pairing or for females during gestation or lactation. Oestrus cycles, mating performance, pre-coital interval, fertility and gestation lengths were unaffected by treatment. The 1200 ppm F0 females had marginally higher absolute (by 12%) and relative (by 11%) liver weights compared to controls, which is consistent with the effects seen in repeated dose toxicity studies. The number of implantations and subsequent litter size, sex ratio and offspring survival were unaffected by treatment. The clinical condition of the male and female offspring and offspring bodyweights, bodyweight gains to weaning, macropathology findings and liver weights were also unaffected by treatment. It should be noted that, although no histopatholy was performed in this study, the macroscopic examination carried out, which involved opening the body cavities and the cranial cavity, should have been able to pick up any significant (sufficient to cause death) haemorrhage; this is because in small animals (pups) haemorrhage are likely to be visible macroscopically as red or dark areas on the surface of the different organs. Overall, based on the results of this study, it can be concluded that dietary administration of C_{14-17} MCCPs (52% chlorination) at levels up to 1200 ppm (100 mg/kg/d) had no adverse effects on pre- and post-natal survival and growth of the F1 offspring up to weaning, following treatment of F0 males and females for 4 weeks prior to pairing and throughout mating, gestation and lactation (for a total treatment duration of 11-12 weeks).

Similar data were not available for SCCPs (SCCP ESR Risk Assessment Report, 2000).

Developmental studies

Two conventional teratolgy studies are available for MCCPs, one in rats and one in rabbits.

Studies in rats

Groups of 25 mated female rats received 0, 500, 2000 or 5000 mg/kg/day C_{14-17} MCCP (52% chlorination) in corn oil by oral gavage on gestational days 6-19 with sacrifice on day 20 (IRDC, 1984). The dose levels were chosen based on the results of two preliminary sighting studies (IRDC, 1981 and IRDC, 1983). The numbers and location of viable and non-viable fetuses, resorption sites and total number of implantations and ovarian corpora lutea were determined. All fetuses were examined for external malformations, and one half of the fetuses from each litter were then examined for visceral malformations and the other half for skeletal malformations.

One mid-dose group female died on gestational day 16; the cause of death was not established but was probably not MCCP-related. Clinical signs of maternal toxicity were seen at 2000 and 5000 mg/kg/day, and constituted wet and/or matted fur in the anogenital region (with red or yellow staining) and an increased incidence of soft stool prior to sacrifice. No treatment-related effects on the uterine parameters examined were seen. There were no treatment-related effects on pup weight. No malformations were observed as a result of treatment. In this study, there were no developmental effects observed at levels up to 5000 mg/kg/day.

Studies in rabbits

Groups of 16 previously artificially inseminated rabbits received 0, 10, 30 or 100 mg/kg/day C_{14-17} MCCP (52% chlorination) in corn oil by oral gavage on days 6-27 of gestation (IRDC, 1983). The doses were selected on the basis of two unpublished range-finding studies, both of which were available for assessment (IRDC, 1982a and IRDC, 1982b). Dams were sacrificed on day 28 of gestation at which time the numbers and location of viable and non-viable fetuses, resorption sites and total number of implantations and ovarian corpora lutea were determined. An examination for external malformations was conducted upon all the fetuses, followed by examination of half of the fetuses from each litter for visceral malformations and the other half for skeletal malformations. There were no treatment-related mortalities or clinical signs of toxicity in the dams. Abortions occurred at 0 (1 dam), 30 (2 dams) and 100 mg/kg/day (2 dams). However, rabbits are known to have a high spontaneous abortion rate, and the pattern of results suggests that this is not indicative of a treatment-related effect. The only difference seen in the offspring was a statistically significantly increased number of viable fetuses at 30 mg/kg/day compared with the controls; the value was within the historical control range for this parameter and is of no toxicological significance. No treatment-related malformations were seen.

A limitation of this study was that it was not conducted up to maternally toxic dose levels. However, its findings are valid for doses up to 100 mg/kg/day. On the basis of the outcome of this study, the MCCP (52% chlorination) was not toxic to development in the rabbit at dose levels up to 100 mg/kg/day.

4.1.2.9.2 Human data

No data are available.

4.1.2.9.3 Research into the mechanisms of the internal haemorrhages

Following on from previous work (see Section on Effects on fertility), a study was conducted with the aim of investigating the possible mechanism of internal haemorrhages seen to develop post-natally in pups (Hart *et al*, 1985). Groups of male and female Wistar rats were treated with 0 or 6250 ppm C_{14-17} MCCP (52% chlorination) in the diet for 4 weeks before mating. After confirmation of mating (presence of sperm in a vaginal smear), the females were placed into one of the 5 following treatment groups:

Group 1) 16 females fed control diet rearing their own pups

Group 2) 26 females fed chlorinated paraffin diet rearing pups fostered from group 3 control females

Group 3) 26 females fed control diet rearing pups fostered from group 2 treated females

Group 4) 16 females fed chlorinated paraffin diet rearing their own pups

Group 5) 16 females fed chlorinated paraffin diet up to day 10 of pregnancy, rearing their own pups while fed control diet.

Blood samples were obtained from one pup/litter on days 3, 4, 5, 8, and 11, and 2 pups/litter on day 22 (the day of sacrifice) post-partum and analysed for clotting factors VIII and X.

Prothrombin times were also measured at these timepoints and platelet counts on days 11 and 22 of the study. Activated partial thromboplastin time was not measured.

Samples of breast milk were taken from lactating dams of groups 1, 2 and 4 on day 14 post-partum only, and analysed for the test substance. Sampling proved difficult and only one sample was obtained for each of groups 2 and 4; these were found to contain 570 and 1280 ppm (570 and 1280 mg/l) MCCP respectively.

No deaths or clinical signs of toxicity were seen in the parental animals during the pre-mating period and pregnancy. During days 12-22 post-partum, statistically significant increase in pup mortality was seen in control pups fostered to treated mothers (group 2) and treated pups reared by their own treated mothers (group 4); (77% and 67% deaths respectively compared to 4% for group 1). Increased mortality was not observed in any other groups. Of the total number of pups found dead, haemorrhages were seen in 17 and 8% respectively of group 2 and group 4 offspring, with no sign of haemorrhaging noted in the pups born to the other dams. Several findings indicative of the occurrence of internal haemorrhages were found in pups raised by dams treated with chlorinated paraffin during lactation (i.e. groups 2 and 4). These findings consisted of dark red bulging eyes, blood clots within the membranes lining the cranium and pale livers. In group 2, a significant reduction in pup bodyweight was observed from day 5 post-partum onwards and this was reduced by up to 11% on day 22.

Throughout lactation, haematological analysis revealed a marked and statistically significant reduction in the concentration of clotting factor X amongst control pups fostered to treated mothers (i.e. group 2 - reduced by up to 45%) and pups reared by their own treated mothers (ie group 4 - reduced by up to 63%) relative to group 1 pups. The concentration of factor X in groups 3 and 5 was essentially similar to control group 1. Prothrombin times were increased (but not statistically significant) in these two groups. No toxicologically significant changes were seen in factor VIII. Significant increases in liver weight were seen in pups from group 2 (both sexes up to a 5% increase) and in female pups (up to an 18% increase) from group 4. The low (similar to control) incidence of death in pups from groups 3 and 5 treated mothers, and the high incidence in group 2 and 4 pups clearly indicate that the effect on the pups is focused on mother-to-pup transfer during weaning. Comparing the absence of effects in group 5 pups, where dams received MCCP until day 10 of gestation, to the effects seen in group 2 and 4 pups where there was continued feeding with MCCP throughout the study suggests that for the effect to be mediated there may be a need for continued availability of MCCP. The lack of effect in group 5 suggests that uptake of MCCP into fatty tissue (with subsequent mobilisation into breast milk) may not be a significant factor in this case. However, in the absence of specific measurement of MCCP levels in breast milk from group 5 dams, it is not possible to determine whether the lack of toxicity in the pups of this group was due to no MCCP being present in the breast milk or whether the levels of MCCP (including any derived from fatty tissue) were below a threshold for this effect, however mediated.

On the basis of the observed decreases in clotting factor X, the study authors proposed that the chlorinated paraffin tested was either transferred in the breast milk, causing disruption of the clotting system in the pups, or alternatively that the pups received less vitamin K in the breast milk due to treatment-related effects upon their mothers and as a consequence the vitamin K-dependent clotting pathway was impaired. Either mechanism could have led to the manifestation that chlorinated paraffin treatment of the dams led to a reduction in the haemostatic mechanism in the pups, resulting in pup deaths. This conclusion would appear to be reasonable. Overall, therefore, MCCPs are considered to present a hazard to the neonatal offspring via the lactating mother. A NOAEL of 47 mg/kg/day as a maternal dose can be identified for this effect, from the recent one-generation study (CXR, 2006).

Further work has been carried out to investigate these two hypotheses. For background information, it is important to borne in mind that vitamin K controls the formation of clotting factors II (prothrombin), VII, IV and X in the liver; that in adults it is synthesised by the gut microflora and it is also obtained from ingested plant and animal tissues. A preliminary study (CXR Biosciences Ltd, 2003) has been performed to test the hypothesis that MCCPs induce the catabolism of vitamin K in adult female rats leading to decreased plasma concentrations. If this occurred in the lactating rat, this could lead to low levels of vitamin K in the milk and a decreased supply to the neonates, which are already physiologically compromised in their vitamin K status (vitamin K is synthesised by the gut microflora; in the very early days of life, the neonatal gut is sterile, therefore the only source of vitamin K in the neonate is from breast milk; however breast milk has relatively low levels of vitamin K. Furthermore, the neonatal liver is immature with respect to prothrombin synthesis).

Groups of 6 female adult Sprague-Dawley rats on a normal diet or on a vitamin K_3 deficient diet were administered by oral gavage 0, 500 or 1000 mg/kg/day MCCPs for 21 days. Furthermore, two groups of 6 female rats, one maintained on normal diet and one maintained on vitamin K_3 deficient diet, were treated for 21 days with 0.1% phenobarbitone (PB, an inducer of liver cytochrome P450 enzymes), in drinking water (equivalent to a dose of 20 mg/kg/day). The PB-treated groups were included to test the hypothesis that induction of PB-type inducible enzymes may increase vitamin K metabolism. At termination, body and liver weights were recorded, and blood samples were taken. These were analysed for prothrombin clotting times, clotting factors VII and X and vitamin K levels. In addition, liver microsomal fractions were prepared and analysed by SDS-PAGE and Western immunoblotting for assessment of induction of CYP2B1 and/or CYP2B2 isozymes.

No treatment-related deaths, clinical signs of toxicity or effects on body weight were observed, but there was a statistically significant, dose-related increase in liver weight in both the normal and the vitamin K_3 deficient diet groups (by 42% and 56% at 500 and 1000 mg/kg/day respectively for the normal diet groups, and by 42% and 49% at 500 and 1000 mg/kg/day respectively for the vitamin K_3 deficient diet groups). Liver weights for the PB treated animals were not markedly different from their respective control groups. Factor X levels were unaffected by treatment for both dietary regimes, and plasma vitamin K levels were lower (by 34%) only in the high dose animals fed vitamin K_3 deficient diet. A statistically significant, dose-related decrease (by 18% and 42% at the low and high dose respectively) in Factor VII levels was observed in the MCCPs-treated animals fed normal diet. A marked decrease in Factor VII levels was also seen in both control and MCCPs-treated animals fed vitamin K_3 deficient diet (by 25%, 24% and 44% of the normal diet control group levels at 0, 500 and 1000 mg/kg/day respectively). PB-treated animals fed normal diet showed conversely a statistically significant increase of 43% in Factor VII levels. Prothrombin clotting times were slightly statistically significantly decreased (by 12 %) but only at the low dose in the normal diet group. The results of the Western immunoblot analysis showed that the expression of CYP2B1 and CYP2B2 isozymes was induced at both MCCPs dosages, at similar levels in the normal and in the vitamin K_3 deficient diet groups. The extent of induction by MCCPs was also similar to that observed with PB administration.

In conclusion, MCCPs administration to adult female rats at dose levels up to 1000 mg/kg/day for 21 days produced significant decreases in plasma concentrations of clotting Factor VII in the normal diet animals; however these were not of a sufficient magnitude to cause a biologically significant increase in prothrombin clotting times. The decrease in Factor VII levels observed in the vitamin K_3 deficient diet animals was seen not only in the treated groups but also in the control rats. It is therefore unlikely that this reduction was due to

treatment with MCCPs. Plasma vitamin K levels were unaffected by treatment in the normal diet animals, but they were lower in the high dose animals fed vitamin K_3 deficient diet. It has been speculated by the authors that rats have a homeostatic mechanism which enables them to maintain normal plasma levels of vitamin K even when the diet they are consuming is deficient in vitamin K_3, but that this mechanism might have been compromised by the administration of a very high dose of MCCPs (1000 mg/kg/day). It also appears that MCCPs cause induction of CYP2B1 and CYP2B2 isozymes in both the normal and vitamin K_3 deficient diet groups.

Overall, it can be concluded that MCCPs are without effect on the blood clotting system in adult female rats treated for 3 weeks up to a dose level of 1000 mg/kg/day, and it can be deduced that the haemorrhaging effects on the offspring are unlikely to be mediated by reduced vitamin K levels in breast milk under the conditions of this preliminary study (CXR Biosciences Ltd, 2003).

However, in order to test the other hypothesis, i.e. that MCCPs transferred to the pups through breast milk, cause disruption of the pups' clotting system, a further investigation has been recently performed (CXR Biosciences Ltd, 2004). The study design adopted for this investigation was a limited one-generation assay modified to provide milk, blood and liver samples from lactating dams, and blood and liver samples from suckling pups. The blood and milk samples were analysed for levels of MCCPs, clotting factors and vitamin K, while the liver samples were examined for induction of the liver isozymes CYP2B1 and CYP2B2.

Groups of 16 male and 32 female Sprague-Dawley rats representing the parental generation (F0) were treated in the diet with 0 or 6250 ppm MCCPs (equivalent to a dose averaged over the first 4 week of treatment of 0 or 513 and 538 mg/kg/day for males and females, respectively) for 4 weeks prior to mating, then throughout mating, gestation and lactation. However, because of a very high increase in pup mortality in the test animals, the study was terminated prematurely approximately 2 weeks after the first litters were born. The F0 animals were monitored for clinical signs of toxicity, body weight, food consumption and mating performance. The F1 offspring were monitored for survival and growth. Half of the dams from each group were assigned for pup sampling and half for milk sampling. Blood and liver samples (pup sampling) were obtained from one male and one female pup removed from half of the litters on days 1 and 4 of lactation (day 0 is the day of parturition) and at study termination (day 12 of lactation). From the remaining females not used for pup sampling, a milk sample was obtained on days 1 and 4 of lactation and at study termination when samples of maternal liver were also collected.

Five test dams (16%) died or were killed around the time of parturition. All 5 deaths were associated with littering although there was no obstruction or other hindrance to the delivery process (dystocia), and were considered treatment-related. It is noted that 4 of the 5 dams either gave birth to normal litters or were found to have a normal complement of live foetuses in their uterus. One exposed male was also found dead during the experiment. The clinical/necropsy findings in 3 out of these 5 dams and in the male rat found dead showed signs (abnormal red coloured urine, cage stained red, blood around vagina, placenta dark red, skin stained, eyes pale, skin pale) suggestive of haemorrhaging. No difference was seen between the control dams and the treated dams in relation to clinical signs of toxicity. Body weight gains of males and females prior to mating were similar in both groups. Test females showed a slight reduction in body weight gain during gestation (by 8%) and lactation (by 18%). There were slight reductions in food consumption prior to mating in both treated sexes (by 10% in males during the first week of treatment and by 13 and 8% in females during the first and the fourth week of treatment respectively). In addition, treated females consumed

less food (by 17%) compared to the controls during lactation. There were no effects of MCCPs on mating performance or duration of gestation.

There were no effects of MCCPs on litter size at birth and on pup mortality from birth to day 4 of lactation. However, after day 4, pup mortality increased dramatically among the test animals (for example, there was a mean number of 5.4 live pups per litter on day 7 of lactation vs a mean number of 11.5 live pups per litter on day 1 of lactation) such that only few pups survived until the study was terminated, prematurely, around day 12 of lactation. At necropsy, the majority of these pups showed internal haemorrhages. Mean pup weight on day 1 of lactation was marginally lower (by 7-18%) in litters of treated females compared to controls. By day 4 of lactation, the weights of treated pups were noticeably lower (by 12-27%) than controls, and the difference had become more apparent (by 44-48%) by day 7 of lactation. On day 1 of lactation, liver weights were only marginally greater (by 7%) in pups from treated females compared to controls, however, on day 4, pup liver weights in the test group were statistically significantly increased above control pups (by up to 29%).

Levels of MCCPs were analysed in dam milk on day 1 of lactation. Samples from 3 MCCPs treated dams and from 3 control dams were obtained. A mean level of 1057 mg/l (SD=±530 mg/l) was measured. This value was consistent with that obtained in the cross-fostering study (925 mg/l) from dams treated with the same dose level of MCCPs (6250 ppm). No MCCPs were detected in control milk. Plasma vitamin K levels measured in samples from 10 animals from each group on day 12 of lactation were significantly decreased in the treated dams (0.03±0.05 ng/ml) compared to the control dams (0.41±0.14 ng/ml). This finding seems to be in contradiction with the result obtained in the previous investigation (CXR Biosciences Ltd, 2003) in which the plasma levels of vitamin K were unaffected by treatment. However, we note that this apparent inconsistency could be explained by the fact that in the CXR Biosciences Ltd (2003) study treatment with MCCPs was only for 3 weeks while in this investigation it was for 7-8 weeks. Furthermore, in the CXR Biosciences Ltd (2003) study adult females were treated while in this new study, the treated females went through the critical stages of pregnancy and lactation. Decreased maternal plasma vitamin K in the treated dams was reflected by decreased vitamin K levels in treated dam milk. Vitamin K was not found in pooled days 1 and 4 samples from 4 treated dams compared to a mean level of 0.28 ng/ml (SD=±0.10) in samples from 5 control dams. This finding was confirmed on pooled days 9 and 12 samples from treated dams (0.36±0.11 ng/l) and control dams (0.61±0.29 ng/l) which showed an approximate 50% decrease in breast milk levels of vitamin K in the test dams.

As described above, the concentration of vitamin K in the plasma of adult females having gone through pregnancy and lactation was markedly decreased by MCCP treatment. This in turn produced a decrease in activity of the plasma clotting factors VII (24.2±13.1) and X (87.0±40.7) in the treated dams compared to controls (58.6±19.6 and 119±27.8 for factor VII and factor X respectively) on day 12 of lactation. However, this did not affect the prothrombin times in the dams, suggesting that the functional reserve in these adult animals was sufficient.

Pup plasma volumes were insufficient to measure vitamin K directly, however, it was possible to analyse clotting factor activities as surrogates. The data showed that MCCPs treatment led to decreased clotting factor VII and X activities after day 4. Activities of 7.46, 6.6 and 6.47 were measured for factor VII in plasma of the treated pups on days 4, 9-11 and 12 post-partum compared to activities of 25.7, 17.4 and 22.7 in the control pups. Activities of 7.12, 6.36 and 3.47 were detected for factor X in plasma of the treated pups on days 4, 9-11 and 12 post-partum compared to activities of 14.3, 7.6 and 9.69 in the control pups.

The results on liver enzyme induction in both dams and pups are not yet available.

These new data suggest that MCCPs at a dose level of 6250 ppm (538 mg/kg/day) induce a perturbation of the clotting system in lactating neonates of treated mothers. In adult animals, decreased levels of vitamin K and of the clotting factors VII and X were found. However, these did not affect their prothrombin times, indicating that the functional reserve in these adult animals is sufficient. The foetus *in utero* apparently receives sufficient vitamin K via the placenta, but after birth becomes severely deficient in vitamin K and related clotting factors when reliant of these factors via the mothers'milk. They also receive through the milk considerable levels of MCCPs which may also further reduce their vitamin K levels. This in turn will lead to a severe vitamin K deficiency in these neonates (who are already compromised in their vitamin K status) and consequently to haemorrhaging.

Maternal death was also seen during parturition in 5 out of 32 dams treated with 538 mg/kg/day MCCPs. The observation of excessive bleeding in the clinical/necropsy findings of these dams and the observed decreased maternal blood levels of vitamin K indicate that these deaths were most likely to be due to haemorrhaging and not a direct consequence of parturition. It is also expected that the act of parturition would place the dams at a higher risk of the consequences of low vitamin K levels.

4.1.2.9.4 Summary of toxicity for reproduction

With regard to effects upon fertility, no information is available in humans. The two available animal studies showed that administration of up to approximately 100 and 400 mg/kg/day respectively in the diet had no apparent effect upon fertility. The evidence in one study (out of the 3 reported) of maternal death during parturition observed in 5 out of 32 dams given 6250 ppm (538 mg/kg/day) MCCPs in the diet is not considered a direct consequence of parturition, but the consequence of low levels of vitamin K and related haemorrhaging. It is also expected that the act of parturition would place the dams at a higher risk of the consequences of low vitamin K levels.

In relation to developmental effects, there are no data available in humans. No adverse effects occurring during gestation were produced in rats or rabbits in two conventional teratology studies using doses up to 5000 and 100 mg/kg/day respectively. In contrast, exposure of rats to a C14-17 52% chlorinated paraffin from 74 mg/kg/day (1000 ppm) up to approximately 400 mg/kg/day (6250 ppm) in the diet produced internal haemorrhaging and deaths in the neonatal pups, although no such effects were seen in a more recent study with exposure to MCCPs for 11-12 weeks at maternal dose levels of 23 (300 ppm), 47 (600 ppm) and up to 100 mg/kg/day (1200 ppm). This would appear to be a repeated dose effect to which newborns during lactation, and possibly pregnant females at the time of parturition, are particularly susceptible.

A recent investigation (CXR Biosciences Ltd., 2004) has shown that MCCPs at a dose level of 6250 ppm (538 mg/kg/day) induce a perturbation of the clotting system in lactating neonates of treated mothers. In adult females that had been treated for 7-8 weeks including pregnancy and lactation, decreased levels of vitamin K and of the clotting factors VII and X were found, and 5 out of 32 dams showed signs of haemorrhaging during parturition. However, these decreases did not affect their prothrombin times, indicating that the functional reserve in the majority of these adult animals was sufficient. This implies that the foetus *in utero* receives sufficient vitamin K via the placenta, but after birth the neonate becomes severely deficient in vitamin K and related clotting factors when reliant of these factors via

the mothers'milk. It has also been shown that the neonate receives through the milk considerable levels of MCCPs, which may also further reduce his vitamin K levels. This in turn will lead to a severe vitamin K deficiency in these neonates (who are already compromised in their vitamin K status) and consequently to haemorrhaging. It has been argued that these effects should be considered as developmental toxicity effects as the development during the neonatal period of rats corresponds to the development period during the last trimester of human pregnancy. Although it is generally accepted that the rat post-natal period is equivalent to the last trimester of a human pregnancy, by taking into account what is known of the mechanism of these effects, such haemorrhaging effects could only be entirely post-natal even in humans as they cannot occur *in utero* as there are supplies of vitamin K from the dams. Also, although some dams died as a consequence of haemorrhaging, it should be noted that the dams died at parturition and not during the pregnancy and that the act of parturition puts the dams at higher risk, maybe as a consequence of blood loss.

From the studies available, an overall NOAEL of 47 mg/kg/day (600 ppm) as a maternal dose can be identified for these effects mediated via lactation. However, it should be noted that the effects (11% reduction in pup survival and related haemorrhaging) observed at the LOAEL (74 mg/kg/day; 1000 ppm) were not statistically significant. Haemorrhaging was also seen in one study at the time of parturition in 16% of dams given 538 mg/kg/day (6250 ppm) MCCPs, but not up to 100 mg/kg (1200 ppm) in other studies. The NOAEL of 100 mg/kg/day (1200 ppm) is therefore selected for the risk characterisation of haemorrhaging effects potentially occurring in pregnant women at the time of parturition.

During the technical discussions of this RAR, a small number of Member States disagreed with this interpretation of the data, which was endorsed by the majority of Member States. Denmark, Sweden and Norway found that effects concerning internal haemorrhaging and death in neonatal pups described in section 4.1.2.9.1 (Fertility) and section 4.1.2.9.3 (Research into mechanisms of the internal haemorrhages) should be considered as developmental toxicity effects and not exclusively as repeated dose toxicity effects as mentioned in this summary. The development during the neonatal period of rats corresponds to the development period during the last trimester of human pregnancy. It was argued that as the effect may be a consequence of increased sensitivity towards low level of vitamin K of the new-born rats this would then correspond to increased sensitivity in the human foetus during the last trimester. It was also argued that the effect would further imply classification for developmental toxicity as the criteria for classification include any effect interfering with normal development from gestation up to and including puberty.

4.1.3 Risk characterisation (with regard to the effects listed in Annex 1A of Regulation 1488/94)

The section below, entitled 'General Aspects' provides an overview of the occupational use, exposure and toxicological profile of medium-chained chlorinated paraffins identifying the lead effects and where appropriate, identifying NOAELs and/or LOAELs.

General aspects

Occupational exposure to MCCPs occurs during the:

manufacture of MCCPs;

manufacture and use of PVC formulations containing MCCPs;

manufacture and use of paints containing MCCPs;

manufacture and use of sealants and adhesives containing MCCPs;

manufacture of rubber containing MCCPs;

manufacture and use of MWFs containing MCCPs;

manufacture and use of fat liquors containing MCCPs for leather treatment; and

manufacture of carbonless copy paper containing MCCPs.

MCCPs are viscous liquids with very low vapour pressures. MCCPs, 52% chlorinated with a vapour pressure of 2.7×10^{-7} kPa at 20 °C, have a saturated vapour concentration of 0.0027 ppm or 0.051 $mg.m^{-3}$ (assuming a molecular weight of 450) at 20 °C. Thus personal exposures to MCCP vapour at ambient temperature in the workplace will be very low, the maximum theoretical vapour concentration being 0.0027 ppm. This prediction for maximum vapour concentration based on the SVC will still hold where the process is at a higher temperature, since the actual working environment will usually be about 20 °C. At the point of release of hot vapour from the process there will be a mixture of vapour and mist. The mist is formed as the hot vapour cools and condenses to form liquid droplets, thus in the worker's breathing zone there will be vapour, at a maximum of the SVC, and mist. The extent of the exposure to the mist will be dependent on the processing temperature and the controls.

A range of 9 to 18 $mg.m^{-3}$ 8-hour TWA was derived from EASE data for the mist in situations where poor control of this mist was felt to be a possibility. These scenarios were calendering of plasticized PVC, compounding of plasticised PVC, extrusion and moulding of plasticised PVC, and rubber manufacture. In other scenarios, exposure to the mist was discounted as a significant contributor to exposure. Either process temperatures were too low or the nature of the process was such that releases were very unlikely.

In addition to the possibility of exposure to MCCP aerosols created by condensation, there are situations where aerosols may be created by mechanical agitation, in particular, during the use of metal working fluids containing MCCPs in the engineering industry and, to a much lesser extent, during the spraying of paints which contain MCCPs. Values for exposure to airborne MCCPs derived from a recent unpublished HSE survey of the exposure of workers to metal working fluids, indicate exposures between 0.09 and 0.5 $mg.m^{-3}$ 8-hour TWA. De Pater *et al,* 1999 (draft), provide a model for predicting exposure to non-volatile compounds during spray painting, which gave a result of 5 $mg.m^{-3}$ 8-hour TWA.

Dermal exposure to MWFs was predicted using EASE to be 0.006 to 0.75 $mg/cm^2/day$. Seven activities gave rise to EASE predicted dermal exposures to MCCPs in the range 0.1 to 1 $mg/cm^2/day$, namely,

Drumming off MCCPs at the production plant

Manufacture of PVC plastisol

Calendering of PVC

Compounding of plasticised PVC

Application of paints

Rubber manufacture

Use of fat liquors in leather treatment

The remaining activities described in the report give rise to EASE predictions of dermal exposure in the range 0 to 0.1 mg/cm^2/day. These values have again been provided as a first approximation of this exposure and are based on the limited information obtained.

The only human toxicokinetics data relate to information on the presence of chlorinated paraffins in human breast milk, indicating the potential for excretion via this route. No studies have been undertaken to investigate the toxicokinetics of MCCPs following exposure of animals via the inhalation or dermal routes. A recent GLP- and OECD-compliant *in vitro* study using human skin showed that after 24 hours, approximately 0.7% of a C_{15} chlorinated paraffin was absorbed. A dermal absorption value of 1% is therefore taken forward to the risk characterisation.

Absorption following oral exposure in animals has been demonstrated to be significant (probably at least 50% of the total administered dose). Overall, therefore, 50% absorption by this route will be assumed for risk characterisation purposes. There is no specific information for the inhalation route of exposure; however, given that the data indicate 50% absorption by the oral route and only 1% by the dermal route, and in view of the very high log Pow and the very low water solubility of MCCPs, it reasonable to assume that inhalation absorption is also unlikely to be higher than 50%. This figure will therefore be taken to the risk characterisation in relation to absorption via the inhalation route of exposure. No conclusions can be drawn regarding the way in which the degree of chlorination of these substances may affect the extent of absorption following oral or any other route of administration.

Following absorption of radiolabelled MCCP via the oral route, there is an initial preferential distribution of radiolabel to tissues of high metabolic turnover/cellular proliferation. Subsequently, there is a re-distribution of radiolabelled material to fatty tissue. Following single gavage dosing in the rat, an elimination half-life of approximately 2-5 days was estimated for tissues such as the liver and kidney, and of about 2 weeks for tissues such as white adipose. Following repeated dietary administration, retention in fatty tissue occurs, with one study in rats showing a half-life for elimination from the abdominal fat of around 8 weeks. Results of a very recent study in the rat have shown that steady state in adipose tissue is reached at approximately 13 weeks and that elimination of MCCPs from this tissue appears to be biphasic, with an initial half-life of approximately 4 weeks, followed by a markedly slower second phase with a terminal half-life of approximately 43 weeks. There is no clear information on whether or not the degree of chlorination affects distribution. Also, generally, it is unclear whether or not the distributed material is the parent compound and/or metabolites although one recent study clearly indicates that it is the parent compound that is taken up in adipose tissue and liver. There is evidence from animal studies and human data to indicate that MCCPs have the potential to be transferred to offspring via breast milk. Transmission of MCCPs (34% chlorination) or metabolites via the mother to the developing fetus *in utero* was evident although it is not clear if this occurs with all forms of MCCPs.

In relation to metabolism, one study with a 65% chlorinated MCCP indicated conjugation with glutathione. The production of CO_2 from MCCPs has also been demonstrated and was quite extensive (~30%) with MCCPs of lower chlorination (e.g. 34% chlorination), but appeared to be much more limited (~1%) with more heavily chlorinated MCCPs (e.g. 69% chlorination). Elimination of MCCPs and/or their metabolites occurs via the faeces, via exhaled CO_2 with lower chlorinated MCCPs, and to a limited extent in the urine.

No toxicological information is available on the effects of single exposure to MCCPs in humans. In animals, MCCPs are of low acute oral toxicity, and it is anticipated that the MCCPs are likely to be of low acute toxicity by inhalation and dermal routes. No information is available relating to the way in which the degree of chlorination might affect results, but given the low acute toxicity, this is unlikely to be of significance for this endpoint.

No data are available in humans relating to skin or eye irritation. However, based upon animal studies, MCCPs have been shown to cause only slight skin irritation on single exposure, although more pronounced irritation was observed following repeated application. MCCPs produce only slight eye irritation, and it is anticipated that they are unlikely to cause respiratory tract irritation. Amongst the limited range of compounds studied, the degree of chlorination was not of significance for these endpoints.

No data are available on skin sensitisation potential in humans but no evidence of skin sensitisation was produced in guinea pig maximisation tests and it is expected that MCCPs do not possess the potential to cause respiratory sensitisation.

No information is available on the effects of repeated exposure in humans. In animals there are no data relating to repeated inhalation or dermal exposure. A number of oral dosing studies (up to 90 days duration) in rodents are available which have investigated the repeated dose toxicity of C_{14-17}, 40% or 52% chlorinated paraffins. However, the extent of the data are such that it is not possible to assess whether or not the degree of chlorination, particularly outside this range, would have an effect upon the resulting toxicity.

The liver, thyroid and kidney are the target organs for repeated dose toxicity of MCCPs. For the liver, increases in weight were seen in rats and dogs at exposure levels of 100 mg/kg/day and above. In addition, enzyme induction and histopathological changes (centrilobular hepatocyte hypertrophy) were seen in rats starting from 222 mg/kg/day, and, from a limited study in dogs, at 30 mg/kg/day and above. These changes are likely to be related to an increase in metabolic demand as an adaptive response, possibly combined with peroxisome proliferation in the rat at higher dose levels. Both of these hepatic effects are considered of no or limited toxicological significance to human health. However, in rats, at higher exposure levels (around 360 mg/kg/day) single cell necrosis was observed; this effect is not thought to be related to increased metabolic demand or to peroxisome proliferation and therefore is considered to be of relevance to human health.

For the thyroid, clear pathology (follicular hypertrophy and hyperplasia) was seen at relatively high dose levels (312 mg/kg/day and above). Increased TSH levels and decreased T4 levels were also seen at similar dose levels. However, no toxicologically significant effects on thyroid hormones and TSH were observed up to top dose of 222/242 mg/kg/day (males/females) in a recent, well-conducted 90-day study in rats. The thyroid pathology observed at relatively high doses of MCCPs is likely to have occurred due to repeated stimulation of this organ because of a negative feedback control effect arising from plasma T_4 depletion following increased excretion of this hormone. This depletion results from an increase in the activity of hepatic UDPG-transferase. Humans, unlike rodents, possess T_4-globulin binding protein and are therefore less susceptible to plasma T_4 depletion and hence any resultant thyroid stimulation. Overall based on these considerations, the thyroid effects observed in rats should be considered not to be of relevance to human health at relevant levels of exposure.

From the data that are available, no adverse renal effects were seen in males and females at 23 mg/kg/day in a recent and well-conducted rat 90-day study. Changes seen in the kidneys at

222 mg/kg/day and above (increased weight, 'chronic nephritis' and tubular pigmentation) are considered as being potentially relevant to human health. Mechanistic studies indicated some deposition of α2u globulin in proximal convoluted tubules of male rats only at higher dose levels. However, this was unrelated to the pathological findings described above. Thus, these changes are not considered to be a male rat-specific phenomenon. In terms of severity, an increase in kidney weight of 9-13% was observed at the top dose of 222 mg/kg/day in one study and of 18% at the top dose of 625 mg/kg/day in another study. The increase above controls in the incidence and severity of what has been misleadingly termed 'chronic nephritis' ('a mixed population of interstitial inflammatory cells, tubular regeneration and minimal degenerative changes in the tubular epithelium occurring alone or in combination') was seen in treated males and females at 10 mg/kg/day and above. At 10 mg/kg/day the severity of these changes was graded as 'trace', and even at the highest exposure level, 625 mg/kg/day, was only 'mild'. Furthermore, a significant increase above controls in the incidence of this lesion (10/15 vs 1/15) was only seen at the top dose of 625 mg/kg/day with 3/15 and 4/15 animals affected at 10 and 100 mg/kg/day respectively. It is therefore concluded that, although kidney changes were observed from 10 mg/kg/day, a lesion considered to be of toxicological significance only occurred at the top dose of 625 mg/kg/day. Tubular pigmentation was also seen in females at the top dose of 625 mg/kg/day.

Overall, a NOAEL of 23 mg/kg/day is identified for repeated dose toxicity based upon effects seen in rat kidney (increased weight at the next dose level of 222 mg/kg/day and 'chronic nephritis' and tubular pigmentation at 625 mg/kg/day). It is noted that at 222 mg/kg/day there were also slight decreases in plasma triglycerides and cholesterol levels.

Few data are available on the genotoxicity of MCCPs, but the information that is available on MCCPs (and by comparison with SCCPs) indicates that MCCPs do not possess genotoxic activity.

No carcinogenicity studies in human populations with potential exposure to MCCPs are available, and similarly no investigations in animals have been conducted. Although no direct information is available, MCCPs are generally unreactive and not mutagenic. In the absence of experimental carcinogenicity data on MCCPs, given the similarities between MCCPs and SCCPs in physicochemical properties and in the results obtained in relation to other toxicological endpoints, particularly the effects seen on the liver, thyroid and kidneys on repeated exposure, it seems reasonable to presume that the carcinogenic potential of MCCPs will be similar, at least in qualitative terms, to that of SCCPs. SCCPs have been investigated in animal studies and found to induce liver and thyroid adenomas and carcinomas and kidney tubular cell adenomas and carcinomas. On mechanistic considerations, the liver and thyroid tumours were considered to be of little or no relevance to human health. The position agreed within the EU for SCCPs is that the underlying mechanism for the kidney tumours has not been elucidated and hence the possibility of carcinogenic potential relevant to humans could not be ruled out. However, since that evaluation, further evidence for the male rat specific mechanism for SCCPs has become available, indicating that α2u globulin formation is the likely underlying cause for tumour formation in male rats. Therefore, overall, SCCPs, and by analogy MCCPs, should be considered not to pose a carcinogenic hazard to humans.

In discussions with Member States, uncertainties about this mechanism for the kidney tumours have been highlighted. Hence, in January 2004, this issue was referred to the EC Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity.

The Specialised Experts agreed that there were still data gaps leading to uncertainty about the relevance of these tumours for humans. Some experts argued that there were inconsistencies and contradictions in the mechanistic studies, which might indicate that alternative mechanisms could not be excluded. The relation between α2u mechanism and the kidney tumours was not adequately established in this case. These data gaps led the Experts to conclude that the criteria for no classification for SCCPs were not met, and hence, they recommended that the current classification of SCCPs with Carc Cat 3 be retained.

However, the Specialised Experts agreed that a read-across from SCCPs to MCCPs was not justified for carcinogenicity, and consequently MCCPs could not be classified for this endpoint. They noted the absence of animal tumour data for MCCPs, the toxicological differences seen between SCCPs and LCCPs, and the heterogenous nature of all these compounds.

Hence, based on the opinion of the Specialised Experts read-across from SCCPs to MCCPs for this endpoint is not appropriate in terms of classification. However, in terms of hazard and risk, the carcinogenic potential of MCCPs still needs to be addressed. Taking into account all the other existing data on MCCPs, specifically the genotoxicity and the repeated dose toxicity data, it is noted that MCCPs lack genotoxicity activity, but produce kidney toxicity in male and female rats (increased weight at 222 mg/kg/day and 'chronic nephritis' and tubular pigmentation at 625 mg/kg/day). Based on this evidence, it cannot be completely ruled out that this form of kidney toxicity might lead to cancer in male and female rats through a non-genotoxic mode of action, even though with SCCPs kidney tumours were seen in male rats only. Therefore, a risk characterisation for the carcinogenicity endpoint will be conducted using the same NOAEL of 23 mg/kg/day identified for repeated dose effects on the kidney.

With regard to effects upon fertility, no information is available in humans. The two available animal studies (in rats) showed that administration of up to approximately 100 and 400 mg/kg/day respectively in the diet had no apparent effect upon fertility. The evidence in one study (out of the 3 reported) of maternal death during parturition observed in 5 out of 32 dams given 6250 ppm (538 mg/kg/day) MCCPs in the diet is not considered a direct consequence of parturition, but the consequence of low levels of vitamin K and related haemorrhaging. It is expected that the act of parturition would place the dams at a higher risk of the consequences of low vitamin K levels.

In relation to developmental effects, there are no data available in humans. No adverse effects occurring during gestation were produced in rats or rabbits in two conventional teratology studies using maternal doses up to 5000 and 100 mg/kg/day respectively. In contrast, exposure of rats to a C_{14-17} 52% chlorinated paraffins from 74 mg/kg/day (1000 ppm) up to approximately 400 mg/kg/day (6250 ppm) as a maternal dose in the diet produced internal haemorrhaging and deaths in the pups, although no such effects were seen in a more recent study with exposure to MCCPs for 11-12 weeks at maternal dose levels of 23 (300 ppm), 47 (600 ppm) and up to 100 mg/kg/day (1200 ppm). This would appear to be a repeated dose effect to which newborns during lactation, and possibly pregnant females at the time of parturition, are particularly susceptible. A recent investigation (CXR Biosciences Ltd., 2004) has shown that MCCPs at a dose level of 6250 ppm (538 mg/kg/day) induce a perturbation of the clotting system in lactating neonates of treated mothers. In adult females that had been treated for 7-8 weeks including pregnancy and lactation, decreased levels of vitamin K and of the clotting factors VII and X were found, and 5 out of 32 dams showed signs of haemorrhaging during parturition. However, these decreases did not affect their prothrombin times, indicating that the functional reserve in the majority of these adult animals is sufficient. The foetus *in utero* apparently receives sufficient vitamin K via the placenta, but after birth

becomes severely deficient in vitamin K and related clotting factors when reliant of these factors via the mothers'milk. They also receive through the milk considerable levels of MCCPs, which may also further reduce their vitamin K levels. This in turn will lead to a severe vitamin K deficiency in these neonates (who are already compromised in their vitamin K status) and consequently to haemorrhaging.

From the studies available, an overall NOAEL of 47 mg/kg/day (600 ppm) as a maternal dose can be identified for these effects mediated via lactation. However, it should be noted that the effects (11% reduction in pup survival and related haemorrhaging) observed at the LOAEL (74 mg/kg/day; 1000 ppm) were not statistically significant. Haemorrhaging was also seen in one study at the time of parturition in 16% of dams given 538 mg/kg/day (6250 ppm) MCCPs, but not up to 100 mg/kg (1200 ppm) in other studies. The NOAEL of 100 mg/kg/day (1200 ppm) is therefore selected for the risk characterisation of haemorrhaging effects potentially occurring in pregnant women at the time of parturition.

Overall, the lead health effects of concern are irritation of the skin as a result of repeated exposure via a defatting mechanism, repeated dose toxicity, carcinogencity, effects on the dams during parturition and effects on the offspring mediated via lactation. There are no concerns for acute toxicity, irritation, sensitisation, genotoxicity or effects on fertility and therefore conclusion (ii) is reached for these endpoints.

To conduct the risk characterisation for workers and consumers, it is necessary to compare human exposure for the inhalation and dermal routes with oral N(L)OAELs from repeated-dose animal studies, because of the absence of inhalation toxicity data. The human inhalation and dermal exposures have been converted to internal body burdens. A breathing rate of 1.25 $m^3.hour^{-1}$ and body weights of 70 and 60 kg for workers and consumers respectively have been assumed. Absorption is considered to be 50% by the oral and inhalation routes and 1% by the dermal route.

A NOAEL of 23 mg/kg/day has been identified for repeated dose toxicity based upon effects seen in rat kidney (increased weight at the next dose level of 222 mg/kg/day and 'chronic nephritis' at 625 mg/kg/day). It is noted that at 222 mg/kg/day there were also slight decreases in plasma triglycerides and cholesterol levels.

In relation to carcinogenicity, there are no animal or human data available. Furthermore, read across from SCCPs was not considered appropriate by the SE. Hence, taking into account all the other existing data on MCCPs, specifically the genotoxicity and the repeated dose toxicity data, it is noted that MCCPs lack genotoxicity activity, but produce kidney toxicity in rats (increased weight at 222 mg/kg/day and 'chronic nephritis' at 625 mg/kg/day). Based on this evidence, it cannot be completely ruled out that this form of kidney toxicity might lead to cancer through a non-genotoxic mode of action. Therefore, a risk characterisation for carcinogenicity will be conducted using the same NOAEL of 23 mg/kg/day identified for repeated dose effects on the kidney.

Severe effects (internal haemorrhaging and deaths) have been observed in suckling rat pups where the dams had received MCCPs orally. This haemorrhaging would appear to be a repeated dose effect to which newborns during lactation, and possibly pregnant females at the time of parturition, are particularly susceptible. A very recent investigation (CXR Biosciences Ltd., 2004) has shown that MCCPs at a dose level of 6250 ppm (538 mg/kg/day) induce a perturbation of the clotting system in lactating neonates of treated mothers. In adult females that had been treated for 7-8 weeks including pregnancy and lactation, decreased levels of vitamin K and of the clotting factors VII and X were found, and 5 out of 32 dams showed

signs of haemorrhaging during parturition. However, these decreases did not affect their prothrombin times, indicating that the functional reserve in the majority of these adult animals is sufficient. The foetus *in utero* apparently receives sufficient vitamin K via the placenta, but after birth becomes severely deficient in vitamin K and related clotting factors when reliant of these factors via the mothers'milk. They also receive through the milk considerable levels of MCCPs, which may also further reduce their vitamin K levels. This in turn will lead to a severe vitamin K deficiency in these neonates (who are already compromised in their vitamin K status) and consequently to haemorrhaging.

The maternal NOAEL (47 mg/kg/day; 600 ppm) identified in a recent one-generation study for effects on the F1 offspring, following treatment of F0 males and females for 4 weeks prior to pairing and throughout mating, gestation and lactation (for a total treatment duration of 11-12 weeks) will be used in the risk characterisation of an adult population of breastfeeding mothers that might be exposed to MCCPs via work activities, consumer products or the environment. However, it should be noted that the effects (11% reduction in pup survival and related haemorrhaging) observed at the LOAEL (74 mg/kg/day; 1000 ppm) were not statistically significant. Haemorrhaging was also seen in one study at the time of parturition in 16% of dams given 538 mg/kg/day (6250 ppm) MCCPs, but not up to 100 mg/kg/day (1200 ppm) in other studies. The NOAEL of 100 mg/kg/day (1200 ppm) is therefore selected for the risk characterisation of haemorrhaging effects potentially occurring in pregnant women at the time of parturition.

The cross-fostering study and this recent investigation have also identified a concentration of MCCPs in samples of rat dam breast milk inducing haemorrhaging effects in the pups, and three surveys have measured MCCPs levels in human breast and cow's milk samples. Therefore, a risk characterisation for these effects will also be performed for an infant population potentially exposed to MCCPs via breast or cow's milk.

4.1.3.1 Workers

Irritation

There is evidence for slight irritation of the skin as a result of repeated exposures to MCCPs. However, this property is unlikely to be expressed during normal handling and use providing good occupational hygiene practices are in operation. Overall, conclusion (ii) is reached.

Repeated exposure toxicity

The body burdens arising from inhalation and dermal exposure in each different worker exposure scenario, and the resultant MOSs derived from comparison with the NOAEL for effects on the kidney are shown in **Table 4.10**

Table 4:10 Body burdens and MOSs for repeated dose toxicity

Process	Inhalation exposure (mg/m^3)	Inhalation body burden (mg/kg)	Dermal exposure (mg/day)	Dermal body burden (mg/kg)	Total body burden (mg/kg)	MOS based on kidney toxicity NOAEL[1]	Conclusion
Manufacture of MCCPs	0.05	0.0035	210	0.03	0.034	338	(ii)
PVC formulation/manufacture	0.08	0.0057	420	0.06	0.066	174	(ii)
Plastisol use	0.05	0.0035	126	0.02	0.024	479	(ii)
Calendering	1	0.07	420	0.06	0.13	88	(ii)
Compounding of PVC	0.15	0.011	84	0.012	0.023	500	(ii)
Extrusion/Moulding	0.1	0.007	21	0.003	0.01	1150	(ii)
Paint manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)
Paint spraying	0.19	0.014	126	0.02	0.034	338	(ii)
Sealant manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)
Rubber manufacture	0.07	0.005	420	0.06	0.065	178	(ii)
MWF manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)
Water-based MWF use	0.008	0.0006	180	0.026	0.0266	432	(ii)
Oil-based MWF use	2.4	0.17	25,000	3.6	3.77	3	(iii)
Preparation and use of fat liquor	0.05	0.0035	84	0.012	0.016	719	(ii)
Copy paper manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)

Based on NOAEL of 23 mg.kg-1 equivalent to an internal NAEL of 11.5 mg.kg-1based on 50% oral absorption

For all scenarios except PVC calendering and oil-based MWF use, the MOSs are ≥ 174. These values are considered to provide sufficient reassurance that adverse repeated dose effects will not occur even after taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified (subchronic to chronic extrapolation). Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within the exposure duration of the study from which the NOAEL has been identified. Therefore conclusion (ii) is proposed for these scenarios.

For PVC calendering, the MOS is 88. This value would not normally be sufficient to account for variability between and within species and for the relatively short duration (90 days) of the study from which the NOAEL has been identified (subchronic to chronic extrapolation). However, given that the exposure estimate is likely to be an overestimate of chronic exposure as workers are exposed 2-3 times per week rather than 5 days per week, conclusion (ii) is proposed for this scenario.

For oil-based MWF use, the MOS is 3. This value is considered to be too low for taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified. Therefore conclusion (iii) is proposed for this scenario. It is important to note that for the oil-based MWF use scenario the MOS is heavily affected by the dermal contribution to total body burden.

Carcinogenicity

Table 4.11 shows the body burdens arising from inhalation and dermal exposure in each different worker scenario, and the resultant MOSs derived from comparison with the NOAEL of 23 mg/kg/day identified for kidney toxicity, which is considered to have the potential to lead to cancer formation through a non-genotoxic mode of action.

Table 4:11 Body burdens and MOSs for carcinogencic effects

Process	Inhalation exposure (mg/m^3)	Inhalation body burden (mg/kg)	Dermal exposure (mg/day)	Dermal body burden (mg/kg)	Total body burden (mg/kg)	MOS based on kidney toxicity NOAEL[1]	Conclusion
Manufacture of MCCPs	0.05	0.0035	210	0.03	0.034	338	(ii)
PVC formulation/manufacture	0.08	0.0057	420	0.06	0.066	174	(ii)
Plastisol use	0.05	0.0035	126	0.02	0.024	479	(ii)
Calendering	1	0.07	420	0.06	0.13	88	(ii)
Compounding of PVC	0.15	0.011	84	0.012	0.023	500	(ii)
Extrusion/Moulding	0.1	0.007	21	0.003	0.01	1150	(ii)
Paint manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)
Paint spraying	0.19	0.014	126	0.02	0.034	338	(ii)
Sealant manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)
Rubber manufacture	0.07	0.005	420	0.06	0.065	178	(ii)
MWF manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)
Water-based MWF use	0.008	0.0006	180	0.026	0.0266	432	(ii)
Oil-based MWF use	2.4	0.17	25,000	3.6	3.77	3	(iii)
Preparation and use of fat liquor	0.05	0.0035	84	0.012	0.016	719	(ii)
Copy paper manufacture	0.05	0.0035	42	0.006	0.01	1150	(ii)

[1] Based on NOAEL of 23 $mg.kg^{-1}$ equivalent to an internal NAEL of 11.5 $mg.kg^{-1}$ based on 50% oral absorption

For all scenarios except PVC calendering and oil-based MWF use, the MOSs are ≥ 174. These values are considered to provide sufficient reassurance that carcinogenic effects will not occur even after taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified (subchronic to chronic extrapolation). Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within the exposure duration of the study from which the NOAEL has been identified. Although, normally, the severity of the endpoint would require an additional safety factor, since, in this case, the risk characterisation for potential carcinogenicity is based on repeated dose toxicity, no additional factor is required. Therefore conclusion (ii) is proposed for these scenarios.

For PVC calendering, the MOS is 88. This value would not normally be sufficient to account for variability between and within species and for the relatively short duration (90 days) of the

study from which the NOAEL has been identified (subchronic to chronic extrapolation). However, given that the exposure estimate is likely to be an overestimate of chronic exposure as workers are exposed 2-3 times per week rather than 5 days per week, conclusion (ii) is proposed for this scenario.

For oil-based MWF use, the MOS is 3. This value is considered to be too low for taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified. Therefore conclusion (iii) is proposed for this scenario. It is important to note that for the oil-based MWF use scenario the MOS is heavily affected by the dermal contribution to total body burden.

Effects mediated via lactation

Table 4.12 shows the body burdens arising from inhalation and dermal exposure in each different worker exposure scenario, and the resultant MOSs derived from comparison with the maternal NOAEL (47 mg/kg/day; 600 ppm) for effects mediated via lactation. It should be noted that whilst it is possible that a woman might return to work immediately after her confinement and start to breastfeed her infant, the blood levels of MCCPs, and, as a consequence, the levels in her milk, will have been reduced as a consequence of her period of absence from work. This anticipated reduction in body burden has therefore been reflected in the calculation of a corrected total body burden by the application of a dividing factor of 2.

Table 4:12 Inhalation body burdens and resultant MOSs for effects mediated via lactation

Process	Inhalation exposure (mg/m^3)	Inhalation body burden (mg/kg)	Dermal exposure (mg/day)	Dermal body burden (mg/kg)	Total body burden (mg/kg)	Corrected total body burden for a breastfeeding mother returning to work after maternity leave	MOS based on NOAEL[1] for effects via lactation	Conclusion
Manufacture of MCCPs	0.05	0.0035	210	0.03	0.034	0.017	1382	(ii)
PVC formulation/manufacture	0.08	0.0057	420	0.06	0.066	0.033	712	(ii)
Plastisol use	0.05	0.0035	126	0.02	0.024	0.012	1958	(ii)
Calendering	1	0.07	420	0.06	0.13	0.065	362	(ii)
Compounding of PVC	0.15	0.011	84	0.012	0.023	0.0115	2042	(ii)
Extrusion/Moulding	0.1	0.007	21	0.003	0.01	0.005	4700	(ii)
Paint manufacture	0.05	0.0035	42	0.006	0.01	0.005	4700	(ii)
Paint spraying	0.19	0.014	126	0.02	0.034	0.017	1382	(ii)
Sealant manufacture	0.05	0.0035	42	0.006	0.01	0.005	4700	(ii)
Rubber manufacture	0.07	0.005	420	0.06	0.065	0.0325	722	(ii)
MWF manufacture	0.05	0.0035	42	0.006	0.01	0.005	4700	(ii)
Water-based MWF use	0.008	0.0006	180	0.026	0.0266	0.0133	1767	(ii)
Oil-based MWF use	2.4	0.17	25,000	3.6	3.77	1.885	12.4	(iii)
Preparation and use of fat liquor	0.05	0.0035	84	0.012	0.016	0.008	2938	(ii)
Copy paper manufacture	0.05	0.0035	42	0.006	0.01	0.005	4700	(ii)

[1] Based on NOAEL of 47 mg/kg equivalent to an internal NAEL of 23.5 mg/kgbased on 50% oral absorption

For all scenarios except oil-based MWF use, the MOSs are ≥ 362. These MOSs are considered to provide sufficient reassurance that these effects will not occur after allowing for the potential toxicokinetic and toxicodynamic differences between and within species, for the need to adjust for time to staedy state (13 wk vs an exposure duration in the study from which the NOAEL has been identified of 11-12 wk) and for the severity of the effects (11% mortality at the LOAEL of 74 mg/kg/day). Further reassurance for subchronic to chronic extrapolation is not required, as, for effects via lactation, exposure is not chronic. Hence, conclusion (ii) is reached for these scenarios.

For the remaining scenario, oil-based MWF use, the MOS is 12.4. This MOS value does not provide sufficient reassurance that these effects will not occur and therefore conclusion (iii) is reached.

Effects at the time of parturition

Table 4.13 shows the body burdens arising from inhalation and dermal exposure in each different worker exposure scenario, and the resultant MOSs derived from comparison with the NOAEL (100 mg/kg/day; 1200 ppm) for effects at the time of parturition. It seems reasonable to assume that a pregnant woman would not be at work conducting the manual tasks described by the exposure scenarios right up to the time of parturition. It is suggested that a pregnant woman is likely to cease work at least four weeks prior to her impending confinement. Given that the first phase of elimination of MCCPs has been shown to have a half-life of 4 weeks (see section 4.1.2.1.3), it seems reasonable to calculate a corrected total body burden for the time of parturition by applying a dividing factor of 2.

Table 4:13 Inhalation body burdens and resultant MOSs for effects at the time of parturition

Process	Inhalation exposure (mg/m^3)	Inhalation body burden (mg/kg)	Dermal exposure (mg/day)	Dermal body burden (mg/kg)	Total body burden (mg/kg)	Corrected total body burden for a pregnant woman going on maternity leave at least four weeks prior to her confinement	MOS based on NOAEL[1] for effects at the time of parturition	Conclusion
Manufacture of MCCPs	0.05	0.0035	210	0.03	0.034	0.017	2940	(ii)
PVC formulation/manufacture	0.08	0.0057	420	0.06	0.066	0.033	1515	(ii)
Plastisol use	0.05	0.0035	126	0.02	0.024	0.012	4167	(ii)
Calendering	1	0.07	420	0.06	0.13	0.065	770	(ii)
Compounding of PVC	0.15	0.011	84	0.012	0.023	0.0115	4348	(ii)
Extrusion/Moulding	0.1	0.007	21	0.003	0.01	0.005	10,000	(ii)
Paint manufacture	0.05	0.0035	42	0.006	0.01	0.005	10,000	(ii)
Paint spraying	0.19	0.014	126	0.02	0.034	0.017	2941	(ii)
Sealant manufacture	0.05	0.0035	42	0.006	0.01	0.005	10,000	(ii)
Rubber manufacture	0.07	0.005	420	0.06	0.065	0.0325	1538	(ii)
MWF manufacture	0.05	0.0035	42	0.006	0.01	0.005	10,000	(ii)
Water-based MWF use	0.008	0.0006	180	0.026	0.0266	0.0133	3759	(ii)
Oil-based MWF use	2.4	0.17	25,000	3.6	3.77	1.885	26	(iii)
Preparation and use of fat liquor	0.05	0.0035	84	0.012	0.016	0.008	6250	(ii)
Copy paper manufacture	0.05	0.0035	42	0.006	0.01	0.005	10,000	(ii)

[1] Based on NOAEL of 100 mg/kg equivalent to an internal NAEL of 50 mg/kg based on 50% oral absorption

For all scenarios except oil-based MWF use, the MOSs are ≥ 770. These MOSs are considered to provide sufficient reassurance that these effects will not occur after allowing for the potential toxicokinetic and toxicodynamic differences between and within species, for the need to adjust for time to staedy state (13 wk vs an exposure duration in the study from which the NOAEL has been identified of 11-12 wk) and for the severity of the effect (16% mortality) at the LOAEL (538 mg/kg/day). Hence, conclusion (ii) is reached for these scenarios. For the remaining scenario, oil-based MWF use, the MOS is 26. This MOS value does not provide sufficient reassurance that these effects will not occur and therefore conclusion (iii) is reached.

Summary of risk characterisation for workers

The MOSs for effects on the kidney following repeated exposure, for carcinogenicity, for effects via lactation and for effects at the time of parturition for oil-based MWF use are unacceptably low, and therefore conclusion (iii) is reached for this scenario. For all remaining scenarios, the MOSs for all of these effects are considered to be sufficient, and therefore conclusion (ii) is reached.

4.1.3.2 Consumers

The lead health effects for MCCPs are the repeated exposure effects to the kidneys seen in adult animals, the potential carcinogenic effects and the internal haemorrhaging observed in suckling pups. MCCPs are not skin, eye or respiratory tract irritants following single exposures although there is evidence for slight defatting of the skin as a result of repeated exposure. This defatting of the skin is considered to be slight and the levels of MCCPs in consumer products are very low such that none of the consumer exposure scenarios result in repeated dermal exposures that are likely to give rise to concern.

There are two consumer exposure scenarios for which significant exposures could occur: the wearing of leather clothes treated with MCCPs and the use of metal working fluids. The wearing of leather clothes results in dermal exposure only (estimate of 1 mg/day). For the use of metal working fluids, the estimated exposure is 0.5 mg/event (see section 4.1.1.2). The endpoints of concern relevant to the consumer are kidney effects following repeated exposure, for which a NOAEL of 23 mg/kg/day has been identified, potential carcinogenic effects for which the repeated dose toxicity NOAEL of 23 mg/kg/day has been established, effects mediated via lactation, for which a maternal NOAEL of 47 mg/kg/day (600 ppm) has been identified and effects at the time of parturition, for which a NOAEL of 100 mg/kg/day (1200 ppm) has been selected.

Repeated exposure toxicity

Dermal exposure resulting from wearing leather clothes treated with MCCPs is estimated to be 1 mg/day (see section 4.1.1.2.1). Assuming 1% absorption, this represents a body burden of 1.6×10^{-4} $mg.kg^{-1}$ for a 60 kg consumer. Comparing this body burden with the NOAEL of 23 mg/kg/day for effects on the kidney (equivalent to an internal NAEL of 11.5 mg/kg/day based on 50% oral absorption) gives a MOS of 70,000. This MOS is considered to be sufficient even taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified. Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within the exposure duration of the study from which the NOAEL has been identified. Therefore, conclusion (ii) is reached.

Inhalation exposure during the use of metal working fluids is estimated to be 0.5 mg/event. Assuming 50% absorption, this represents a body burden of 4×10^{-3} $mg.kg^{-1}$ for a 60 kg consumer. Comparing this body burden with the NOAEL of 23 mg/kg/day for effects on the kidney (equivalent to an internal NAEL of 11.5 mg/kg/day based on 50% oral absorption) gives a MOS of 2,875. This MOS is considered to be sufficient, even taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified. Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within

the exposure duration of the study from which the NOAEL has been identified. Thus, conclusion (ii) is reached.

Carcinogenicity

The body burden arising from wearing leather clothes is estimated at 1.6×10^{-4} $mg.kg^{-1}$. Comparing this body burden with the NOAEL of 23 mg/kg/day (equivalent to an internal NAEL of 11.5 mg/kg/day based on 50% oral absorption) for potential carcinogenic effects gives a MOS of 70,000. This MOS is considered to be sufficient even taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified. Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within the exposure duration of the study from which the NOAEL has been identified. Although, normally, the severity of the endpoint would require an additional safety factor, since in this case, the risk characterisation for potential carcinogenicity is based on repeated dose toxicity, no additional factor is required. Therefore, conclusion (ii) is reached.

The body burden arising from the use of metal working fluids is estimated at 4×10^{-3} $mg.kg^{-1}$. Comparing this body burden with the NOAEL of 23 mg/kg/day (equivalent to an internal NAEL of 11.5 mg/kg/day based on 50% oral absorption) for potential carcinogenic effects gives a MOS of 2,875. This MOS is considered to be sufficient even taking into account variability between and within species, the relatively short duration (90 days) of the study from which the NOAEL has been identified. Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within the exposure duration of the study from which the NOAEL has been identified. Although, normally, the severity of the endpoint would require an additional safety factor, since, in this case, the risk characterisation for potential carcinogenicity is based on repeated dose toxicity, no additional factor is required. Therefore conclusion (ii) is reached.

Effects mediated via lactation

The body burden arising from wearing leather clothes is estimated to be 1.6×10^{-4} $mg.kg^{-1}$. Comparing this body burden with the NOAEL of 47 mg/kg/day (equivalent to an internal NAEL of 23.5 mg/kg/day based on 50% oral absorption) for effects mediated via lactation gives an MOS of 147,000.

The body burden arising from the use of metal working fluids is estimated to be 4×10^{-3} $mg.kg^{-1}$. Comparing this body burden with the NOAEL of 47 mg/kg/day (equivalent to an internal NAEL of 23.5 mg/kg/day based on 50% oral absorption) for effects mediated via lactation gives an MOS of 5,875.

These MOSs are considered to be sufficient that these effects will not occur after allowing for toxicokinetic and toxicodynamic differences between and within species, for the need to adjust for time to staedy state and for the severity of the effects. Conclusion (ii) is reached for both scenarios.

Effects at the time of parturition

The body burden arising from wearing leather clothes is estimated to be 1.6×10^{-4} $mg.kg^{-1}$. Comparing this body burden with the NOAEL of 100 mg/kg/day (equivalent to an internal NAEL of 50 mg/kg/day based on 50% oral absorption) for effects at the time of parturition gives an MOS of 312,000.

The body burden arising from the use of metal working fluids is estimated to be 4×10^{-3} mg.kg^{-1}. Comparing this body burden with the NOAEL of 100 mg/kg/day (equivalent to an internal NAEL of 50 mg/kg/day based on 50% oral absorption) for effects at the time of parturition gives an MOS of 12,500.

These MOSs are considered to be sufficient that these effects will not occur after allowing for toxicokinetic and toxicodynamic differences between and within species, for the need to adjust for time to staedy state and for the severity of the effect (16% mortality) at the LOAEL (538 mg/kg/day). Conclusion (ii) is reached for both scenarios.

4.1.3.3 Humans exposed indirectly via the environment

4.1.3.3.1 Regional exposure

Repeated exposure toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition

From section 4.1.1.3 the total daily human exposure to medium chain chlorinated paraffins from regional sources is 1.3×10^{-4} mg.kg^{-1}.day^{-1}. The MOSs for repeated exposure toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are shown in **Table 4.14**.

Table 4:14 MOSs for repeated exposure toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition

Effect	Regional exposure (mg.kg^{-1}.day^{-1})	NOAEL (mg.kg^{-1}.day^{-1})	MOS	Conclusion
Kidney toxicity	1.3×10^{-4}	11.5	88,000	(ii)
Carcinogenicity	1.3×10^{-4}	11.5	88,000	(ii)
Effects mediated via lactation	1.3×10^{-4}	23.5	~181,000	(ii)
Effects at the time of parturition	1.3×10^{-4}	50	385,000	(ii)

In relation to effects on the kidney, the MOS is 88,000. This MOS is considered to be sufficient even taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified. Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within the exposure duration of the study from which the NOAEL has been identified. Thus, conclusion (ii) is proposed.

For potential carcinogenic effects, the MOS is 88,000. This MOS is considered to be sufficient even taking into account variability between and within species and the relatively short duration (90 days) of the study from which the NOAEL has been identified. Further reassurance for the potential of MCCPs to biopersist in adipose tissue is not required, as steady state should have been reached within the exposure duration of the study from which the NOAEL has been identified. Although, normally, the severity of the endpoint would require an additional safety factor, since in this case, the risk characterisation for potential

carcinogenicity is based on repeated dose toxicity, no additional factor is required. Thus, conclusion (ii) is proposed.

For effects mediated via lactation, the MOS is 181,000. This MOS is considered to be sufficient to provide reassurance that adverse health effects would not occur, after allowing for toxicokinetic and toxicodynamic differences between species, for the need to adjust for time to staedy state and for the severity of the effects. Overall, conclusion (ii) is reached.

For effects at the time of parturition, the MOS is 385,000. This MOS is considered to be sufficient to provide reassurance that adverse health effects would not occur, after allowing for toxicokinetic and toxicodynamic differences between species, for the need to adjust for time to staedy state and for the severity of the effect (16% mortality) at the LOAEL (538 mg/kg/day). Overall, conclusion (ii) is reached.

4.1.3.3.2 Local exposure

Repeated exposure toxicity, carcinogenicity and effects mediated via lactation

In section 4.1.1.3 the highest continuous local exposure is estimated to be 0.016 $mg.kg^{-1}.day^{-1}$ in the locality of a leather fat liquor plant.

The margins of safety for local exposure have been calculated using the NOAELs for repeated exposure effects on the kidney and for potential carcinogenic effects (internal NAEL of 11.5 mg/kg/day), for effects mediated via lactation (internal NAEL of 23.5 mg/kg/day) and for effects at the time of parturition (internal NAEL of 50 mg/kg/day) in **Table 4.15**.

Table 4:15 MOSs based on NOAELs for repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition

Effect	Exposure (mg/kg/day)	NOAEL ($mg.kg^{-1}.day^{-1}$)	MOS	Conclusion
Kidney and thyroid toxicity	0.016	11.5	719	(ii)
Carcinogenicity	0.016	11.5	719	(ii)
Effects mediated via lactation	0.016	23.5	1469	(ii)
Effects at the time of parturition	0.016	50	3125	(ii)

The calculated margins of safety are large for the effects considered. Therefore, conclusion (ii) is proposed.

4.1.3.3.3 Infants exposed via milk

Severe effects (internal haemorrhaging and deaths) have been observed in suckling rat pups from dams that had received MCCPs orally. Internal haemorrhaging or similar haematological effects have not been seen in adult rats, so the effects may be associated with an intrinsic sensitivity of the pups. A very recent investigation (CXR Biosciences Ltd., 2004) has shown

that MCCPs at a dose level of 6250 ppm (538 mg/kg/day) induce a perturbation of the clotting system in lactating neonates of treated mothers. In adult females that had been treated for 7-8 weeks including pregnancy and lactation with 6250 ppm MCCPs, decreased levels of vitamin K and of the clotting factors VII and X were found. However, these decreases did not affect their prothrombin times, indicating that the functional reserve in these adult animals is sufficient. The foetus *in utero* apparently receives sufficient vitamin K via the placenta, but after birth becomes severely deficient in vitamin K and related clotting factors when reliant of these factors via the mothers'milk. They also receive through the milk considerable levels of MCCPs, which may also further reduce their vitamin K levels. This in turn will lead to a severe vitamin K deficiency in these neonates (who are already compromised in their vitamin K status) and consequently to haemorrhaging. Since a cross-fostering study in rats and this new study have identified a concentration of MCCPs in samples of rat dam breast milk inducing haemorrhaging effects in the pups, and three surveys have measured MCCPs levels in human breast and cow's milk samples, a risk characterisation for these effects will be performed for an infant population potentially exposed to MCCPs via breast or cow's milk.

Infants exposed via human breast milk

There is a study that reports levels of chlorinated paraffins (C_{10-24}) in human breast milk (Greenpeace, 1995) from which further information on the breast milk sampling was obtained from the author of the report. The total level measured (on a fat weight basis) was 45 µg/kg fat. The average chlorine content of the chlorinated paraffins detected was around 33% and MCCPs were deduced to make up 10 and 22% of the total chlorinated paraffins found in groups of non-fish eating and fish eating women respectively. Thus, taking an average level of MCCPs of 16%, the concentration of MCCPs present in breast milk can be estimated at about 7 µg/kg fat; taking the highest concentration of MCCPs, of 22%, the concentration present in milk is about 9.0 µg/kg fat.

More recently, an Industry sponsored study has also found MCCPs to be present in human breast milk samples from the United Kingdom (Thomas and Jones, 2002). 22 breast milk samples were analysed (8 from Lancaster and 14 from London) and MCCPs were found in one sample from London at a concentration of 61µg/kg fat but was below the limit of detection in the remaining 21 samples. The detection limit of the method varied with sample size ranging from 16 µg/kg fat to 740 µg/kg fat (mean level of 100 µg/kg fat). It is noted that these detection limits are higher than the measured levels in breast milk reported in the Greenpeace study. This suggests that the analytical method used in Thomas and Jones, 2002 was less sensitive than that used in the Greenpeace study. The fact that MCCPs were only found in 1/22 samples does not mean that it was not present in the other samples at levels below the detection limit.

Thomas et al (2003) have recently carried out a further investigation of the levels of medium-chain chlorinated paraffins in human breast milk samples from the United Kingdom. In this study, relatively large samples of human milk-fat were collected from the London (20 samples) and Lancaster (5 samples) areas of the United Kingdom between late 2001 and June 2002. Medium-chain chlorinated paraffins were found to be present in all 25 samples analysed. The median, 97.5th percentile value and range of concentrations found were 21 µg/kg lipid, 130.9 µg/kg lipid and 6.2-320 µg/kg lipid respectively. The levels found in the samples from Lancaster were not thought to be significantly different from the levels found in the samples from London.

Overall, given that of the three studies that are now available on levels of MCCPs in breast milk, the most recent one, Thomas et al., 2003 is a very well conducted study, a risk

characterisation will be performed using the 97.5th percentile level of 130.9 µg/kg fat identified from this study. To perform a risk characterisation on the basis of this exposure information, it is necessary to derive an estimated daily infant intake of MCCPs for comparison with an estimated intake for the rat pup. Information is available on the levels of MCCPs in the milk of lactating female rats from two studies (the cross-fostering investigation and the CXR Biosciences Ltd., 2004 study) in which 100% mortality and haemorrhaging was seen in the offspring or fostered pups of dams administered 6250 ppm MCCPs in the diet. This was the only exposure level used in these studies. The levels of MCCPs measured in the milk of these dams were 570 and 1280 ppm (mean of 925 ppm) in the cross-fostering study (570 and 1280 mg/l, equivalent to about 570 and 1280 mg/kg milk, assuming a density of 1 g/l) and 1561, 504 and 1106 mg/l (mean 1057 mg/l) in the CXR Biosciences Ltd., (2004) study (equivalent to about 1561, 504 and 1106 mg/kg milk, assuming a density of 1 g/l). These levels are fairly consistent. For risk characterisation purposes, a very conservative approach will be taken using the lowest level of MCCPs in dam breast milk (504 mg/kg milk) causing haemorrhaging effects and mortality in 100% of the suckling pups (a sort of LOAEL for very severe effects). Although there is no information on the levels of MCCPs in the milk of lactating female rats at which no effects occurred, a NOAEL could be extrapolated based on the assumption of a linear relationship between the dose of MCCPs administered to the dams and the level of MCCPs excreted in milk. As no haemorrhaging effects occurred at a maternal dose of 600 ppm, but severe effects occurred at a maternal dose of 6250 ppm, which elicited a level of MCCPs in milk of 504 mg/kg milk, the equivalent NOAEL of MCCPs in milk is 48.5 mg/kg milk. The risk characterisation will therefore also be conducted against this extrapolated no effect level.

In evaluating the body burden of MCCPs in an infant as a result of breast-feeding, the MCCPs daily intake during the first 3 months only of the infant life will be calculated as the data indicate that given the occurrence of the haemorrhaging effects in the suckling rat pups within the first 12 days post-partum, the period of infant life of the first 3 months might represent the most susceptible stage. It is assumed that over the first 3 months the infant has an average weight of 6 kg (data taken from the UK growth charts, published by the Child Growth Foundation, 1995; Freeman *et al*, in press and Cole, 1994), that the infant ingests 0.8 kg of milk per day, that 50% of the ingested MCCPs is absorbed and that the breast milk has an average fat content of 3.5% (WHO, 1998). It is also assumed that the content of MCCPs remains constant during the breast-feeding period.

Using the following equation and the assumptions detailed above, the average daily uptake of the breast-feeding infant (ADU_{infant}) is estimated for the 0-3 month period of infant life.

$$ADU_{\text{inf } ant} = \frac{C_{milk-fat} xf3 xf4 xIR_{milk}}{BW_{\text{inf } ant}}$$

where:

$C_{milk\text{-}fat}$	is the concentration of MCCPs in mg.kg^{-1} fat in breast milk
f3	is the fraction of fat in breast milk (3.5%)
f4	is the fraction of ingested MCCPs absorbed (50%)
IR_{milk}	is the ingestion rate of milk (kg.day^{-1})
BW_{infant}	is the average infant body weight over the exposure period (kg)

MCCPs uptake during 0-3 months, assuming a concentration of MCCPs in human breast milk of 130.9 µg/kg (97.5th percentile value):

$$ADU_{\text{inf } ant} = \frac{130.9x10^{-3} x0.035 x0.5 x0.8}{6} = 30.5x10^{-5}\, mg.kg^{-1}.day^{-1}$$

Based on these estimates, the daily uptake of MCCPs for the first 3 months is 30.5×10^{-5} mg.kg^{-1}.day^{-1}.

A similar calculation can be performed for the rat. Pup body weight at birth is around 6 g and at weaning is about 40-50 g; an average weight of about 20 g will be assumed for the purposes of this calculation. Milk production in the lactating rat varies over the lactation period. Sampson and Jansen (1984) derived a model to estimate daily milk yield in the lactating rat. Based on this model, on day 10 of lactation, milk yield was estimated to be 29.5 ml for a dam nursing 8 pups. This equates to about 3.7 ml (or 3.7 g) milk per pup, and will be used as the average daily milk consumption for this calculation.

Based on these assumptions, and using the very conservative LOAEL value of 504 mg.kg^{-1} milk for MCCP content in rat milk, estimated daily pup intake is about 46.5 mg.kg^{-1}.day^{-1} (i.e. level of MCCP per kg whole milk x daily milk consumption (kg)/ pup body weight (kg) = 504 mg.kg^{-1} x 3.7 x 10^{-3} x 0.5/ 20 x 10^{-3} mg.kg^{-1}.day^{-1}). If the extrapolated NOAEL value of 48.5 mg.kg^{-1} milk is used instead, estimated daily pup intake is about 4.5 mg.kg^{-1}.day^{-1}.

Comparing the MCCPs daily pup intake at the LOAEL (46.5 mg.kg^{-1}.day^{-1}) with the human infant intake, there is a difference of 5 orders of magnitude (MOE = 152,000) between the levels of MCCPs producing severe effects in pups (100% mortality) and human infant exposure. Comparing the MCCPs daily pup intake at the extrapolated NOAEL (4.5 mg.kg^{-1}.day^{-1}) with the human infant intake, there is a difference of 4 orders of magnitude (MOE = 14,800) between the levels of MCCPs without effect in the pups and human infant exposure. Normally such large Margin of Exposure (MOE) values would lead to little cause for concern and thus to a conclusion (ii), especially if it is considered that the calculation of this MOE was based on a very conservative approach (the 97.5th percentile value for MCCPs levels in human breast milk and the lowest concentration of MCCPs in animals causing haemorrhage and mortality in 100% of the pups or no effects). However, it is important to consider the interpretation of the MOE values in light of the current state of knowledge and uncertainties in the analysis. We are of the opinion that a number of uncertainties in the analysis have now been reduced/removed. New good quality information on current levels of MCCPs in human breast milk has been obtained; new mechanistic data on the haemorrhaging effects seen in lactating pups have clarified the underlying mechanism leading to this effect (perturbation of the clotting system in lactating neonates; see reproductive toxicity section). Furthermore, due to concerns identified by the environmental risk assessment, an environmental risk reduction programme is currently under development and this could lead to reductions in point source and diffuse environmental emissions in due course. Finally, industry has shown a formal commitment to initiating a monitoring programme of levels of MCCPs in breast milk for the future years. In our view, this monitoring programme with its implications in terms of time trends is able to relieve any residual concern related to the risks of effects mediated via lactation in infants exposed to MCCPs via breast milk. Therefore, overall, taking into account the knowledge of the likely mechanism, the reliability of the current breast milk levels, the downward trend in environmental exposure and the very large MOEs obtained in spite of the very conservative approach adopted, conclusion (ii) is proposed for this scenario.

Infants exposed via cow's milk

Greenpeace (1995) reported levels of total chlorinated paraffins in cow's milk to be 74 µg/kg fat. The actual content of MCCPs can be deduced to be 21% of the total chlorinated paraffins content, i.e. 16 µg/kg fat. Thomas and Jones (2002) also determined the levels of MCCPs in a single sample of cow's milk from Lancaster and single butter samples from various regions of

Europe (Denmark, Wales, Normandy, Bavaria, Ireland, and Southern and Northern Italy). MCCPs were present in the cow's milk sample at a concentration of 63µg/kg fat and were found in the butter samples from Denmark at 11µg/kg fat, Wales at 8.8µg/kg fat and Ireland at 52µg/kg fat. MCCPs were not detected in any other sample. The detection limit for the other butter samples ranged between 8.0 and 11 µg/kg fat. Butter is regularly used as a convenient way of obtaining milk-fat samples and therefore the MCCPs levels measured in these butter samples can be considered equivalent to the levels present in cow's milk.

Using the value of 63 µgMCCPs/kg fat as the worst-case estimate, and applying the same assumptions as for infants exposed via breast milk, the infant uptake of MCCPs from cow's milk is 14.5×10^{-5} $mg.kg^{-1}.day^{-1}$. Again, the difference between infant uptake and the lowest level producing severe effects in pups is 5 orders of magnitude (MOE = 320,000). If the extrapolated level of MCCPs without effect is used instead, the resultant MOE is 30,800. Again, as for the risk characterisation for infants exposed via breast milk, normally such large MOE values would lead to little cause for concern and thus to a conclusion (ii), especially if it is considered that the calculation of this MOE was based on a very conservative approach (the worst-case estimate for MCCPs levels in cow's milk and the lowest concentration of MCCPs in animals causing haemorrhage or no effects). However, it is important to consider the interpretation of the MOE values in light of the current state of knowledge and uncertainties in the analysis. We are of the opinion that a number of uncertainties in the analysis have now been reduced/removed. New good quality information on current levels of MCCPs in cow's milk has been obtained; new mechanistic data on the haemorrhaging effects seen in lactating pups have clarified the underlying mechanism leading to this effect (perturbation of the clotting system in lactating neonates; see reproductive toxicity section). Furthermore, due to concerns identified by the environmental risk assessment, an environmental risk reduction programme is currently under development and this could lead to reductions in point source and diffuse environmental emissions in due course. Finally, industry has shown a formal commitment to initiating a monitoring programme of levels of MCCPs in cows' milk for the future years. In our view, this monitoring programme with its implications in terms of time trends is able to relieve any residual concern related to the risks of effects mediated via lactation in infants exposed to MCCPs via cow's milk. Therefore, overall, taking into account the knowledge of the likely mechanism, the reliability of the current cow's milk levels, the downward trend in environmental exposure and the very large MOEs obtained in spite of the very conservative approach adopted, conclusion (ii) is proposed for this scenario.

4.1.3.4 Combined exposure

As indicated in section 4.1.1.4, a combined exposure scenario is not relevant, given the nature of the consumer exposures to MCCPs, and therefore no risk characterisation for this scenario will be performed.

4.2 HUMAN HEALTH (PHYSICOCHEMICAL PROPERTIES) (RISK ASSESSMENT CONCERNING THE PROPERTIES LISTED IN ANNEX IIA OF REGULATION 1488/94)

The physicochemical properties of MCCPs are not clearly defined and the particular values depend on the actual composition of the material, which can vary between manufacturers. However, given the low vapour pressure, lack of flammability and the general stability of these substances, the risks arising from the physicochemical properties are small. Thus, conclusion (ii) is reached .

5 RESULTS

5.1 HUMAN HEALTH

The minimum data requirements according to Article 9(2) of Regulation 793/93 have been met. The lead health effects of concern arising from exposure to MCCPs are repeated dose toxicity, carcinogenicity, effects on the offspring mediated via lactation and effects at the time of parturition. There are no concerns for acute toxicity, irritation, sensitisation, genotoxicity or effects on fertility.

5.1.1 Workers

MCCPs are viscous liquids with very low vapour pressures. Thus personal exposures to MCCPs vapour at ambient temperature in the workplace are very low, the maximum theoretical vapour concentration being 0.0027 ppm. However, there are some situations where there is the potential for exposure to a mixture of vapour and mist; the mist is formed as the hot vapour cools and condenses to form liquid droplets. In addition, some scenarios give rise to the potential for aerosol generation. Exposures are generally expected to be higher where there is the potential for exposure to MCCPs in mist or aerosol form. Dermal exposure to MCCPS can also occur; estimates of dermal exposure have been derived from modelling, although in some cases measured data were available.

The MOSs for oil-based MWF use in relation to repeated dose toxicity, carcinogenicity, effects via lactation and effects at the time of parturition are unaccepatably low. Therefore conclusion (iii) is reached.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The MOSs for all remaining scenarios in relation to repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are considered sufficient to provide reassurance that adverse effects would not occur and thus conclusion (ii) is reached.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.

5.1.2 Consumers

The exposure to MCCPs is generally very low. Most applications of MCCPs are not designed for consumer contact and therefore most exposures are negligible. The only consumer exposure scenarios for which significant exposure and uptake could occur are the wearing of leather clothes treated with MCCPs and the use of metal working fluids.

The calculated margins of safety (MOS) for repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition for both scenarios were sufficient to provide reassurance that adverse effects would not occur and thus conclusion (ii) is reached.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.

5.1.3 Indirect exposure via the environment

The exposure estimates for regional sources of exposure are based on measured data; however, the local environment exposures are calculated from a model. This model uses various assumptions, giving rise to uncertainty in the predicted exposure values.

Regional exposure

The calculated margins of safety for repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are considered to provide sufficient reassurance that adverse health effects would not occur and thus conclusion (ii) is reached.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already.

Local exposure

The calculated margins of safety for repeated dose toxicity, carcinogenicity, effects mediated via lactation and effects at the time of parturition are considered to provide sufficient reassurance that adverse health effects would not occur and thus conclusion (ii) is reached.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already.

Exposure of infants via milk

Very large MOEs have been calculated between estimated infant uptake levels and the levels of MCCPs which have been found to produce adverse effects via the breast milk. Also, due to concerns identified by the environmental risk assessment, an environmental risk reduction programme is currently under development and this could lead to reductions in point source and diffuse environmental emissions in due course. Furthermore, industry has shown a formal commitment to initiating a monitoring programme of levels of MCCPs in breast and cow's milk. Therefore, overall, conclusion (ii) is proposed.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.

5.1.4 Combined exposure

A combined exposure scenario, taking account of the potential for exposure as a consumer and via environmental sources is not relevant, given that consumer exposures are infrequent rather than repeated daily exposures. Therefore no risk characterisation for this scenario has been performed.

5.1.5 Risks from physicochemical properties

There are no significant risks to humans from the physicochemical properties of medium-chained chlorinated paraffins. Therefore conclusion (ii) is reached.

Conclusion (ii) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied already.

6 REFERENCES

Ahlman M, Bergman A, Darnerud P, Egestad B and Sjovall J (1986). Chlorinated paraffins: formation of sulphur-containing metabolites of polychlorohexadecane in rats. *Xenobiotica*. **16**: 225-232.

Ashby J, Brady A *et al* (1994). Mechanistically-based human hazard assessment of peroxisome proliferator-induced hepatocarcinogenesis. *Human Experimental Toxicol.* **13** Suppl 2.

Bentley P, Calder I *et al* (1993). Hepatic peroxisome proliferation in rodents and its significance for humans. *Food Chem. Toxicol.* **31**: 857-907.

Biessmann A, Darnerud PO and Brandt I (1983). Chlorinated paraffins: Disposition of a highly chlorinated polychlorohexadecane in mice and quail. *Arch. Toxicol.* **53**: 79-86.

Birtley RDN, Conning DM, Daniel JW, Ferguson DM, Longstaff E and Swan AAB (1980). The toxicological effects of chlorinated paraffins in mammals. *Toxicol. Appl. Pharmacol.* **54**: 514-525.

Chater B (1978). Acute oral toxicity, skin and eye irritation and skin sensitisation. Report No. CTL/T/1168. ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Child Growth Foundation (1995). Child growth charts. Published by Child Growth Foundation 1995/1. London.

Cherrie JW (2006) Dermal exposure to metal working fluids and MCCPs – Estimates based on data from existing studies. IOM Report No. P888-0002.

Cole TJ (1994). Do growth chart centiles need a facelift? *British Medical Journal.* **308**: 641-642.

CXR Biosciences Ltd (2003) Powrie RH. Effects of medium chain chlorinated paraffins (MCCPs) on vitamin K concentrations and clotting factors in female Sprague Dawley rats. *Unpublished report.*

CXR Biosciences Ltd (2004) Barton Sjand Daly PM. MCCP – study to assess maternal milk and neonate plasma. *Unpublished report*.

CXR Biosciences Ltd (2005a) Elcombe BM. Study to investigate the elimination of medium chain chlorinated paraffins in male F344 rats. CXR0204. CXR Biosciences Ltd, Dundee, UK. *Unpublished report.*

CXR Biosciences Ltd (2005b) Elcombe BM. A dietary study to investigate the toxicokinetics of medium chain chlorinated paraffins (Cereclor S52) in male and female Fisher 344 rats. CXR0282. Biosciences Ltd, Dundee, UK. *Unpublished interim report.*

CXR Biosciences Ltd (2005c) Elcombe BM. A dietary study to determine the 90 day NOAEL of medium chain chlorinated paraffins (Cereclor S52) in male and female Fisher 344 rats. CXR0273. CXR Biosciences Ltd, Dundee, UK. *Unpublished report.*

CXR Biosciences Ltd (2006) Stamp SL. $C_{14\text{-}17}$ n-alkane, 52% chlorinated study of post-natal offspring mortality following dietary administration to CD rats. DAR0001/062390. Huntingdon Life Sciences Ltd., Huntingdon, UK. *Unpublished report*.

Darnerud PO and Brandt I (1982). Studies on the distribution and metabolism of a ^{14}C-labelled chlorinated alkane in mice. *Environ. Pollut.* (Series A). **27**: 45-46.

Darnerud P and Lundkvist U (1987). Studies on implantation and embryonic development in mice given a highly chlorinated hexadecane. Letter to the Editor. *Pharmacol. Toxicol.* **60**: 239-240.

De Pater *et al* (1999). Inhalation exposure to non-volatile compounds during spray painting. TNO Report (V98.1340), Zeist, The Netherlands.

Dohler K-D, Wong C and von zur Muhlen A (1979). The rat as a model for the study of drug effects on thyroid function: consideration of methodological problems. *Pharmacol. Therapeutics.* **5**: 305-318.

Elcombe C (1999). Mechanisms of nephrotoxicity and carcinogenicity of short chain chlorinated paraffins in male Fischer 344 rats: relevance to human health. *Unpublished report, August 1999,* Centre for Xenobiotic Research, University of Dundee, UK.

Elcombe C, Bars R, Hasmall S and Foster J (1997). Hepatic effects of chlorinated paraffins in mice, rats and guinea pigs: Species differences and implications for hepatocarcinogenicity. *Unpublished report.*

Eriksson P and Darnerud P (1985). Distribution and retention of some chlorinated hydrocarbons and a phthalate in the mouse brain during the pre-weaning period. *Toxicol.* **37**: 189-203.

EU (2005). Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment of new notified substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances.

Freeman, JV *et al*. Child growth charts. *Archives of Disease in Childhood*. In Press.

Greenpeace (1995). Greenpeace Zur Sache: Chlorparaffine. May 1995.

Hart D, Wickramaratne G, De S, Banham P, Chart I and Gaskell B (1985). Chlorinated paraffin (52% chlorination of intermediate chain length n-paraffins): Investigation into the possible mechanism of haemorrhage in offspring rats. Report Number CTL/P/1293. ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Hasmall S, Foster J and Elcombe C (1997). Lack of liver, thyroid and kidney effects of a short-chain chlorinated paraffin (Chlorowax 500C) in guinea pigs. *Arch Toxicol*.

Hughson G (2003a). Occupational hygiene assessment of workplace exposure to MCCPs - Interim report on workplace monitoring surveys. IOM Report No. 899/0010/008.

Hughson G (2003b). Occupational hygiene assessment of workplace exposure to MCCPs – plastisol coating. IOM Report No. 899/0010/009.

Hughson G (2003c). Occupational hygiene assessment of workplace exposure to MCCPs –calendering PVC. IOM Report No. 899/0010/0011.

Hughson G (2006a) Draft report Occupational hygiene assessment of workplace exposure to MCCPs – Dermal MCCP exposures during PVC compounding. IOM Report No. P888-0003.

Hughson G (2006b) Occupational hygiene assessment of workplace exposure to MCCPs - Results of spray painting monitoring survey. IOM Report No. P888-0001.

IARC (1999). Capen CC, Dybing E, Rice JM and Wilbourn JD. Species differences in thyroid, kidney and urinary bladder carcinogenesis. *IARC Sci.Publ.*147

IRDC (1984). 13-week dietary toxicity study in rats with combined excretion, tissue level and elimination study/determination of excretion, tissue level and elimination after single oral gavage administration to rats. IRDC Report No. 438-026/438-023. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IRDC (1981). Chlorinated paraffin: Range-finding teratology study in rats. IRDC Report No. 438/034. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IRDC (1982a). Chlorinated paraffin: Range-finding teratology study in rabbits. IRDC Report No. 438/020. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IRDC (1982b). Chlorinated paraffin: Second range-finding teratology study in rabbits. IRDC Report No. 438/036. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IRDC (1982c). Chlorinated paraffin: 5-day oral range-finding study in rats. IRDC Report No. 438-041. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IRDC (1983). Chlorinated paraffin: Teratology study in rabbits. IRDC Report No. 438/032. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IRDC (1984). Chlorinated paraffin: Teratology study in rats. IRDC Report No. 438/017. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IRDC (1985). Chlorinated paraffin: Reproduction range-finding study in rats. IRDC Report No. 438/049. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

IPCS (1996). Environmental Health Criteria 181: Chlorinated paraffins. International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland. ISBN 92 4 157181 0.

Johnson I (2005). Cereclor S52: in vitro absorption through human epidermis. Central Toxicology Laboratory. Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK. Report number CTL/JV1833/REG/REPT.

Kuhnert R (1986a). Acute oral toxicity of Chloroparaffin 40G (with 1% stabiliser B74) for rats. Huls AG Report Number 0568. Huls AG, Marl, Germany.

Kuhnert R (1986b). Acute oral toxicity of Chloroparaffin 52G (with 1% stabiliser B74) on rats. Huls AG Report Number 0571. Huls AG, Marl, Germany.

Kuhnert R (1986c). Testing of the acute skin irritating effect of Chloroparaffin 40G (with 1% stabiliser B74) on rabbits. Huls AG Report Number 0569. Huls AG, Marl, Germany.

Kuhnert R (1986d). Testing for acute dermal irritation in rabbits caused by Chloroparaffin 52G (with 1% stabiliser B74). Huls AG Report Number 0572. Huls AG, Marl, Germany.

Kuhnert R (1986e). Testing for acute irritation of the eyes and mucous membranes in rabbits caused by Chloroparaffin 40G (with 1% stabiliser B74). Huls AG Report Number 0570. Huls AG, Marl, Germany.

Kuhnert R (1986f). The testing of the acute irritant effects of Chloroparaffin 52G (containing 1% stabiliser B74) on the eyes and conjunctiva of the rabbit. Huls AG Report Number 0573. Huls AG, Marl, Germany.

Meijer J, Rundgren M, Astrom A, DePierre J, Sundvall A and Rannug U (1981). Effects of chlorinated paraffins on some drug-metabolising enzymes in rat liver and in the Ames test. *Adv. Exp. Med. Biol.* **A136**: 821-828.

Meijer J and DePierre J (1987). Hepatic levels of cytosolic, microsomal and 'mitochondrial' expoxide hydrolases and other drug-metabolising enzymes after treatment of mice with various xenobiotics and endogenous compounds. *Chem. Biol. Interactions.* **62**: 249-269.

Moses S (1980). Cloparin 1049 and 'Meflex' DC029: a comparison of skin irritation potential. Report CTL/T/1431. ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Murmann P (1988). The testing of the skin-sensitising effect of Chloroparaffin 40G (containing 1% stabiliser B74) in the guinea pig. Huls AG Report No. 1336. Huls AG, Marl, Germany.

Nilsen O, Toftgard R and Glaumann H, (1981). Effects of chorinated paraffins on rat liver microsomal activities and morphology. *Arch. Toxicol.* **49**: 1-13.

Poon R, Lecavalier P, Chan P, Viau C, Hakansson H, Chu I and Valli V (1995). Subchronic toxicity of a medium-chain chlorinated paraffin in the rat. *J. Appl. Toxicol.* **15**: 455-463.

Roff M, Bagon DA, Chambers H, Dilworth EM, Warren N (2004). Dermal exposure to electroplating fluids and metalworking fluids in the UK. *The Annals of Occupational Hygiene.* **48**: 209-217.

Sampson DA and Jansen GR (1984). Measurement of milk yield in the lactating rat from pup weight and weight gain. *J. Ped. Gastroent. Nutr.* **3**: 613-617.

SCCP ESR Risk Assessment Report (2000). Draft Risk Assessment Report for short-chain chlorinated paraffins. Prepared by the UK Competent Authority.

Scott R (1984). *In vitro* absorption of ^{14}C Cereclor S52 through human skin. Report No. CTL/L/758. ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Semple S, Graham M, Cowie H, and Cherrie JW (2005). The causative factors of dermatitis among workers exposed to metalworking fluids. Final report to HSE. Aberdeen, University of Aberdeen.

Serrone D, Birtley R, Weigand W and Millischer R (1987). Toxicology of chlorinated paraffins. *Fd. Chem. Toxic.* **25**: 553-562.

Sonich-Mullin C, Fielder R, Wiltse J, Baetcke K, Dempsey J, Fenner-Crisp P, Grant D, Hartley M, Knaap A, Kroese D, Mangelsdorf I, Meek E, Rice JM and Younes M (2001) IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. *Regulatory Toxicology and Pharmacology*. **34**:146-152.

Spicer E (1981). 14-day dietary administration to rats. Report No. 438-003. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

Spicer E (1983a). *In vivo* cytogenetic evaluation by analysis of rat bone marrow cells. Report No. 438-014. International Research and Development Corporation, Mattawan, Michigan, USA 49071.

Thomas GO and Jones KC (2002). Chlorinated paraffins in human and bovine milk-fat. *Unpublished report*.Unpublished Report (1971). Report Number CLT/T/831. ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Thomas G. O., Braekevelt E., Stern G., Martin F. L. and Jones K. C. (2003). Further Work on Chlorinated Paraffins in Human Milk-Fat. A report on a research project funded by the Eurochlor Chlorinated Paraffin Sector Group. Department of Environmental Sciences, Lancaster University, 10th November 2003.

Thompson R. S., Smyth D. V. and Gillings E. (2005). Medium-chain chlorinated paraffins (C_{14-17}, 52% chlorinated): Accumulation from soil by the root of carrot (*Daucus carota*). Brixham Environmental Laboratory, AstraZeneca UK Limited, Study Number BL8221/B, December 2005.

Van Wendel de Joode B, Bierman EP, Brouwer DH, Spithoven J, Kromhout H (2005). An assessment of dermal exposure to semi-synthetic metal working fluids by different methods to group of workers for an eoidemiological study on dermatitis. *Occupational and Environmental Medicine.* **62**: 633-641.

Warnasuriya G, Elcombe B, Foster J and Elcombe C (2001). A mechanism for the induction of renal tumours in male Fischer 344 rats by short-chain chlorinated paraffins. Unpublished report. Biomedical Research Centre, University of Dundee, Dundee, UK.

WHO (1998). GEMS/Food international dietary survey: infant exposure to certain organochlorine contaminants from breast milk – a risk assessment. Food Safety Issues. WHO/FSF/FOS/98.4, Geneva, Switzerland.

Wiegand W (1989). Determination of the mutagenic effects of Chloroparaffin 40G. Report No. AM-89/08. Huls AG, Marl, Germany.

Wyatt I, Coutts C and Elcombe C (1993). The effect of chlorinated paraffins on hepatic enzymes and thyroid hormones. *Toxicology.* **77**: 81-90.

Wyatt I, Coutts C *et al* (1997). Chlorinated Paraffins: Mechanisms of non-genotoxic carcinogenesis. Draft submitted to *Arch. Toxicol.*

Yang J, Roy T *et al* (1987). Percutaneous and oral absorption of chlorinated paraffins in the rat. *Toxicol. Ind. Health.* **3**: 405-412.

Abbreviations

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw, bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau

ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GC	Gas chromatography
GC-ECD	Gas chromatography with an electron capture detector
GC-ECNI-HRMS	Gas chromatography with electron capture negative ion high resolution mass spectrometry
GC-EI-MS	Gas chromatography with electron impact mass spectrometry
GC-FID	Gas chromatography with a flame ionisation detector
GC-HRMS	Gas chromatography with high resolution mass spectrometry
GC-LRMS	Gas chromatography with low resolution mass spectrometry
GC-MS	Gas chromatography with a mass spectrometry detector
GC-NCI-MS	Gas chromatography with negative ion chemical ionisation mass spectrometry
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient

Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MS	Mass spectrometry
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report

RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TLC	Thin layer chromatography
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix E

Assessment of possible replacement of short-chain chlorinated paraffins with medium-chain chlorinated paraffins

Introduction

The current risk assessment report for short-chain chlorinated paraffins (CAS No: 85535-84-8) recommended that risk reduction measures should be undertaken for two uses. The uses were formulation and use in metal cutting/working fluids and formulation and use in leather treatment (fat liquors).

Draft risk reduction strategies have been developed for these two areas. In both cases marketing and use restrictions were recommended, and it was identified that the medium-chain chlorinated paraffins could be used as an alternative in these applications. This Appendix considers the possible effects of replacement of the short-chain by the medium-chain chlorinated paraffins in these applications.

Quantities and trends

The available data on the amounts of both short-chain and medium-chain chlorinated paraffins used in the EU in these applications are given in Table E.1.

Table E. 1 Trends in use of chlorinated paraffins in the EU

Use	Year	Quantity of chlorinated paraffin supplied in EU (t/year)		
		Short-chain	Medium-chain	Total
Metal cutting/working fluids	**1989**	11,300[a]		
	1990	10,050[a]		
	1991	8,350[a]		
	1992	7,300[a]		
	1993	6,150[a]; 7,510[c]		
	1994	9,380[b]; 8,690[c]	2,611[b]	11,301-11,991
	1995	8,502[c]; 8,490[c]	2,765[b]	11,255-11,267
	1996		3,302[b]	
	1997		5,953[b]	
	1998		increased[d]	
Leather treatment (fat liquors)	**1994**	390[b]	1,614[b] (ca 807)	2,004 (ca 1,000)
	1995		1,270[b] (ca 635)	
	1996	decreased[d]	1,172[b] (ca 586)	decreased[d]
	1997		1,048[b] (ca 524)	
	1998		decreased[d]	

a) Figures refer to UK, Ireland and continental Western Europe, excluding Italy.

b) CEFIC data for amounts supplied to the EU. For leather treatment, around 50% of the chlorinated paraffin supplied is exported from the EU after the formulation stage. The figures given in brackets represent the amount of chlorinated paraffin taking into account these exports.

c) Reported in RPA, 1996 (figures for EU (excluding Luxembourg)).

d) Figures known but considered as confidential information

Metal working/cutting fluids

The available data indicate that in 1994, a combined total of around 12,000 t/year of short and medium-chain chlorinated paraffins were used in this application in the EU. Before this date, the available information indicates that there was a general decrease in the amounts of chlorinated paraffin used in this application. Since this time, there has been a rapid increase in the amounts of medium-chain chlorinated paraffin used. This increase is most probably due to a move from the short-chain to medium-chain chlorinated paraffins for this application, rather than an increase in the total amounts of chlorinated paraffins used.

The draft risk reduction strategy on short-chain chlorinated paraffins (RPA, 1996) indicates that medium-chain chlorinated paraffins are most likely to be the preferred alternative for neat oil applications. With emulsion-based fluids, the majority of users are expected to move to chlorine-free alternatives, due to concerns over the stability of the fluid, although medium-chain chlorinated paraffins may also be used.

The individual members of Euro Chlor have voluntarily agreed to reduce the use of short-chain chlorinated paraffins in metal cutting fluids to the following timetable: 80% reduction in use (from 1993 levels) by 1997, and elimination in use by year 2000.

The switch to medium-chain chlorinated paraffins as replacements for the short-chain chlorinated paraffin may result in some changes in the fluid formulation for a given application. This arises because the relationship between chlorine content and viscosity is slightly different for the two groups of additives. For a given chlorine content, the medium-chain chlorinated paraffin generally has a higher viscosity than the short-chain chlorinated paraffin. Two important considerations in the formulation of metal cutting/working fluids are viscosity and chlorine content of the fluid. Thus, if short-chain chlorinated paraffins are replaced by medium-chain length chlorinated paraffins two approaches can be taken. Firstly for a given application, a medium-chain chlorinated paraffin of similar chlorine content to, but higher viscosity than, the short-chain chlorinated paraffin can be used. In this case, in order to maintain the viscosity of the final fluid, the base oil may have to be reformulated. The second approach would be to use a medium-chain chlorinated paraffin of similar viscosity (and hence lower chlorine content) as the short-chain chlorinated paraffin. In this case, the chlorine content of the fluid would be lower than the fluid containing short-chain chlorinated paraffin and so the result is that higher concentrations of medium-chain chlorinated paraffins (up to 10% by weight rather than the typical level of 5% by weight) may have to be used in the fluids (RPA, 1996).

In order to take into account the possible replacement of short-chain chlorinated paraffins by medium-chain chlorinated paraffins, it can be assumed as a worst case that the total usage of medium-chain chlorinated paraffins could reach a total of around 12,000 t/year (the sum of medium- and short-chain chlorinated paraffins for this use in 1994). This should represent the likely foreseeable maximum usage of medium-chain chlorinated paraffins in this area as other non-chlorinated alternatives for short-chain chlorinated paraffins may be used, particularly in emulsifiable fluids (RPA, 1996).

In addition, the effects of a possible increase in concentration of the chlorinated paraffin in the fluid from around 5% to 10% will also need to be taken into account.

Leather fat liquors

The draft risk reduction strategy for short-chain chlorinated paraffins (RPA. 1997) indicated that the following substances could possibly be used as alternatives if marketing and use restrictions were applied:

medium-chain chlorinated paraffins (and also longer chain length chlorinated paraffins);

animal oils (usually derived from beef tallow);

vegetable oils (e.g. corn, soya, palm and to some extent rapeseed).

It is clear from the available data reported in Table E1 that there is a general decrease in the amounts of chlorinated paraffins used in leather fat liquors in the EU. Further, the medium-chain length chlorinated paraffins are much more commonly used that the short-chain length chlorinated paraffins in this application. If all the short-chain were replaced by medium-chain chlorinated paraffins, then the amount supplied for formulation may reach around 2,000 t/year, with around 1,000 t/year of this being subsequently applied to leather in the EU. These figures relate to 1994, and represent the highest usage in recent years. These figures are likely to represent the foreseeable upper limit of the amount of medium-chain chlorinated paraffin used in this application, as it is clear that a decline in use of both medium- and short-chain chlorinated paraffins is occurring.

Effect on predicted environmental concentrations

Environmental releases for regional and continental modelling

Using the extrapolated use figures above, and the release factors detailed in the main report, the following releases to the environment can be estimated:

Metal cutting/working fluids

Assuming a total usage of 12,000 t/year of medium-chain chlorinated paraffins and the same split between oil-based and emulsion fluids as in the main report, gives around 8,060 t/year in oil-based fluids and 3,940 t/year in emulsion fluids, then the following releases can be estimated:

Formulation of fluids:

Quantity of medium-chain chlorinated paraffins used = 12,000 t/year

Release to the environment = 0.25% to waste water

Total EU release = 30 t/year to waste water

Regional release = 3 t/year to waste water

Continental release = 27 t/year to waste water

Use in Emulsifiable fluids:

Quantity of medium-chain chlorinated paraffins used = 3,940 t/year

Release to the environment = 50% to waste water

Total EU release = 1,970 t/year to waste water

Regional release = 197 t/year to waste water

Continental release = 1,773 t/year to waste water

Use in Oil-based fluids:

Quantity of medium-chain chlorinated paraffins used = 8,060
Release to the environment =4% (large/medium facility with swarf reprocessing) to waste water
=18% (small and medium sized facilities with no swarf reprocessing) to waste water
Fraction of total use in large/medium facilities = 60%
Fraction of total use in medium/small facilities = 40%

Total EU release to environment = $8{,}060 \cdot ((0.04 \cdot 0.6)+(0.18 \cdot 0.4))$ = 774 t/year to waste water
Regional release = 77.4 t/year to waste water
Continental release = 696.6 t/year to waste water

Leather fat liquors

Assuming a total usage of 2,000 t/year of medium-chain chlorinated paraffins in the formulation of leather fat liquors, with around 50% of these liquors (containing 1,000 t/year of medium chain chlorinated paraffins) in the EU, then the following releases can be estimated:

Formulation of leather fat liquors (default calculation):

Quantity of medium-chain chlorinated paraffins used	= 2,000 t/year
Release to the environment	= 0.1% to air = 0.3% to waste water
Total EU release	= 2.0 t/year to air = 6.0 t/year to waste water
Regional release	= 0.2 t/year to air = 0.6 t/year to waste water
Continental release	= 1.8 t/year to air = 5.4 t/year to waste water

Use of leather fat liquors:

Quantity of medium-chain chlorinated paraffins used	= 1,000 t/year
Release to the environment	= 2% to waste water
Total EU release	= 20 t/year to waste water
Regional release	= 2 t/year to waste water
Continental release	= 18 t/year to waste water

Overall regional and continental releases

Table E.2 shows the total regional and continental releases estimated from the main report for the current usage of medium-chain chlorinated paraffins, and the estimated total taking into account the revised figures for use in metal working/cutting and leather treatment, assuming that medium-chain chlorinated paraffins will totally replace the short-chain chlorinated paraffins in these applications.

Table E. 2 Revised releases for the regional and continental environment

Use	Lifestage	Estimated release from original report (current situation)[a]		Estimated release assuming replacement of short-chain by medium-chain chlorinated paraffins in metal working and leather treatment applications	
		Regional	Continental	Regional	Continental
Metal cutting/working fluids	**Formulation**	1,488 kg/year to water	13,875 kg/year to water	3,000 kg/year to water	27,000 kg/year to water
	Use in oil-based fluids	38,100 kg/year to water	342,900 kg/year to water	77,400 kg/year to water	696,600 kg/year to water
	Use in emulsifiable fluids	99,200 kg/year to water	892,800 kg/year to water	197,000 kg/year to water	1,773,000 kg/year to water
Leather fat liquors	**Formulation**	315 kg/year to water 105 kg/year to air	2,829 kg/year to water 943 kg/year to air	600 kg/year to water 200 kg/year to air	5,400 kg/year to water 1,800 kg/year to air
	Use	1,050 kg/year to water	9,430 kg/year to water	2,000 kg/year to water	18,000 kg/year to water
All other uses	**All**	30,255 kg/year to water 16,922 kg/year to air	271,748 kg/year to water 152,250 kg/year to air	30,255 kg/year to water 16,922 kg/year to air	271,748 kg/year to water 152,250 kg/year to air
Total		170,408 kg/year to water (split 119,286 kg/year to WWTP and 51,122 kg/year direct to surface water) 17,027 kg/year to air	1,533,582 kg/year to water (split 1,073,482 kg/year to WWTP and 460,101 kg/year direct to surface water) 153,193 kg/year to air	310,255 kg/year to water (split 217,179 kg/year to WWTP and 93,077 kg/year direct to surface water) 17,122 kg/year to air	2,791,748 kg/year to water (split 1,954,198 kg/year to WWTP and 837,550 kg/year direct to surface water) 154,050 kg/year to air

a) Figures derived in main report

Local release estimates

In this Section, the local release estimates have been re-calculated using the methods given in the main report, but based on the extrapolated use volumes for medium-chain chlorinated paraffins.

Metal working/cutting fluids

The releases estimated below are based on the same methods as used in the main report. In addition, the possible increase in the medium-chain chlorinated paraffin content from 5% (as assumed in the main assessment) to 10%, as may occur when they are used to replace short-chain chlorinated paraffins for some applications, is also taken into account.

Formulation of fluids:

Quantity of medium-chain chlorinated paraffins used = 12,000 t/year

Quantity of medium-chain chlorinated paraffins used in region = 1,200 t/year

Fraction used at one site = 1/6 = 200 t/year

Release to the environment = 0.25% to waste water

Number of days = 300 days/year

Local release = 500 kg/year = 1.67 kg/day to waste water

Use in Emulsifiable fluids:

Concentration of chlorinated paraffin in oil phase = 10%

Dilution rate of oil in water = 1:20 oil:water

Weekly loss rate of fluid = 60 litres/week to waste water

Loss rate of chlorinated paraffin = 0.30 kg/week

Number of days = 300 days/year = 6 days/week

Local release = 0.050 kg/day

In addition, there will be an intermittent loss of 50 kg/event of medium chain chlorinated paraffin when the whole system (10,000 litres) is replaced

Use in Oil-based fluids:

Concentration of chlorinated paraffin in fluid = 10%

Amount of cutting fluid contained at large site = 50,000 litres (containing 5,000 kg of medium-chain chlorinated paraffin)

Amount of cutting fluid contained at small site = 10,000 litres (containing 1000 kg of medium-chain chlorinated paraffin)

Release to environment from large site = 4% to waste water

Release to environment from small site = 18% to waste water

Number of days = 300 days/year

Local release (large site) = 200 kg/year = 0.67 kg/day

Local release (small site) = 180 kg/year = 0.6 kg/day

Leather fat liquors

The local release estimates and PEC calculations will be the same as in the main report as they do not depend on the total amount of medium-chain chlorinated paraffins used in the application.

$PEC_{regional}$ and $PEC_{continental}$

The values for $PEC_{regional}$ and $PEC_{continental}$ estimated using the release data given in Table E.2 are shown in Table E.3. The values for the current situation are taken from the main report.

Table E. 3 $PEC_{regional}$ and $PEC_{continental}$ for medium-chain chlorinated paraffins for the current situation and possible future increased use as a result of risk reduction measures on short-chain chlorinated paraffins

PEC	Current situation (from main report)	Possible future situation
$PEC_{regional(air)}$	$3.35 \cdot 10^{-6}$ mg/m³	$5.45 \cdot 10^{-6}$ mg/m³
$PEC_{regional(surface\ water)}$	0.39 µg/l	0.71 µg/l
$PEC_{regional(agricultural\ soil)}$	50.4 mg/kg wet wt.	91.6 mg/kg wet wt.
$PEC_{regional(sediment)}$	8.80 mg/kg wet wt.	16.0 mg/kg wet wt.
$PEC_{continental(air)}$	$1.03 \cdot 10^{-6}$ mg/m³	$1.7 \cdot 10^{-6}$ mg/m³
$PEC_{continental(surface\ water)}$	0.053 µg/l	0.096 µg/l
$PEC_{continental(agricultural\ soil)}$	5.31 mg/kg wet wt.	9.62 mg/kg wet wt.
$PEC_{continental(sediment)}$	1.21 mg/kg wet wt.	2.18 mg/kg wet wt.

From the PECs reported in Table E3, it can be seen that in a worst case, replacement of short-chain chlorinated paraffins by medium-chain chlorinated paraffins in metal working/cutting and leather fat liquoring applications could increase the regional concentrations by around a factor of 2.

It should be born in mind that the available monitoring data indicate that the current regional concentrations in surface water, sediment and soil are less than predicted using the EUSES model. This indicates that the actual regional emissions may be overestimated and/or the actual removal rate in the environment may be underestimated in the model used. This adds uncertainty to the predicted future concentrations.

PEC_{local}

The values obtained for the PEClocal for metal working/cutting use, taking into account the possible increased emissions of medium-chain chlorinated paraffins are shown below. For most of the other uses a change in the PEClocal may result as a consequence of the increase in the PECregional. The consequences of these changes are considered in later.

Metal cutting/working

The revised PEC_{local} for use in metal working fluids are as follows:

Formulation:	$PEC_{local(water)}$	= 3.81 µg/l
	$PEC_{local(sediment)}$	= 48.8 mg/kg wet wt.
	$PEC_{local(soil)}$	= 30.0 mg/kg wet wt.
	$PEC_{fish(secondary\ poisoning)}$	= 2.15-6.45 mg/kg wet wt.
	$PEC_{worm(secondary\ poisoning)}$	= 10.3 mg/kg wet wt.
Use in oil-based fluids:	$PEC_{local(water)}$	= 1.95 µg/l
(large site)	$PEC_{local(sediment)}$	= 25.0 mg/kg wet wt.
	$PEC_{local(soil)}$	= 13.1 mg/kg wet wt.
	$PEC_{fish(secondary\ poisoning)}$	= 1.32-3.96 mg/kg wet wt.
	$PEC_{worm(secondary\ poisoning)}$	= 8.9 mg/kg wet wt.
Use in oil-based fluids:	$PEC_{local(water)}$	= 1.82 µg/l
(small site)	$PEC_{local(sediment)}$	= 23.3 mg/kg wet wt.
	$PEC_{local(soil)}$	= 11.9 mg/kg wet wt.
	$PEC_{fish(secondary\ poisoning)}$	= 1.26-3.78 mg/kg wet wt.
	$PEC_{worm(secondary\ poisoning)}$	= 8.8 mg/kg wet wt.
Use in emulsifiable fluids:	$PEC_{local(water)}$	= 0.80 µg/l
	$PEC_{local(sediment)}$	= 10.2 mg/kg wet wt.
	$PEC_{local(soil)}$	= 2.63 mg/kg wet wt.
	$PEC_{fish(secondary\ poisoning)}$	= 0.81-2.43 mg/kg wet wt.
	$PEC_{worm(secondary\ poisoning)}$	= 8.01 mg/kg wet wt.
Use in emulsifiable fluids:	$PEC_{local(water)}$	= 93.6 µg/l
(intermittent release)	$PEC_{local(sediment)}$	= 1,200 mg/kg wet wt.
	$PEC_{local(soil)}$	= 93.5 mg/kg wet wt.
	$PEC_{fish(secondary\ poisoning)}$	= 1.60-4.80 mg/kg wet wt.
	$PEC_{worm(secondary\ poisoning)}$	= 15.7 mg/kg wet wt.

Effect on PEC/PNEC ratios

The effects of a total replacement of short-chain chlorinated paraffins by medium-chain chlorinated paraffins in metal working and leather uses on the PEC/PNEC ratios for all uses are considered in Tables E4 to E7. The current situation is taken from the main risk assessment report. The future situation includes the effects of the predicted increase in regional concentrations on the PEC/PNEC ratios for all uses.

The results shown in Tables E.4 to E7 indicate that the biggest potential of the impact of replacement occurs on the PEC/PNECs for the aquatic (surface water, sediment, fish) compartment, with very little change predicted to occur on the PEC/PNEC for the terrestrial compartment.

For surface water and sediment, it can be seen that for many uses, the PEC is dominated by the regional contribution. The use of medium-chain chlorinated paraffins in metal cutting/working fluids is predicted to have the highest contribution to the total releases of the substance to water. In the current situation, the regional contribution to water from this use is around 81% (138,788 kg/year out of a total of 170,408 kg/year), and this is predicted to increase to around 89% (277,400 kg/year out of a total of 310,255 kg/year).

Table E. 4 Estimated PEC/PNEC ratios for surface water (PNEC = 1 µg/l)

Scenario	Step	Current situation using measured regional concentrations		Future situation	
		PEC (µg/l)	PEC/PNEC	PEC (µg/l)	PEC/PNEC
Production	4 Sites	0.10-0.27	0.10-0.27	0.70-0.87	0.70-0.87
Use in PVC – plastisol coating	Compounding - O	0.15	0.15	0.75	0.75
	Conversion – O	0.44	0.44	1.05	1.05
	Compounding/conversion – O	0.49	0.49	1.10	1.10
Use in PVC – extrusion/other	Compounding - O	0.27	0.27	0.88	0.88
	Compounding – PO	1.03	1.03	1.63	1.63
	Compounding – C	0.18	0.18	0.78	0.78
	Conversion – O	0.62	0.62	1.23	1.23
	Conversion – PO	0.66	0.66	1.26	1.26
	Conversion – C	0.57	0.57	1.18	1.18
	Compounding/conversion – O	0.79	0.79	1.40	1.40
	Compounding/conversion – PO	1.59	1.59	2.19	2.19
	Compounding/conversion – C	0.65	0.65	1.26	1.26
Use in plastics/rubber	Compounding	0.19	0.19	0.79	0.79
	Conversion	0.39	0.39	0.99	0.99
	Compounding/conversion	0.48	0.48	1.08	1.08
Use in sealants	Formulation and use	negligible	<1	negligible	<1
Use in paints	Formulation	0.38	0.38	0.98	0.98
	Industrial application	0.21	0.21	0.82	0.82
	Domestic application	0.10	0.10	0.71	0.71
Use in metal cutting/ working fluids	Formulation	1.64	1.64	3.81	3.81
	Use in oil-based fluids (large)	0.71	0.71	1.32[a] [1.95][b]	1.32[a] [1.95][b]
	Use in oil-based fluids (small)	0.66	0.66	1.26[a] [1.82][b]	1.26[a] [1.82][b]
	Use in emulsifiable fluids	0.15	0.15	0.75[a] [0.80][b]	0.75[a] [0.80][b]
	Use in emulsifiable fluids – intermittent release	46.6	46.6	47.1[a] [93.6][b]	47.1[a] [93.6][b]
Use in leather fat liquors	Formulation	0.29	0.29	0.89	0.89
	Use – complete processing of raw hides	1.77	1.77	2.38	2.38
	Use – processing of wet blue	6.79	6.79	7.39	7.39
Use in carbonless copy paper	Paper recycling	0.43	0.43	1.03	1.03
Regional sources		0.1	0.1	0.71	0.71

a) Assuming a 5% medium-chain chlorinated paraffin content in the base fluid.

b) Assuming a 10% medium-chain chlorinated paraffin content in the base fluid.

Table E. 5 Estimated PEC/PNEC ratios for sediment (PNEC = 5 mg/kg wet wt.)

Scenario	Step	Current situation using measured regional concentrations		Future situation	
		PEC (mg/kg wet wt.)	PEC/PNEC	PEC (mg/kg wet wt.)	PEC/PNEC
Production	4 Sites	1.28-3.46	0.26-0.70	9.0-11.2	1.8-2.2
Use in PVC – plastisol coating	Compounding - O	1.88	0.38	9.6	1.9
	Conversion – O	5.68	1.1	13.4	2.7
	Compounding/conversion - O	6.27	1.3	14.0	2.8
Use in PVC – extrusion/other	Compounding - O	3.46	0.7	11.2	2.2
	Compounding - PO	13.2	2.6	20.9	4.2
	Compounding – C	2.30	0.46	10.0	2.0
	Conversion – O	7.94	1.6	15.7	3.1
	Conversion – PO	8.45	1.7	16.2	3.2
	Conversion – C	7.30	1.5	15.1	3.0
	Compounding/conversion – O	10.1	2.0	17.9	3.6
	Compounding/conversion - PO	20.4	4.1	28.1	5.6
	Compounding/conversion - C	8.32	1.7	16.1	3.2
Use in plastics/rubber	Compounding	2.38	0.48	10.1	2.0
	Conversion	4.99	1.0	12.7	2.5
	Compounding/conversion	6.14	1.2	13.8	2.8
Use in sealants	Formulation and use	negligible	<1	negligible	<1
Use in paints	Formulation	4.86	0.98	12.6	2.5
	Industrial application	2.69	0.54	10.4	2.1
	Domestic application	1.28	0.26	9.04	1.8
Use in metal cutting/working fluids	Formulation	21.0	4.2	48.8	9.8
	Use in oil-based fluids (large)	9.09	1.8	16.9[a] [25.0][b]	3.4[a] [5.0][b]
	Use in oil-based fluids (small)	8.45	1.7	16.2[a] [23.3][b]	3.2[a] [4.7][b]
	Use in emulsifiable fluids	1.92	0.38	9.63[a] [10.2][b]	1.9[a] [2.0][b]
	Use in emulsifiable fluids – intermittent release	597	119	604[a] [1,200][b]	121[a] [240][b]
Use in leather fat liquors	Formulation	3.71	0.74	11.4	2.3
	Use – complete processing of raw hides	22.7	4.5	30.5	6.1
	Use – processing of wet blue	86.9	17.4	94.7	18.9
Use in carbonless copy paper	Paper recycling	5.50	1.1	13.2	2.6
Regional sources		0.7	0.14	16.0	3.2

a) Assuming a 5% medium-chain chlorinated paraffin content in the base fluid.

b) Assuming a 10% medium-chain chlorinated paraffin content in the base fluid.

Table E. 6 Estimated PEC/PNEC ratios for soil (PNEC = 10.6 mg/kg wet wt.)

Scenario	Step	Current situation using measured regional concentrations		Future situation	
		PEC (mg/kg wet wt)	PEC/PNEC	PEC (mg/kg wet wt.)	PEC/PNEC
Production	4 Sites	negligible	<1	negligible	<1
Use in PVC – plastisol coating	Compounding - O	0.51	0.048	2.21	0.21
	Conversion – O	3.21	0.30	4.92	0.46
	Compounding/conversion – O	3.64	0.34	5.34	0.50
Use in PVC – extrusion/other	Compounding - O	1.64	0.15	3.34	0.32
	Compounding – PO	8.53	0.80	10.2	0.96
	Compounding – C	0.81	0.076	2.51	0.24
	Conversion – O	4.82	0.45	6.52	0.62
	Conversion – PO	5.16	0.49	6.86	0.65
	Conversion – C	4.40	0.42	6.10	0.58
	Compounding/conversion – O	6.37	0.60	8.07	0.76
	Compounding/conversion – PO	13.6	1.28	15.3	1.44
	Compounding/conversion – C	5.12	0.48	6.82	0.64
Use in plastics/rubber	Compounding	0.87	0.082	2.57	0.24
	Conversion	2.71	0.26	4.41	0.42
	Compounding/conversion	3.5	0.33	5.20	0.49
Use in sealants	Formulation and use	negligible	<1	negligible	<1
Use in paints	Formulation	2.62	0.25	4.32	0.41
	Industrial application	1.08	0.10	2.79	0.26
	Domestic application	negligible	<1	negligible	<1
Use in metal cutting/working fluids	Formulation	14.1	1.33	30.0	2.83
	Use in oil-based fluids (large)	5.66	0.53	7.36[a] [13.1][b]	0.69[a] [1.24][b]
	Use in oil-based fluids (small)	5.15	0.49	6.85[a] [11.9][b]	0.64[a] [1.12][b]
	Use in emulsifiable fluids	0.51	0.048	2.21[a] [2.63][b]	0.21[a] [0.25][b]
	Use in emulsifiable fluids – intermittent release	46	4.3	47.6[a] [93.5][b]	4.49[a] [8.82][b]
Use in leather fat liquors	Formulation	1.78	0.17	3.49	0.33
	Use – complete processing of raw hides	15.3	1.44	17.0	1.60
	Use – processing of wet blue	60.8	5.74	62.5	5.90
Use in carbonless copy paper	Paper recycling	3.02	0.28	4.76	0.45
Regional sources		0.088	0.008	91.6	8.64

a) Assuming a 5% medium-chain chlorinated paraffin content in the base fluid.

b) Assuming a 10% medium-chain chlorinated paraffin content in the base fluid.

Table E. 7 Estimated concentrations in fish and earthworms for secondary poisoning (PNEC = 0.17 mg/kg)

Scenario	Step	Current situation using measured regional concentrations				Future situation			
		Fish[c]		Earthworms		Fish[c]		Earthworms	
		PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC
Production	Site A	0.11-0.33	0.64-1.9	negligible	<1	0.77-2.31	4.5-13.6	negligible	<1
	Site B	0.15-0.45	0.88-2.6	negligible	<1	0.81-2.43	4.8-14.3	negligible	<1
	Site C	0.19-0.57	1.1-3.4	negligible	<1	0.84-2.52	4.9-14.8	negligible	<1
	Site D	0.11-0.33	0.64-1.9	negligible	<1	0.77-2.31	4.5-13.6	negligible	<1
Use in PVC – plastisol coating	Compounding - O	0.13-0.39	0.76-2.3	1.7	10.0	0.79-2.37	4.6-13.9	264	1,553
	Conversion – O	0.26-0.78	1.5-4.3	9.3	54.7	0.92-2.76	5.4-16.2	270	1,588
	Compounding/conversion - O	0.28-0.84	1.6-4.9	10.4	61.2	0.94-2.82	5.5-16.6	270	1,588
Use in PVC – extrusion/other	Compounding - O	0.19-0.57	1.1-3.4	4.8	28.2	0.84-2.52	4.9-14.8	267	1,571
	Compounding - PO	0.52-1.56	3.1-9.2	24.1	142	1.18-3.54	6.9-20.8	287	1,688
	Compounding – C	0.14-0.42	0.82-2.5	2.5	14.7	0.80-2.40	4.7-14.1	264	1,553
	Conversion – O	0.34-1.02	2.0-6.0	13.7	80.6	1.00-3.00	5.9-17.6	273	1,606
	Conversion – PO	0.36-1.08	2.1-6.4	14.7	86.4	1.02-3.06	6.0-18.0	277	1,629
	Conversion – C	0.32-0.96	1.9-5.6	12.6	74.1	0.98-2.94	5.8-17.3	273	1,606
	Compounding/conversion – O	0.42-1.26	2.5-7.4	18.1	106	1.08-3.24	6.4-19.1	280	1,647
	Compounding/conversion - PO	0.77-2.31	4.5-13.6	38.3	225	1.43-4.29	8.4-25.2	300	1,764
	Compounding/conversion - C	0.36-1.08	2.1-6.4	14.6	85.9	1.01-3.03	5.9-17.8	277	1,629
Use in plastics/rubber	Compounding	0.15-0.45	0.88-2.6	2.7	15.9	0.81-2.43	4.8-14.3	264	1,553
	Conversion	0.24-0.72	1.4-4.2	7.8	45.9	0.90-2.70	5.3-15.9	270	1,588

Table E7 continued Estimated concentrations in fish and earthworms for secondary poisoning (PNEC = 0.17 mg/kg)

Scenario	Step	Current situation using measured regional concentrations				Future situation			
		Fish[c]		Earthworms		Fish[c]		Earthworms	
		PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC
	Compounding/conversion	0.28-0.84	1.6-4.9	10.0	58.8	0.93-2.79	5.5-16.4	270	1,588
Use in sealants	Formulation and use	negligible	<1	negligible	<1	negligible	<1	negligible	<1
Use in paints	Formulation	0.23-0.69	1.4-4.1	7.6	44.7	0.89-2.67	5.2-15.7	270	1,588
	Industrial application	0.16-0.48	0.94-2.8	3.3	19.4	0.82-2.46	4.8-14.5	264	1,553
	Domestic application	negligible	<1	negligible	<1	negligible	<1	negligible	<1
Use in metal cutting/working fluids	Formulation	0.80-2.40	4.7-14.1	39.7	234	2.15-6.45	12.6-37.9	339	1,994
	Use in oil-based fluids (large)	0.38-1.14	2.2-6.7	16.1	94.7	1.04-3.12[a] [1.32-3.96][b]	6.1-18.4[a] [7.8-23.3][b]	277[a] [293][b]	1,629[a] [1,723][b]
	Use in oil-based fluids (small)	0.36-1.08	2.1-6.4	14.7	86.5	1.02-3.06[a] [1.26-3.78][b]	6.0-18.0[a] [7.4-22.2][b]	277[a] [290][b]	1,629[a] [1,706][b]
	Use in emulsifiable fluids	0.13-0.39	0.76-2.3	1.7	10.0	0.79-2.37[a] [0.81-2.43][b]	4.6-13.9[a] [4.8-14.3][b]	264[a] [264][b]	1,552[a] [1,552][b]
	Use in emulsifiable fluids – intermittent release	0.52-1.56	3.1-9.2	129	759	1.18-3.54[a] [1.6-4.8][b]	6.9-20.8[a] [9.4-28.2][b]	389[a] [517][b]	2,288[a] [3,041][b]
Use in leather fat liquors	Formulation	0.19-0.57	1.1-3.4	5.2	30.6	0.85-2.55	5.0-15.0	267	1,571
	Use – complete processing of raw hides	0.86-2.58	5.1-15.2	43.0	253	1.51-4.53	8.9-26.6	303	1,782
	Use – processing of wet blue	3.10-9.30	18.2-54.7	171	1,006	3.75-11.3	22.1-66.2	432	2,541
Use in carbonless copy paper	Paper recycling	0.23-0.69	1.4-4.1	8.8	51.8	0.89-2.67	5.2-15.7	270	1,588

a) Assuming a 5% medium-chain chlorinated paraffin content in the base fluid.

b) Assuming a 10% medium-chain chlorinated paraffin content in the base fluid.

c) The concentration in fish is estimated using the methods outlined in the Technical Guidance Document, taking into account accumulation through the food chain. The range reflects the rangefor the BMF (1-3).

References

RPA (1996). Risk-benefit analysis on the use of short chain length chlorinated paraffins in cutting fluids in the metal working industry. Produced for the Department of the Environment. Risk and Policy Analysts Limited.

RPA (1997). Risk-benefit analysis on the use of short-chain chlorinated paraffins in leather processing. Stage 1 Report for the Department of the Environment, Transport and the Regions. Risk and Policy Analysts Limited.

Appendix H

Effects of variability in physico-chemical properties and degradation rate on the environmental modelling of medium-chain chlorinated paraffins

Physico-chemical properties

Medium-chain chlorinated paraffins are complex mixtures. This presents some problems over the values of physico-chemical properties to be chosen for the environmental modelling of these substances. In order to simplify the environmental modelling the main risk assessment report a set of physical chemical properties were chosen as being representative of the medium chain chlorinated paraffins as a group. However, for the majority of the physico-chemical properties relevant for the environmental modelling, a range of values has been determined. This Appendix considers the effect of varying some of the key physico-chemical properties within the range measured on the predicted environmental concentration. In order to do this simply, the EUSES model was run several times using the release estimates for one local scenario (Use in rubber/plastics – conversion site; this is chosen as an example as it has releases to both air and waste water) and the total regional and continental releases as determined in the main report. This then allows the resulting concentrations to be compared directly with those obtained in the main report.

The physico-chemical properties for medium-chain chlorinated paraffins are discussed in Chapter 1 of the main risk assessment report. The values used as input data used in the various example calculations are shown in Table H1. The values chosen reflect the range of values measured for medium-chain chlorinated paraffins. In all calculations, 93% removal in the waste water treatment plant due to adsorption onto sewage sludge was assumed. Table H2 gives the resulting PECs from this approach.

Table H3 outlines the PEC/PNEC ratios obtained for surface water, sediment, soil and secondary poisoning, using the various physico-chemical properties (the PNECs for sediment and soil are based on the equilibrium partitioning approach). For the soil and sediment endpoints, both the PEC and PNEC depend on the value for the organic carbon-water partition coefficient used.

Table H. 1 Input data for EUSES model for the various scenarios considered

Model input	Value used in EUSES calculation										
	Main assessment	A	B	C	D	E	F	G	H	I	J
Molecular weight (g/mole)	488	488	405[c]	419[d]	468[e]	481	488	488	488	488	488
Water solubility (µg/l)	27	5	27	27	27	27	27	27	27	27	27
Vapour pressure (Pa)	$2.7 \cdot 10^{-4}$	$2.7 \cdot 10^{-4}$	$5 \cdot 10^{-5}$ c	$2 \cdot 10^{-5}$ d	$2 \cdot 10^{-6}$ e	$9 \cdot 10^{-7}$ f	$2.7 \cdot 10^{-4}$	$2.7 \cdot 10^{-4}$	$2.7 \cdot 10^{-4}$	$2.7 \cdot 10^{-4}$	$2.7 \cdot 10^{-4}$
Henrys Law constant[a] ($Pa.m^3.mole^{-1}$)	4.88	26.4	0.75	0.31	0.035	0.016	4.88	4.88	4.88	4.88	4.88
Log Kow	7	7	7	7	7	7	5.5	6	6.5	7.5	8
Koc[b] (l/kg)	$5.89 \cdot 10^5$	$5.89 \cdot 10^5$	$5.89 \cdot 10^5$	$5.89 \cdot 10^5$	$5.89 \cdot 10^5$	$5.89 \cdot 10^5$	$3.59 \cdot 10^4$	$9.13 \cdot 10^4$	$2.32 \cdot 10^5$	$1.5 \cdot 10^6$	$3.8 \cdot 10^6$
$PNEC_{water}$ (µg/l)	1	1	1	1	1	1	1	1	1	1	1
$PNEC_{sediment}$ (mg/kg wet wt.)[g]	12.8	12.8	12.8	12.8	12.8	12.8	0.78	2.0	5.0	32.6	82.6
$PNEC_{soil}$ (mg/kg wet wt.)[g]	10.4	10.4	10.4	10.4	10.4	10.4	0.63	1.6	4.1	26.5	67.1
$PNEC_{secondary\ poisoning}$ (mg/kg food)	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Continental release	153,193 kg/year to air, 1,073,482 kg/year to waste water and 460,101 kg/year to surface water										
Regional release	17,027 kg/year to air, 119,286 kg/year to waste water and 51,122 kg/year to surface water										
Local release (Use in rubber/plastics – conversion site)	0.155 kg/day to air and 0.155 kg/day to waste water over 300 days										

a) Henrys law constant estimated from water solubility and vapour pressure (also depends on the molecular weight).

b) Koc estimated by EUSES from log Kow.

c) Vapour pressure and molecular weight appropriate for C_{14}, 51-53% wt. Cl congeners.

d) Vapour pressure and molecular weight appropriate for C_{15}, 51-53% wt. Cl congeners.

e) Vapour pressure and molecular weight appropriate for C_{16}, 51-53% wt. Cl congeners.

f) Vapour pressure and molecular weight appropriate for C_{17}, 51-53% wt. Cl congeners.

g) PNECs for sediment and soil calculated by the equilibrium partitioning method – dependent on Koc value.

Table H. 2 Resulting concentrations for the various scenarios considered

Endpoint	Value estimated in EUSES calculation										
	Main assessment	A	B	C	D	E	F	G	H	I	J
Local concentrations (use in rubber/plastics – conversion site)											
Surface water (µg/l)	0.68	0.48	0.87	0.91	0.93	0.93	1.23	1.14	0.96	0.39	0.18
Sediment (mg/kg wet wt.)	8.7	6.1	11.2	11.6	11.9	12.0	0.96	2.27	4.84	12.5	15.1
Agricultural soil (30 days average) (mg/kg wet wt.)	3.72	3.58	3.88	3.79	3.67	3.66	2.41	2.96	3.45	3.64	3.43
Pore water (agricultural soil) (µg/l)	0.36	0.34	0.37	0.36	0.35	0.35	3.8	1.83	0.84	0.14	0.051
Air (during emission episode) (mg/m³)	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$	$4.3 \cdot 10^{-5}$
Fish (for secondary poisoning) (mg/kg wet wt.)[a]	0.55-1.65	0.33-0.99	0.76-2.28	0.80-2.40	0.83-2.49	0.83-2.49	1.01-3.03	0.94-2.82	0.79-2.37	0.31-0.93	0.15-0.45
Earthworms (for secondary poisoning) (mg/kg wet wt.)	152	92.2	175	178	178	178	30.0	59.3	102	188	204
Total daily human intake (mg/kg bw/day)	0.137	0.127	0.138	0.132	0.126	0.125	0.053	0.076	0.109	0.157	0.172
Predicted regional concentrations											
Surface water (µg/l)	0.39	0.19	0.58	0.62	0.64	0.65	0.72	0.67	0.56	0.22	0.10
Sediment (mg/kg wet wt.)	8.80	4.27	13.2	14.0	14.6	14.6	0.97	2.32	4.95	12.5	15.0
Agricultural soil (mg/kg wet wt.)	50.4	29.4	58.6	59.6	60.2	60.2	8.23	17.9	33.3	63.0	69.9
Pore water (agricultural soil) (µg/l)	4.9	2.8	5.6	5.7	5.8	5.8	13	11.1	8.2	2.4	1.04
Air (mg/m³)	$3.4 \cdot 10^{-6}$	$6.2 \cdot 10^{-6}$	$1.2 \cdot 10^{-6}$	$8.9 \cdot 10^{-7}$	$6.6 \cdot 10^{-7}$	$6.5 \cdot 10^{-7}$	$6.4 \cdot 10^{-6}$	$5.8 \cdot 10^{-6}$	$4.7 \cdot 10^{-6}$	$2.1 \cdot 10^{-6}$	$1.4 \cdot 10^{-6}$
Total daily human intake (mg/kg bw.day)	1.71	1.0	1.99	2.02	2.04	2.04	0.173	0.44	0.97	2.51	3.27

a) The concentration in fish is estimated using the methods outlined in the Technical Guidance Document, taking into account accumulation through the food chain. The range reflects the range for the BMF (1-3).

Table H. 3 Resulting PEC/PNEC ratios for the various scenarios considered

Endpoint	PEC/PNEC ratio										
	Main assessment	A	B	C	D	E	F	G	H	I	J
Local concentrations (use in rubber/plastics – conversion site)											
Surface water	0.68	0.48	0.87	0.91	0.93	0.93	1.23	1.14	0.96	0.39	0.18
Sediment	0.68	0.48	0.87	0.91	0.93	0.93	1.23	1.14	0.96	0.39	0.18
Agricultural soil (30 days average)	0.35	0.34	0.37	0.36	0.35	0.35	3.83	1.85	0.84	0.14	0.05
Fish (for secondary poisoning)	3.3-9.9	2.0-6.0	4.5-13.5	4.8-14.4	5.1-15.3	5.1-15.3	6.0-18.0	5.7-17.1	4.8-14.4	1.8-5.4	0.9-2.7
Earthworms (for secondary poisoning)	894	542	1,029	1,047	1,047	1,047	176	348	600	1,106	1,200
Predicted regional concentrations											
Surface water	0.39	0.19	0.58	0.62	0.64	0.65	0.72	0.67	0.56	0.22	0.10
Sediment	0.69	0.33	1.03	1.09	1.14	1.14	1.24	1.16	0.99	0.38	0.18
Agricultural soil	4.8	2.8	5.6	5.7	5.8	5.8	13.0	11.2	8.1	2.4	1.0

As can be seen from Table H3, there is some variation in the results obtained. Lowering the water solubility (or increasing the Henrys law constant to values of around 25 $Pa.m^3.mole^{-1}$) and increasing the log Kow value above 7-7.5 appeared to have the largest effects on the resulting PEC/PNEC ratio, leading to generally lower ratios for surface water, sediment and soil.

The extremes of the PEC/PNEC ratios obtained vary by a factor of around 7 for surface water and sediment and by a factor of up to 60 for agricultural soil. However, for most scenarios (e.g. B, C, D, E, F, G, H) the variation in PEC/PNEC ratio seen is much less than this, and indicates that only the extremes of the values of the range of physico-chemical properties would result in a significant change to the PEC/PNEC ratios obtained. The values for physico-chemical properties used in the main assessment results in PEC/PNEC ratios that are generally in the middle to upper end of the range determined, and indicate that the results are reasonably representative for the majority of the components of the commercial mixtures.

Degradation rate

Since medium-chain chlorinated paraffins are not readily biodegradable, the appropriate default rate constants for degradation in surface water ($6.93 \cdot 10^{-7}$ day^{-1}), soil ($6.93 \cdot 10^{-7}$ day^{-1}) and sediment ($6.93 \cdot 10^{-8}$ day^{-1}) were used in the EUSES modelling in the main report. These correspond to degradation half-lives of the order of 2,740 years in soil and surface water, and 27,400 years in bulk sediment. The regional concentrations estimated using these values were generally higher than the available monitoring data indicated. One explanation for this would be if medium-chain chlorinated paraffins are less persistent in the environment than is indicated by these default degradation halflives. Therefore the sensitivity of the calculations to these degradation rates was investigated. In this analysis the physico-chemical properties and regional and continental releases were as in the main report and the EUSES model was run several times with different values for the degradation rate constants. The results are shown in Table H4.

Table H. 4 Effects of varying the biodegradation half-life on predicted regional concentrations

Biodegradation		**Half-life**		**$PEC_{regional}$**		
Surface water, soil	**Bulk sediment**	**Surface water, soil**	**Bulk sediment**	**Surface water**	**Sediment**	**Agricultural soil**
$6.93 \cdot 10^{-7}$	$6.93 \cdot 10^{-8}$	2,740 years	27,400 years	0.39 µg/l	8.8 mg/kg wet wt.	50.4 mg/kg wet wt.
$6.93 \cdot 10^{-6}$	$6.93 \cdot 10^{-7}$	274 years	2,740 years	0.27 µg/l	6.04 mg/kg wet wt.	10.6 mg/kg wet wt.
$6.93 \cdot 10^{-5}$	$6.93 \cdot 10^{-6}$	27.4 years	274 years	0.24 µg/l	5.32 mg/kg wet wt.	1.19 mg/kg wet wt.
$6.93 \cdot 10^{-4}$	$6.93 \cdot 10^{-5}$	2.74 years	27.4 years	0.21 µg/l	4.71 mg/kg wet wt.	0.12 mg/kg wet wt.
$1.90 \cdot 10^{-3}$	$1.90 \cdot 10^{-4}$	1 year	10 years	0.19 µg/l	3.92 mg/kg wet wt.	0.044 mg/kg wet wt.
$6.93 \cdot 10^{-3}$	$6.93 \cdot 10^{-3}$	100 days	2.74 years	0.13 µg/l	2.3 mg/kg wet wt.	0.012 mg/kg wet wt.
0.0139	$1.93 \cdot 10^{-3}$	50 days	1.37 years	0.10 µg/l	1.45 mg/kg wet wt.	0.006 mg/kg wet wt.
0.0231	$2.31 \cdot 10^{-3}$	30 days	300 days	0.08 µg/l	0.97 mg/kg wet wt.	0.004 mg/kg wet wt.
Measured data				0.1 µg/l	0.7 mg/kg wet wt.	0.088 mg/kg wet wt.

As can be seen from the data presented in Table H4, the regional soil concentration is particularly sensitive to the value of the degradation rate chosen. A degradation half-life in soil of around 2 years leads to predicted levels that are consistent with the measured data.

Appendix I
MEASUREMENT OF WORKPLACE EXPOSURE

Summary

No references were located which referred specifically to the measurement of occupational exposure to medium-chain chlorinated paraffins. Most work on these materials relates to their occurrence in the general environment such as water, sediments and biological material. There are few references to airborne measurement so there is little experience to draw upon in collecting samples from the air. Given the low vapour pressures of C_{14-17} chloroparaffins, sampling vapour may not be an issue in the workplace. However, aerosols generated from the use of, for example, metal working fluids may contain chloroparaffins which could have an associated vapour. Experience also shows that collection on filters of aerosols of substances with relatively low vapour pressures can lead to losses during sampling due to evaporation from the filter.

The most frequently used analytical methods include GC-HRMS (see abbreviations), GC-LRMS and GC-ECD. Analysis is difficult because medium-chain chlorinated paraffins are a complex mixture of compounds which will have different response factors to the various methods of detection. One paper (Tomy *et al*, 1997) tried to estimate the number of positional isomers possible for C_{10-13} chloroparaffins by assuming no more that one chlorine atom per carbon atom and produced a figure of 6,304 compounds. The authors estimated that the true number of compounds is probably an order of magnitude greater than this because of the possibility of optical isomerism on adding subsequent chlorines. The situation is expected to be no less complex for C_{14-17} chloroparaffins. Thus selectively distinguishing and quantifying C_{14-17} chloroparaffins is an extremely challenging task. With so many possible compounds, calibration of the measurement method becomes a compromise which to some extent relies on matching the profile of the sample to the profile of the substance used to calibrate. Deviations from such profile matching as, for example, in degraded samples can be expected to give rise to measurement errors.

Few attempts have been made to establish the quality of the results from this difficult measurement. No references were located on interlaboratory trials on the measurement of MCCPs. However, an interlaboratory trial involving seven laboratories on the measurement of short-chain chlorinated paraffins resulted in reasonably good agreement between laboratories for one sample but large discrepancies for another sample for reasons which were unclear (Tomy *et al* 1999). The measurement difficulties for medium-chain chlorinated paraffins are similar to short-chain chlorinated paraffins and it might be expected that the problems identified with short-chain materials would also apply to medium-chain chlorinated paraffins.

In measuring airborne exposures in the work place, measurement methods should conform to the requirements of BS EN 482 and its associated standards (BS EN 483, BS EN 1076). While it is likely that the methods used for environmental applications could be adapted for occupational measurement, it is unlikely that they would meet the requirements of BS EN 482, mainly because of the complexity of the mixtures and the calibration difficulties. The analytical method of choice would probably be GC-MS (low or high resolution) but additional work would be required to specify an appropriate method for capturing airborne samples.

If aerosols containing medium-chain chloroparaffins are generated in the workplace then there is the potential for subsequent contamination of surfaces through deposition of the aerosol. No measurement information was found which considered this possibility. Before surface contamination with these materials could be investigated, appropriate means of sampling from the surfaces would have to be validated. There would also be the possibility of preferential evaporation, over time, of the lighter fractions from the surfaces which would make matching of the sample to a suitable calibration standard difficult during analysis.

The summary was drawn from the following publications amongst others. These publications comprise a cross section of material on chloroparaffins and are intended to include examples of the principal methods of measurement.

Hollies *et al* (1979)

Thin layer chromatography methods are described which will are said to distinguish between shorter chain C_{13-17} chloroparaffins and those with longer, C_{20-30}, chains in various environmental media. Samples are cleaned up with solvent extraction and column chromatography followed by analysis with thin layer chromatography in a procedure which is time-consuming. The method is said to be capable of measuring concentrations down to 500 ng/l in water but is likely to be semi-quantitative without a densitometer.

Campbell and McConnell (1980)

The TLC method of Hollies *et al* (1979) was used to analyse various environmental samples but was able to discriminate only between C_{10-20} and C_{20-30} chloroparaffins. It could not differentiate between C_{10-13} and C_{14-17} types and will therefore not fulfil the requirements of this review.

Sistovaris and Donges (1987)

Catalytic reduction of the chloroparaffins to their corresponding alkanes and analysis by GC-FID was proposed. The catalyst is inserted into the GC injector so that samples are reduced on injection producing quite high conversion efficiencies to the alkanes. The method offers a reduction in the complexity of analysing chloroparaffins but clearly alkanes or other materials which can also be reduced to alkanes could be a significant source of interference. Consequently it would be difficult to positively confirm the presence of chloroparaffins in a sample and the technique is likely to produce only a total chloroparaffin figure.

Junk and Meisch (1993)

A measurement method was reported based on GC-EI-MS after clean up of the sample using solid phase extraction. It is claimed that monitoring two fragments with masses 105 and 107, produced by chloroparaffins, overcomes some of the calibration difficulties experienced by other methods. However, the development work used a C_{10-13} chloroparaffin only so it is not clear whether the method could also be used selectively for C_{14-17} types.

Schmid and Muller (1985)

Samples were cleaned up with solid phase extraction and analysed by GC-NCI-MS. Method testing included one chloroparaffin from each type, C_{10-13}, C_{14-18} and C_{20-28} together with various environmental samples. While the method is sensitive and can clearly indicate the presence of chloroparaffins, it was not clear if it could selectively distinguish between the types of chloroparaffin. Accurate quantitation also depends on matching the chloroparaffin used to calibrate with the chloroparaffins in the sample. Any significant deviations from a match will give rise to errors.

Tomy *et al* (1997)

A method is described a sensitive method for quantifying C_{10-13} chloroalkanes using GC-ECNI-HRMS. This approach was adopted to eliminate self-interference between the chloroalkanes and also to overcome the potential interference from other chlorinated materials such as PCBs and organochlorine pesticides. The method attempts to separate the chloroparaffins into formula groups, which is said to allow corrections for differences in patterns between analyte and standard. The method could probably be adapted for C_{14-17} chloroparaffins but it is not clear that they could be selectively measured in the presence of other chloroparaffin types.

Peters *et al* (1998)

Environmental air samples were collected with Graseby-Anderson PS1 and PM10 high volume samplers. Particulates were retained on a glass fibre filter and the vapour phase components on two polyurethane foam plugs. The filters and plugs were solvent extracted together so no phase partitioning information was provided in this study and the samples were analysed with GC-ECNI-HRMS. Concentrations of SCCPs are quoted (C_{10-13}) but there are no data for the higher homologues. The samples from a semi-rural site at Lancaster produced a total chloroalkane concentration of 99 pg/m^3 (±101). No information was provided on collection efficiencies of the sampling devices or recoveries from those media.

Randegger-Volrath (1998)

An application is reported in which cutting fluids and lubricants are classified on the basis of the chain length and degree of chlorination of the chlorinated paraffins in the products. Samples were cleaned up with solid phase extraction and screened using GC-ECD. Positive identification and quantitation was then performed using GC-NCI-MS. The procedure was applied to 37 cutting fluids or lubricants and produced detection limits of 0.02 to 0.08% using the ECD method and 0.2 to 2.6% for the NCI method. Chlorinated paraffins were detected in 57% of the samples comprising 21% short chain and 30% medium chain. Long chain chlorinated paraffins were detected in 2 samples. Only the short chain compounds were quantified producing concentrations from 1 to 70% (w/w). The authors stated that the differing classes of chlorinated paraffins can be characterised based on their specific masses and GC retention times. The prime purpose of the study was to demonstrate the presence of chlorinated paraffins in various products but investigation of quantitation showed NCI to be superior to ECD.

Tomy *et al* (1999)

An interlaboratory study between seven laboratories using two solutions of known concentration and two fish extracts is reported. The laboratories used GC-LRMS, GC-HRMS or GC-EC. The mean concentration in the first sample was 99.3 ng/ml compared with a true value of 74 ng/ml. The mean concentration in the second sample was 297 ng/ml compared with a true value of 118 ng/ml. The reason for the large discrepancy in the second sample was unclear but was taken to imply that different commercial formulations used as calibration standards would provide different estimates of short-chain chlorinated paraffins. Co-eluting substances were thought to contribute to the errors.

Appendix J
Contribution on Biological Monitoring

There are no published occupational studies involving biological monitoring for medium-chain chlorinated paraffins (MCCPs).

It may be possible to develop a biological monitoring method by adapting methods used for environmental and tissue samples. MCCPs have been measured in human adipose tissue (Schmid & Muller 1985) and short-chain chlorinated paraffins in human breast milk (Stern *et al* 1998). Both techniques used extensive sample preparation followed by high resolution gas chromatography with detection by negative ion chemical ionisation mass spectrometry.

However, the analysis is complicated by the fact that MCCPs are a group of substances rather than a single substance, the lack of suitable reference substances and the lack of suitable internal standards. Unlike conventional biological monitoring for single substances any methods for MCCPs are likely to be semiquantitative.

Further contraindications for biological monitoring for MCCPs are:

- the invasive nature of sampling (blood or adipose tissue)
- the long-half life of MCCPs in the body making interpretation difficult
- the likely high cost of sample analysis.

In view of this, it seems likely that any biological monitoring for MCCPs will be confined to specialist investigations rather than occupational hygiene investigations. Overall, therefore, MCCPs are not considered to meet HSE's criteria for the development of a BMGV.

References

BS EN 482 (1994). Workplace atmospheres - General requirements for the performance of procedures for the measurement of chemical agents.

BS EN 838 (1996). Workplace atmospheres - Diffusive samplers for the determination of gases and vapours - requirements and test methods.

BS EN 1076 (1997). Workplace atmospheres - Pumped sorbent tubes for the determination of gases and vapours - requirements and test methods.

Campbell I, McConnell G (1980). Chlorinated paraffins and the environment 1. Environmental occurrence. *Environmental Science and Technology.* **14**: 1209-1214.

Hollies J, Pinnington D, Handley A, Baldwin M, Bennett D (1979). The determination of chlorinated long-chain paraffins in water, sediment and biological samples. *Analytica Chimica Acta.* **111**: 201-213.

Junk S, Meisch H-U (1993). Determination of chlorinated paraffins by GC-MS. *Fresenius Journal of Analytical Chemistry.* **347**: 361-364.

Peters A, Tomy G, Stern G, Jones K (1998). Polychlorinated alkanes in the atmosphere of the United Kingdom and Canada - analytical methodology and evidence of the potential for long-range transport. *Organohalogen Compounds*, **35**: 439-442.

Randegger-Vollrath A (1998). Determination of chlorinated paraffins in cutting fluids and lubricants. *Fresenius Journal of Analytical Chemistry.* **360**: 62-68.

Schmid P, Muller M (1985). Trace level detection of chlorinated paraffins in biological and environmental samples using gas chromatography/mass spectrometry with negative ion chemical ionization. *J Assoc Off Anal Chem.* **68**: 427-430.

Sistovaris N, Donges U (1987). Gas chromatographic determination of total polychlorinated aromates and chloroparaffins following catalytic reduction in the injection port. *Fresenius Journal of Analytical Chemistry*. **326**: 751-753.

Stern G, Tomy G, Muir D, Westmore J, Dewailty E, Rosenberg B (1997). Polychlorinated n-alkanes in aquatic biota and human milk. Convention on long-range transboundary air pollution. Working Group on Strategies (21st session 16-20 June 1997). Informal in-session document No2.

Thomas G. O. and Jones K. C. (2002). Chlorinated paraffins in human and bovine milk-fat. A report on a research project funded by the Eurochlor Chlorinated Paraffin Sector Group. Department of Environmental Sciences, Lancaster University.

Tomy G, Stern G, Muir D, Fisk A, Cymbalisty C, Westmore J (1997). Quantifying C_{10} - C_{13} polychloroalkanes in environmental samples by high resolution gas chromatography/electron capture negative ion high-resolution mass spectrometry. *Analytical Chemistry*. **69**: 2762-2771.

Tomy G, Westmore J, Stern G, Muir D, Fisk A (1999). Interlaboratory study on quantitative methods of analysis of C_{10} - C_{13} polychloro-n-alkanes. *Analytical Chemistry.* **71**: 446-451.

The report provides the comprehensive risk assessment of the substance alkanes, C_{14-17},

chloro (medium-chain chlorinated paraffins or MCCPs). It has been prepared by the United Kingdom in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans the environment, laid down in Commission Regulation (EC) No. 1488/94.

Part II – Human Health

The human health part of the risk assessment concludes that there is concern for Workers, but none for Consumers and Humans exposed via the environment.

European Commission

EUR 25202 **EN – Joint Research Centre – Institute for Health and Consumer Protection**
Title: ALKANES, C14-17, CHLORO, Part II Human Health
Author(s): S. Pakalin, K. Aschberger, S. Munn, H. Olsson, G. Pellegrini, S. Vegro, A. B. Paya Perez
Luxembourg: Publications Office of the European Union
2011 – 183 pp. – 21.0 x 29.7cm
EUR – Scientific and Technical Research series – ISSN 1831-9424 (online), ISSN 1018-5593 (print)
ISBN 978-92-79-23046-2
doi:10.2788/86466

Abstract

This document is the Human Health part of the Risk Assessment Report on ALKANES, C14-17, CHLORO (MCCP), carried out in accordance with Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances, and endorsed by the Technical Committee on New and Existing Substances.

The key health effects of concern arising from occupational exposure to MCCPs during the use of oil-based metal working fluids (MWF), are kidney toxicity following repeated exposure, carcinogenicity, effects on the offspring mediated via lactation and effects at the time of parturition.

There are no concerns for consumers and men indirectly exposed via the environment, in particular for infants exposed to MCCPs via milk.

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, whether private or national.

JRC
EUROPEAN COMMISSION

LB-NA-25202-EN-N

Publications Office

ISBN 978-92-79-23046-2