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Toxicological review of the possible effects associated with inhalation and dermal exposure to drilling fluid production streams

Alison Searl, Karen S Galea

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Drilling fluids are used extensively in the upstream oil and gas industry and are complex mixtures comprising of solids and liquids, including base oils and brine. The fluid has many roles during the drilling process including removing cuttings, cooling and lubricating the drill bit and carrying various chemicals down the borehole. The fluid is cleaned by passing over a shale shaker, where unwanted solids are removed and the resultant cleaned fluid is then re-injected into the well.

Drilling fluid compositions can broadly be divided into oil-based and water-based fluids, but show a wide range of composition within each of these categories. Other substances that may be present in oil-based systems include inorganic salts, emulsifers, titanium dioxide, crystalline silica, thickeners, surfactants, small quantities of strong bases such as lime, sodium hydroxide or potassium hydroxide. The water-based systems show an even wider variability in composition. They typically contain metal salts and may contain natural thickeners (e.g. bentonite) or artificial thickeners (e.g. polyethylene glycol), barium sulphate and other mineral phases. They may also contain preservatives and biocides such as glutaraldehyde. Workers can be exposed to drilling fluids by inhalation and skin contact.

The aims of the toxicological review were to update an earlier review by Eide (1990) of the health effects associated with inhalation exposure to vapour and aerosol generated from oil-based drilling fluids and to evaluate the potential effects dermal exposure to water and oil-based drilling fluids. Our review took into account the concentration of individual components in fluids and the potential influence of different components in determining the toxicity of the mixture, although there are very few data that describe how the toxicity of individual substances may be modified by the presence of other substances in a mixture.

The main/

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The main health effects that may arise from exposure to drilling fluids of any composition are irritation of the skin, eyes and respiratory system with long-term exposure potentially leading to dermatitis or chronic respiratory illness. Exposure levels should be controlled to levels well below those associated with the development of irritation in order to prevent the development of more serious chronic conditions. There are insufficient data to recommend suitable exposure limits, but exposure to oil mist in other workplace settings has been reported to give rise to respiratory irritation at concentrations of <0.2 mgm^{-3}. In addition, long term exposure to hydrocarbon vapours associated with the use of oil based fluids may also give rise to neurotoxicity. Based on published exposure limits for short to medium chain alkanes, it would be desirable to ensure exposures are controlled well below 50 ppm as a long term average. A range of other serious health effects including occupational asthma, allergic dermatitis, pneumoconiosis or even cancer are possible depending on the composition of the fluid and exposure levels. The control of exposures to prevent respiratory irritation should also protect against pneumoconiosis and cancer. Some minor components of drilling fluids such as glutaraldehyde or other biocides may have a disproportionately large impact on health risk. Special care should be taken to minimise exposure to fluids containing glutaraldehyde or other potent sensitisers. Given the paucity of information about actual as opposed to conjectural effects of drilling fluids on worker health, it may be desirable to undertake health surveillance in workers with repeated exposure to drilling fluids.

GLOSSARY

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Average Daily Intake
ATSDR	Agency for Toxic Substances and Disease Registry
CAS	Chemical Abstracts Service
CI	Confidence Internal
CICAD	Concise International Chemical Assessment Document
CNS	Central Nervous System
DECOS	Dutch Expert Committee on Occupational Standards of the Dutch Health Council
DEGBE	2-(2-butoxyethoxy)ethanol
EC50	Median Effective Concentration (required to induce a 50% effect)
EEG	Electroencephalograph
EKG	Electrocardiogram
EPA	Environmental Protection Agency
FEV1	Forced Expiratory Volume in one second
HBO	hydrocracked oil
HDS kerosene	Hydrodesulfurized kerosene
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IUCLID	International Uniform Chemical Information Database
JECFA	Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives
LAS	Linear Alkylbenzene Dulfonate
LOAEL	Lowest Observed Adverse Effect Level
mgm^{-3}	Milligrams per cubic metre
MWF	Metal Working Fluids
NEG	Nordic Expert Group (on OELs)
NIOSH	National Institute of Occupational Safety and Health
NOAEL	No Observed Adverse Effect Level
OEL	Occupational Exposure Limit
OES	Occupational Exposure Standard
OR	Odds Ratio
PAH	Polycyclic Aromatic Hydrocarbons
PEG	Polyethylene Glycol
PIM	Poison Information Monograph
PPG	Propylene Glycol
ppm	Parts Per Million
PR	Prevalence Ratio
PSD	Particle Size Distribution
RCS	Respirable Crystalline Silica

RD50	Concentration associated with a 50% reduction in breathing rate
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RTECS	Registry of Toxic Effects of Chemical Substances
SIDS	Screening Information Data Set
SIR	Standardised Incidence Ratio
SLS	Sodium Lauryl Sulphate
SRA	Sulfurized Ricinoleic Acid
SRO	Solvent Refined Oil
TCE	Trichloroethylene
TEA	Triethanolamine
TiO2	Titanium Dioxide
TLV	Threshold Limit Values
TMB	1,2,4-trimethylbenzene
TMCH	1,2,4-trimethylcyclohexane
TWA	Time Weighted Average
UGEO	Used Gasoline Engine Oil
WEL	Workplace Exposure Limit
WTO	acid-washed white oil

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EXECUTIVE SUMMARY

Drilling fluids are used extensively in the upstream oil and gas industry and are complex mixtures comprising of solids and liquids, including base oils and brine. The fluid has many roles during the drilling process including removing cuttings, cooling and lubricating the drill bit and carrying various chemicals down the borehole. The fluid is cleaned by passing over a shale shaker, where unwanted solids are removed and the resultant cleaned fluid is then re-injected into the well.

Drilling fluid compositions can broadly be divided into oil-based and water-based fluids, but within each of these categories fluids may show a wide range of composition. Typically the oil-based systems are formulated with petroleum distillate, kerosene or synthetic mixes of C_5-C_{20} paraffins. Other substances that may be present include inorganic salts (such as sodium, calcium or potassium carbonate or bicarbonate or calcium chloride, sodium, potassium or caesium formate), emulsifers, titanium dioxide, crystalline silica, thickeners, surfactants, small quantities of strong bases such as lime, sodium hydroxide or potassium hydroxide. The water-based systems show an even wider variability in composition. They typically contain metal salts and may contain natural thickeners (e.g. bentonite) or artificial thickners (e.g. polyethylene glycol), barium sulphate and other mineral phases. They may also contain preservatives and biocides such as glutaraldehyde. Workers can be exposed to drilling fluids by inhalation as well as skin contact.

The main risks to health associated with oil-based drilling fluids are likely to be irritation of the mucous membranes and skin along with potential neurotoxicity. The exact nature of potential effects will vary with oil composition, the other substances present in specific drilling fluids and exposure levels. The oils may increase the bioavailability of other substances in drilling fluid compositions through their impact on skin permeability and/or metabolism. The saturation of specific metabolic pathways by oil components may increase systemic exposures to other substances. Long term inhalation of oil vapours and aerosol may be associated with increased risks of developing chronic respiratory illness including bronchitis. The potential of oil vapour to cause respiratory irritation is likely to be greater than the summed impacts of the individual substances present in oils. It is also likely that the oil vapour also increases the potential for other components in drilling fluids to cause irritation, although there are some limited data that suggest that the irritative response can become saturated. Long term inhalation exposure may also be associated with a risk of permanent neurological impairment, with memory loss, impaired cognition and, at very high levels of exposure, dementia. Although there are limited data that describe the exposure levels associated with neurotoxicity for individual components present in oil vapour, the neurotoxic potential of the mixture is not known. Long term exposure of the skin is likely to lead to dermatitis and potentially more serious skin lesions. The concentrations of carcinogens present in typical drilling fluids are negligible and are unlikely to give rise to a significant increased cancer risk, although there are limited data that may link exposure to oils to an increased risk of cancers of the upper airways.

The main risk to health that is specifically associated with water-based fluids is probably hand dermatitis due to wet-work. Other risks to health will vary depending on the substances present within the fluids. Given the very wide range of different fluid compositions in use, it is unlikely that aqueous-based fluids are consistently more or less toxic than oil-based fluids.

The brines that are used in drilling fluids are typically formulated using low toxicity salts such as sodium, potassium or caesium formate and other salts such as sodium or potassium bicarbonate may also be added. Exposure is highly unlikely to lead to uptakes of these salts that

exceed endogenous levels (apart from caesium). The limited toxicity data for non-radioactive caesium, do not suggest that it represents a substantial risk to health.

The pH adjusters added to drilling fluids such as sodium, potassium or calcium hydroxide are highly corrosive in pure form and would be expected to cause skin irritation or irritation of the mucous membranes at relatively low concentrations in water or in an aqueous mist. However, the presence of other substances within drilling fluids is likely to substantially modify the potential of these substances to cause irritation, providing that the pH of fluids is maintained at near neutral levels.

The emulsifiers and surfactants used in drilling fluids may cause irritation of the skin or mucous membranes at relatively low levels of exposure, although there is little information about the specific substances used or the toxicity of these types of substance. There is limited evidence that some quaternary ammonium salts, for example, may potentially be dermal or respiratory sensitisers.

The mineral powders that may be added to drilling fluids are generally of low toxicity (calcium carbonate, barium sulphate, bentonite, titanium dioxide (TiO_2)). Their presence in fluids may however lead to enhanced uptake of other more toxic substances through the skin or via inhalation. Short term exposure to elevated concentrations of these substances may cause respiratory irritation (as a non-specific response to inhaling aerosols) and long term over exposure to respirable mineral dusts may lead to increased risks of chronic respiratory illnesses including bronchitis and potentially fibrotic lung disease such as pneumoconiosis. Respirable crystalline silica (RCS), which may be present in small quantities in drilling fluids, is considerably more toxic than the other mineral dusts likely to be present. Long-term exposure to even low concentrations (0.1 mgm^{-3}) of RCS is associated with the development of silicosis (a fibrotic lung disease specific to silica) which causes impairment of respiratory function and may contribute significantly to premature mortality (for example, through the associated impacts on cardiovascular health). RCS is also a confirmed human carcinogen, although the lung cancer risks are considerably smaller than those of silicosis. Sodium silicate which was reported to be present in one drilling fluid may be associated with irritation of the skin and mucous membranes.

The biocides that are added to drilling fluids may significantly enhance their toxicity. Glutaraldehyde is highly toxic following dermal or inhalation exposure, causes dermal and mucous membrane irritation at low levels of exposure and is a potent sensitiser. The bioavailability of biocides in drilling fluids may be significantly enhanced by other substances within the fluids that may act to increase skin permeability or as carriers.

The various thickeners that are added to drilling fluids such as polyethylene glycols (PEGs) and PEG derivatives, cellulose and starch, are generally of low toxicity and would not be expected to contribute significantly to the toxicity of the mixture.

In conclusion, the main health effects that may arise from exposure to drilling fluids of any composition are irritation of the skin, eyes and respiratory system with long-term exposure potentially leading to dermatitis or chronic respiratory illness Exposure levels should be controlled to levels well below those associated with the development of irritation in order to prevent the development of more serious chronic conditions. There are insufficient data to recommend suitable exposure limits, but exposure to oil mist in other workplace settings has been reported to give rise to respiratory irritation at concentrations of <0.2 mgm^{-3}. In addition, long term exposure to oil based fluids may also give rise to neurotoxicity. Based on published exposure limits for short to medium chain alkanes, it would be desirable to ensure exposures are controlled well below 50 ppm as a long term average. A range of other serious health effects

including occupational asthma, allergic dermatitis, pneumoconiosis or even cancer are possible depending on the composition of the fluid and exposure levels. The control of exposures to prevent respiratory irritation developing should also protect against pneumoconiosis and cancer. Some minor components of drilling fluids such as glutaraldehyde may have a disproportionately large impact on health risk. Special care should be taken to minimise exposure to fluids containing glutaraldehyde or other potent sensitisers. Given the paucity of information about actual as opposed to conjectural effects of drilling fluids on worker health, it may be desirable to undertake health surveillance in workers with repeated exposure to drilling fluids.

1 INTRODUCTION

Drilling fluids are used extensively in the upstream oil and gas industry and are complex mixtures comprising of solids and liquids, including base oils and brine. The fluid has many roles during the drilling process including removing cuttings, cooling and lubricating the drill bit and carrying various chemicals down the borehole. The fluid is cleaned by passing over a shale shaker, where unwanted solids are removed and the resultant cleaned fluid is then re-injected into the well. A considerable number of workers are employed in drilling operations and may be exposed to drilling fluids either by inhalation or by skin contact. The health risks that may be associated with this type of work have been previously reviewed and we have used key previous reviews by Eide (1990) and IPIECA/OGA (2009) as the starting point for this evaluation. This review addresses exposure by inhalation or skin contact to drilling fluids and the scope is restricted to chemical (including mineral) agents. Drilling fluids contain pesticides to prevent microbial growth and we found no published evidence to suggest that significant exposure to microbial organisms or products results from the use of drilling fluids.

Eide (1990) reviewed the published literature and investigations initiated by Norwegian oil companies and governmental institutions, on the possible health effects of oil-based drilling fluids after inhalation of aerosol and vapour. These health effects included nervous system toxicity, nephropathy, carcinogenicity and pulmonary fibrosis. Respiratory (or ocular) irritation was not considered. Eide's toxicological evaluation primarily dealt with aliphatic and napthenic hydrocarbons in the C_9-C_{15} range. He concluded that reported workplace exposures to oil-based drilling fluids were far below the concentrations of hydrocarbons reported to produce central nervous system depression and neurotoxic effects. The role that the vapour and aerosol could play as potential co-carcinogens or tumour promoters in the lungs, needed further consideration. Eide also recommended further investigation of the potential of drilling fluids to cause pulmonary fibrosis and indicated that, when evaluating effects in the lungs, it was important to determine whether aerosol is 'generated by condensation from vapour or by mechanical means'. Since 1990, there has been a greatly increased recognition of the role of repeated or severe respiratory irritation in giving rise to serious chronic respiratory illness including Reactive Airways Dysfunction Syndrome (a form of occupational asthma). Whereas in the past occupational exposure limits (OELs) for irritant substances would have been set to prevent "severe irritation", limits should now be set to prevent any irritation.

Dermal exposure was not considered within the scope of Eide's original review. The IPIECA/OGA (2009) guidance is a useful starting point when considering the issues around dermal exposure to drilling fluids, with skin irritation and contact dermatitis being the most frequently reported. The symptoms and seriousness of contact dermatitis vary and are dependent on the type and length of exposure to drilling fluid and the susceptibility of the individual. Skin irritation can be associated with petroleum hydrocarbons, specifically with aromatics and C_8-C_{14} paraffins. In addition to the irritancy of the drilling fluid hydrocarbon constituents, several drilling fluid additives may have irritant (eg calcium chloride), corrosive (zinc bromide) or sensitizing (eg polyamine emulsifier) properties. Water-based fluids also contain additives that may cause irritation or dermatitis. Excessive exposure under conditions of poor personal hygiene may lead to oil acne and folliculitis. Chronic irritation may cause small areas of the skin to thicken, eventually forming rough wart-like growths which may become malignant. In addition, repeated exposure to aqueous fluids may give rise to "wet hand" dermatitis, in the absence of any specific dermal irritants.

Eide (1990) focussed primarily on C_9-C_{15} aliphatic and naphthalenic hydrocarbons. It is likely that the composition and range of drilling fluids available have changed since the publication of Eide (1990) and that exposure conditions during drilling operations have changed due to the use

of different fluids and improved control measures. In addition, dermal exposure was not addressed in this earlier review, which is of real concern to the industry and those working with drilling fluids. Finally, Eide's review did not extend to an evaluation of the small number of epidemiological studies involving drilling fluid operators.

2 AIMS AND SCOPE OF REVIEW

A toxicological review was undertaken with the primary aim of updating the Eide (1990) review of the health effects from exposure to oil-based drilling fluids after inhalation of aerosol and vapour, with an additional evaluation of the potential effects to the skin and exposure conditions related to water and oil-based drilling fluids.

Consideration was given to the likely extent of systemic absorption following dermal exposure and the potential role of particle size (aerosols) in determining any adverse health effects, although there is little published information on particle size effects.

The toxicity review took into account the concentration of individual components in fluids and the potential influence of different components in determining the toxicity of the mixture, although there are very few data that describe how the toxicity of individual substances may be modified by the presence of other substances in a mixture.

This review was sponsored by Statoil, who provided relevant information about the drilling fluids and base oils currently in use by their organisation. Both Statoil and IOM are of the opinion that these fluids and base oils are representative of those used within the industry and as such the information provided in this report is more widely applicable.

3 METHODOLOGY

Based on information provided by Statoil (Appendix 1) and information available in the IPIECA/OGA (2009) guidance document on drilling fluid and base oil compositions, a review of the toxicity information available for the key components as individual substances or groups of closely related substances (as appropriate) was carried out.

Toxicity information was obtained from standard information sources including:

- International Programme for Chemical Safety (www.inchem.org);
- US Environmental Protection Agency Integrated Risk Information System (www.epa.gov/iris);
- US Agency for Toxic Substances and Disease Registry (www.cdc.gov/atsdr)
- US National Institute of Occupational Safety and Health (NIOSH) Registry of Toxic Effects of Chemical Substances (RTECS);
- OEL criteria documents published by the American Conference of Governmental Industrial Hygienists (ACGIH, 2005), the Nordic Expert Group, the UK Health and Safety Executive (HSE, 2002) and other organisations;
- The GESTIS database of International workplace exposure limits[1];
- Pubmed (www.ncbi.nlm.nih.gov/pubmed); and
- In addition, Google was also used to identify additional published reviews by regulatory authorities and others that would otherwise be missed.

Where appropriate, substance identification and definition (eg "kerosene") was confirmed using the European Inventory of Chemical Substances[2]. International Uniform Chemical Information Database (IUCLID) chemical data sheets containing toxicological summaries were also obtained from the European Inventory.

In the absence of substance specific information for some components, toxic effects and potency were inferred from information available for similar/related substances.

Summaries of the key findings of relevant published studies were made. It was not intended to make a detailed assessment of the quality and reliability of each available toxicity study for each component. In instances were conflicting data were available, judgements were made about the likely reliability of data from different sources. These judgements were based on the nature and age of the data source, any available information about the study protocol and the consistency of findings with those of other studies. Where information was only available in RTECS and the source references given in RTECS were not easily retrievable (eg published in Russian, 30 years ago), the information was considered to be much less reliable than that available in the accessible published literature.

[1] http://bgia-online.hvbg.de/LIMITVALUE/WebForm_gw.aspx - database hosted by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA)
[2] http://ecb.jrc.ec.europa.eu/esis/index.php?PGM=ein&DEPUIS=autre

4 EXPOSURE TO DRILLING FLUIDS

The purpose of drilling fluids is to remove cuttings, cooling and lubricating the drill bit, maintaining a pressure in the borehole to reduce the influx of crude oil or gas, and to carry various chemicals down the borehole to improve the drilling process. During drilling, a large volume of drilling fluid is circulated in an open or semi-enclosed system, at elevated temperatures, with agitation, providing a significant potential for chemical exposure.

Workers are typically exposed to drilling fluids by inhalation and skin contact, with skin contact being potentially important in governing overall exposure levels to some components of the mix. The IPIECA/OGA (2009) guidance provides an excellent overview of the likely exposure types and durations associated with tasks encountered in a typical drilling operation, as well as influencing factors. In summary, exposure to drilling fluids can occur in the:

- Shaker house, e.g. during sampling, maintenance and inspection/monitoring tasks.
- Mix area, e.g., when introducing solid and liquid chemicals into the drilling system as well as through handling packaging.
- Sack store, e.g., during storage, manual / mechanical handling of chemical additives.
- Mud pits, e.g., during manual / automated pit cleaning.
- Drill floor, e.g., during pipe handling and cleaning.
- Desk operations, e.g., cuttings handling and treatment.

The nature of exposure (both skin and inhalation) encountered in each of the identified drilling operation steps varies due to the nature of the work, as does the duration of exposure. For example, whilst tasks in the sack store tend to be short-term and intermittent in nature, many tasks in other drilling operations are very frequent (e.g. every 15 minutes or less) such as sampling, maintenance and inspection in the shaker house. In addition there are tasks which are carried out continuously, such as those in deck operations and several of those tasks undertaken in the mud pits operation.

Broni-Bediako and Amorin (2010) carried out a literature review on the major areas of drilling fluid exposure in the oil and gas industry. The workers with a highest potential for exposure (dermal and inhalation) fell into the following categories:

- The derrickman: responsible for mixing and adding chemicals to the drilling fluid;
- Mud engineer: responsible for checking the mud conditions;
- Roughneck: responsible for the pipe connections and general housekeeping;
- Deep sea diver: make contact with discarded cuttings on the sea bed during operations;
- Laboratory supervisor: responsible for maintaining the conditions of the mud and;
- Motor man: responsible for general maintenance of all engines.

The following drilling operation areas were identified during Broni-Bediako and Amorin's review as having higher potential for exposure:

- Shale shaker house: for example, during washing the shale shaker, collection of samples and handling contaminated equipment;
- Drilling floor: during handling pipes and spills from drilling operations;
- Mud pit system: through chemical mix splashes;
- Sack room: exposure from handling powder additives (barium sulphate) and;
- Laundry: exposure from handling contaminated clothes.

It was noted that the publicly available literature on occupational exposure levels for this working environment was scarce, despite offshore oil companies measuring exposures on numerous occasions (Steinsvåg *et al*, 2006). Those exposure measurements which have been reported centre mainly around oil mist and vapours.

Personal exposure to total hydrocarbon compounds has been reported to be up to 450 mgm^{-3} for tasks relying on general atmospheric ventilation (when drilling with oil-based fluids), with static measurements reported to be up to 2,400 mgm^{-3} in the shale shaker area and up to 3,200 mgm^{-3} in the mud tank area (Davidson *et al*, 1988). Personal exposures of up to 200 mgm^{-3} were also reported on the drill floor (Davidson *et al*, 1988). Eide (1990) also reported personal time weighted average (TWA) exposures to total hydrocarbons (aerosols and vapour) of up to 300 mgm^{-3} during oil-based drilling fluid work in the mud-handling areas and on the drill floor, with the highest exposures again being observed at the shale-shakers. It was also noted that on installations where control measures were in place, personal exposures to total hydrocarbons were less than 100 mgm^{-3}. For example, James *et al*, (2000) reported airborne oil mist concentrations ranging from 0.03 – 5.52 mgm^{-3} and hydrocarbon vapour concentrations ranging from 3.2 – 96.4 mgm^{-3} in a shaker house where the shakers were enclosed by a ventilation canopy and the other parts of the system including the fluid flow lines, cuttings ditch and shaker trough were covered or part-covered. (James *et al,* also reports results from two personal samples to be 0.06 and 0.40 mgm^{-3} for oils mists and 3.2 and 35.0 mgm^{-3} for oil vapour). Oil vapour TWA personal measurements of 11 mgm^{-3} were reported by Simpson and Keen (2007) in a shaker house where the ventilation rate was reported to be exceptionally high. They also report TWA measurements of 110 mgm^{-3} and 22.5 mgm^{-3} where some form of local exhaust ventilation (LEV) was present on both the shale shakers and mud pits and the mud pits were 90% covered and exposure levels ranging from 101-295 mgm^{-3} where the shakers and mud pit were outdoors, with no LEV, therefore ventilation was dependent upon prevailing weather conditions. Simpson and Keen (2007) also report one real time personal profile which had peak vapour exposures that were approximately twice the average concentration (approximately 30 ppm), with the highest single peak being ~1-07 ppm.

Steinsvåg *et al* (2006) summarized oil mist and vapour exposures from personal samples collected in the Norwegian offshore industry between 1979 and 2004. They showed decreasing levels of exposure for both vapour and mist during this period, with geometric mean concentrations in 2004 being less than 10 mgm^{-3} for vapour and less than 1 mgm^{-3} for mist.

With respect to measurements of other occupational exposures, Hansen *et al* (1991) investigated the elemental composition of airborne dust in a shale shaker room. The drilling operation (approximately 5,000 m) used a water-based alkaline drilling fluid containing mainly barite (BaSO4) and minor amounts of other additives such as chrome lignosulphate and chrome lignates, with the slurry pH being adjusted through the use of sodium carbonate. It was reported that no direct source of hydrocarbon emissions were present. Total airborne dusts levels ranged from 0.06 - 0.16 mgm^{-3} in the working area where operators analyzed mud samples; 0.04 - 3.22 mgm^{-3} at the mud cleaners (with the high concentration thought to be due to splashes of mud) and 0.9 – 1.41 mgm^{-3} at the shale shakers. It was evident that the concentrations of dust was relatively constant at the shale shakers and were lower at the mud cleaners and analyzing station. The elemental composition of the dust particles collected at the mud cleaners and shale shakers showed highest amounts of barium (equivalent to 0.4-0.5 mgm^{-3} barium sulphate), silicon and sulphur. It was concluded that barium sulphate, the main constituent of the drilling mud, was probably the major source of dust in the room.

No published literature were identified which explicitly detailed the collection and reporting of occupational exposure measurements aimed at assessing dermal exposure to drilling fluids.

5 COMPOSITION OF DRILLING FLUIDS

Drilling fluid compositions can be divided into oil-based and water-based but there is a wide range of variability in composition within each of these categories.

Typically the oil-based systems are based on petroleum distillate, kerosene or synthetic mixes of C_5-C_{20} paraffins. Other substances that may be present include inorganic salts such as sodium, calcium or potassium carbonate or bicarbonate or calcium chloride, sodium, potassium or caesium formate, emulsifers, titanium dioxide (TiO_2), crystalline silica, thickeners, surfactants, small quantities of strong bases such as lime, sodium hydroxide or potassium hydroxide.

The water-based systems show an even wider variability in composition. They typically contain metal salts and may contain natural (eg bentonite) or artificial (eg PEG) thickeners, barium sulphate and other mineral phases. They may contain preservatives and biocides such as glutaraldehyde used to prevent microbial growth and the associated development of biofilm on surfaces in contact with the fluids.

The drilling fluids components which were considered further in the subsequent chapters of this toxicological review are listed in Table 1. These represent all the named substances included on the datasheets provided by Statoil.

The presence of substances within a mixture is likely to lead to modification of their toxicity following exposure by inhalation or skin contact. The toxicity of the mixture may be more or less than the sum of the components as some components may increase sensitivity to other components. Alternatively, if several components act through a similar mechanism, a given set of receptors or enzymes in the body may become saturated (see section 13).

Table 1: Drilling fluids components considered in toxicological review

Components	Examples
Petroleum distillates and kerosene	Hydrocarbons having carbon numbers predominantly in the range of C_9 through C_{16} and boiling in the range of approximately 150°C to 290°C (302°F to 554°F).
Water	
Compounds of alkalis and alkali earth metals	Calcium oxide and calcium hydroxide, calcium chloride and calcium hydroxide, sodium hydroxide, potassium hydroxide
Formic salts of alkali and alkali earth metals	Sodium carbonate, potassium carbonate, calcium carbonate, sodium bicarbonate, potassium bicarbonate, sodium silicate, barium sulphate
Other minerals	Bentonite, organic clay, kaolin, crystalline silica, titanium dioxide
Solvents, emulsifers and detergents	Quaternary ammonium salts, 2-(2-butoxyethoxy)ethanol
Thickening agents	(Bentonite, organic clay), polyalkylene glycols, polyalkylene glycol ethers, polyamide, polyanionic cellulose polymer, starch, colloidal cellulose, xanthium gum
Biocides	Gluteraldehyde, citric acid, quaternary ammonium salts

6 PETROLEUM DISTILLATES AND KEROSENE

6.1 SUBSTANCE

The drilling fluid information provided in Appendix 1 indicates that petroleum distillates (CAS no: 8002-05-9) comprise between 20 and 60% of some drilling fluid compositions. Kerosene is also used in combination with other petroleum distillates and one of the formulations used by Statoil includes slightly lighter paraffins (C_5-C_{20}). The petroleum distillates in most formulations are hydrogen treated which should have the effect of reducing their aromatic content, although it is uncertain whether distillates are always hydro-treated.

Hydrotreated light petroleum distillates (CAS no: 64742-47-8) are described in the European Inventory (EINECS) as a complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon numbers predominantly in the range of C_9 through C_{16} and boiling in the range of approximately 150°C to 290°C (302°F to 554°F).

Kerosene (CAS no: 8008-20-6) is described as a complex combination of hydrocarbons produced by the distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of C_9 through C_{16} and boiling in the range of approximately 150°C to 290°C (302°F to 554°F).

The exact nature of distillate used in different oil drilling fluid formulations is likely to be variable depending on the source of the crude oil, the exact fraction collected during distillation and the subsequent treatment of the distillate. It is not clear how much variation in distillate composition may exist between different batches of drilling fluid provided by individual suppliers.

Airborne exposures to these substances will involve possible inhalation of both aerosols and vapours. The health effects associated with each fraction are likely to differ although there are few data on which to assess the relative importance of aerosol versus vapour in terms of potential impact on health. The partitioning between droplets and vapour will vary by substance and environment. The health effects of aerosols will be partly dependent on particle size distribution (PSD) but there are no data describing the relationship between particle size and potential health effects that are specific to oil mist.

There has been only limited investigation of the toxicity of "oil drilling fluids" as such and there are no peer-reviewed studies available. One unpublished in-vivo inhalation study was undertaken involving an oil-based drilling fluid over 20 years ago (see section 6.3.1); there have been no studies of dermal effects. There have been several inhalation and dermal in-vivo studies involving various petroleum fractions (sections 6.3.1 and 6.4) but it is unclear how similar these substances are to those used in drilling fluids.

There are limited human data (section 6.5) describing the effects of exposure to petroleum distillates, including kerosene and other fractions such as white spirit that comprises a mixture of more volatile paraffins (C_5 to C_{13}). Human exposure to these petroleum distillates or kerosene is typically combined with exposure to other substances that may or may not be harmful to human health. It is difficult to separate the role of petroleum distillates or kerosene in giving rise to adverse effects as opposed to effects arising from concurrent co-exposure to other workplace contaminants. In addition, exposure to petroleum distillates/modified petroleum distillates may modify or enhance the toxic effects of other substances present in the mix (see discussion of mixtures below). There has been very little investigation of the health of workers exposed to

petroleum drilling fluids and most of the human health information is from studies of workers exposed to oil mist associated with metal working fluids and workers exposed to white spirits and kerosene and other fuels.

6.2 TOXICOKINETICS

6.2.1 Overview

Factors affecting uptake and absorption of hydrocarbons and distribution in body tissues including the brain include their aqueous and lipid solubility.

6.2.2 Inhalation

SINTEF (1984) reported that inhaled aliphatic and aromatic compounds penetrate the alveolar membrane but aromatic compounds are more readily absorbed into the bloodstream. This is attributed to their greater water solubility. The absorption of aliphatic compounds is limited by their water solubility which reduces with increasing chain length. The absorption of both aromatic and aliphatic compounds is greatly increased during exercise, although the relative increase in absorption is much greater for aromatic compounds. The absorption of aromatic compounds is also much greater than that of aliphatic compounds following ingestion.

Nilsen et al (1988) exposed rats to concentrations of n-C_9 to n-C_{13} alkanes that were close to air saturation at 20^{o}C (4438, 1369, 442, 142 and 41 ppm respectively) and to variable concentrations of C_9 alkanes for 8 hours. The concentration of alkane in the brain after exposure exceeded that of blood for the lower alkanes, while the higher alkanes possessed a brain/blood ratio equal to or less than unity. The uptake of the n-nonane by the brain was observed to be significantly greatly than for the other test substances consistent with the findings of later studies described below.

A series of later experiments investigated the uptake and distribution of different types of C_9-C_{16} compounds. It is important to note, however, that the fraction of aromatic compounds such as naphthalene in modern drilling fluid compositions would normally be very small. Zahlsen et al (1990) measured concentrations of the C_9 hydrocarbons n-nonane, 1,2,4-trimethylbenzene (TMB) and 1,2,4-trimethylcyclohexane (TMCH) in rat blood, brain and perirenal fat after 12 hour exposures to 1000 ppm of the individual compounds following exposure for 1, 3, 7, 10 and 14 days. The relative concentration of nonane in the brain was greater than those of 1,2,4 TMB or 1,2,4-TMCH whereas in blood, concentrations of 1,2,3 TMB and nonane were similar and greater than 1,2,4 TMCH and in perirenal fat, concentrations of 1,2,4 TMB were greater than n-nonane which were greater than those of 1,2,3 TMCH. Brain/blood ratios of 11.4, 2.0 and 11.4, and fat/blood ratios of 113, 63 and 135 were found for n-nonane, 1,2,4 TMB and 1,2,4 TMCH respectively. A marked decrease in biological concentrations of 1,2,4 TMB and 1,2,4 TMCH during the initial phase of exposure was interpreted to indicate that these hydrocarbons are capable of inducing their own metabolic conversion resulting in lower steady state levels.

Zahlsen et al (1992) exposed rats to C_6 to C_{10} n-alkanes, aromates and naphthenes at concentrations of 100 ppm for 12 hours/day for 3 days. Their results indicated the presence of high concentrations of aromatic hydrocarbons in blood but low concentrations in organs and fat and a decrease in fat concentrations throughout the exposure period suggesting a higher rate of metabolic elimination than for the other hydrocarbons. Naphthenic hydrocarbons were present at low concentrations in blood but at high concentrations in organs, including the brain, and fat, but did not accumulate in fat over the exposure period because of their rapid elimination. The n-alkanes were present at very low concentrations in blood and relatively high concentrations in the brain and showed a potential to accumulate in fat with repeated exposures. In general, the

tissue concentrations of hydrocarbons within one class increased with increasing molecular weight although the concentrations of aromatics in blood decreased from benzene (C_6) to o-xylene (C_8) and then increased towards t-butylbenzene (C_{10}). The authors suggested that this may reflect a gradual decrease in water solubility being offset by an increased affinity to blood lipids. The pattern of uptake of C_6-C_9 naphthenes in the brain appeared unrelated to their relative solubility in blood and only indirectly related to lipid solubility. The authors concluded that the accumulation of different classes of C_6-C_{10} hydrocarbon in tissue is influenced by differences in metabolism and enzyme induction potential as well as lipid solubility.

Zahlsen et al (1993) exposed rats to C_8 and C_{10} 1-alkenes and iso-alkanes at concentrations of 100 ppm for 12 hours/day for 3 days. The uptake of the 1-alkenes in blood and accumulation in organs was considerably greater than for the iso-alkanes and the concentration of 1-alkenes and iso-alkanes in blood, brain, liver and fat increased with increasing number of carbon atoms. The C_9 and C_{10} 1-alkenes and iso-alkanes accumulated in fat during the exposure period and high concentrations 12 hr after cessation of exposure.

Eide and Zahlsen (1996) exposed rats for 12 hours to synthetic mixtures of three C_9 n-paraffinic, naphthenic and aromatic hydrocarbons (n-nonane, TMCH and TMB, respectively) at concentrations of 75, 150, 300 and 450 ppm. In general the blood concentrations or body fat of aromatic compounds were 3-4 times higher for a given concentration in air than paraffins or naphthalene which showed similar levels of uptake, whereas the concentration in brain tissue was fairly similar for all three types of compound. The uptake of aromatic compounds and paraffins by the liver was fairly similar and slightly greater than that of naphthalene whereas the uptake of naphthalene and paraffin by the kidneys was fairly similar and less than that of aromatic compounds.

Mortensen et al (2000) investigated the in vitro rates of metabolism for 25 different C_6 to C_{10} hydrocarbons using rat liver slices in a vial head-space equilibration system. The rates of metabolism were compared with steady-state levels obtained in vivo in the same strains of rats after inhalation. Aromates were metabolized at a higher rate than naphthenes n-alkanes, isoalkanes and 1-alkenes. The aromates showed, in contrast to the other hydrocarbons investigated, increased metabolism with increasing number of carbon atoms up to C_8 (o-xylene, the most extensively metabolized compound). The in vivo steady-state concentrations of the aromates in blood were inversely related to the in vitro efficiency of their metabolism, consistent with the pattern of blood levels observed for the C_6 to C_{10} aromates in the rat after inhalation, with o-xylene demonstrating the lowest concentration. The authors speculated that the extent of tissue metabolism of the investigated hydrocarbons might be of greater importance for their body distribution than their lipophilicity, especially for the highly metabolized compounds.

Overall, it is clear that inhaled C_9-C_{16} hydrocarbons are readily absorbed but have different metabolic fates and distribute differently between blood, the brain and other organs. Aromatic compounds are more readily metabolised than alkanes or naphthenes and less likely to accumulate in fat but are likely to accumulate in the brain. Alkanes are present at low levels in blood but are likely to accumulate in fat and in the brain. 1-Alkenes are more readily absorbed than alkanes and are found at higher concentrations in the brain and other organs. The different metabolic fates and distribution of different types of compound is likely to have an important influence on toxicological effect. The oils currently used in drilling fluids are dominantly composed of alkanes with only trace quantities of aromatic compounds, naphthenes or alkenes.

6.2.3 Uptake and absorption through the skin

Organic solvents penetrate the skin barrier and uptake is limited by the extent of dissolution in underlying tissues and blood. In a review prepared for CONCAWE, Kezic et al (2010) reported that studies on the dermal absorption of individual hydrocarbons in petroleum products have shown a reduction in absorption with increasing lipophilicity and molecular weight. This is reflected in the greater reported dermal absorption of aromatics (e.g. toluene, xylene, trimethylbenzene, naphthalene) than that of aliphatics (decane, dodecane, tridecane and hexadecane). Similarly the dermal absorption of the long chain aliphatics (e.g. tetradecane, pentadecane) is less than that of shorter chain aliphatics. However, volatile hydrocarbons (such as aromatics) evaporate from the skin leading to a reduction in dermal exposure and uptake. The dermal absorption of vapours can be considered negligible, as dermal uptake will be much lower than respiratory uptake at identical air concentrations. In a much earlier review, SINTEF (1984) reported that the penetration rate of organic solvents increases with increasing water solubility. In a specific study of kerosene, Koschier (1999) reported that kerosine range mid distillates are rapidly absorbed through the skin, but absorption is limited to approximately 10-15% of the applied dose after 24 hours (Koschier, 1999).

Kezik et al (2010) highlighted the potential for repeated skin contact with petroleum products to cause skin damage, reducing the effectiveness of its barrier function, leading to an enhanced uptake of hydrocarbons.

6.3 ANIMAL TOXICITY DATA: INHALATION EXPOSURE

6.3.1 Respiratory toxicity

The results of animal inhalation studies suggest that C_9-C_{16} oil aerosols and vapours typically have relatively low toxicities, although shorter chain hydrocarbons (such as white spirit; C_5-C_{13}) and other solvents may be associated with respiratory irritation. Exposure of rats to white spirit for 4 hours on 4 days at 214 mgm^{-3} was reported to give rise to irritation of the respiratory tract and exposure of 5 species to $\geq$ 363 mgm^{-3} continuously over 90 days gave rise to increased mortality and irritation of the lung with the guinea pig being the most sensitive of the test species (IPCS, 1996). SINTEF (1984) reported that respiratory tract irritation increases with increasing chain length for alkanes C_5-C_8 as hydrophobicity increases and vapour pressure decreases, leading to a slow removal of these compounds from the airways.

The inhalation studies summarised in the IUCLID chemical data sheet for hydrotreated light petroleum distillates (CAS no: 64742-47-8) indicate a relatively low toxicity. Exposure of rats for 6 hours per day, 5 days per week to a concentration of 24 mgm^{-3} (vapour) for 4 weeks did not cause any adverse effects. In a 13 week study in which rats were exposed 6 hours/day, 5 days/week, the lowest adverse effects level was 100 mgm^{-3}, which was associated with some minor haematological effects. The IUCLID chemical data sheet for kerosene does not provide any information on the effects of repeated exposure to kerosene but does indicate that the median lethal concentration for a four hour inhalation exposure is >5280 mgm^{-3} indicating a relatively low level of acute toxicity.

An unpublished 90 day inhalation study sponsored by Statoil (Huntingdon Research Centre, 1988) exposed groups of rats (20 male and 20 female per group) to “unweighted drilling fluid” which was described as “brown emulsified oil”. The four exposure groups were exposed to vapour concentrations of 0, 18, 50 and 125 mgm^{-3} respectively and it was established that the exposure chambers were virtually free of aerosol. No treatment related effects were observed on clinical signs, bodyweight, food consumption and eye defects. Small haematological differences and differences in blood biochemistry were observed between exposed and control group

animals but, with the exception of a slight lowering of sodium levels in the intermediate and high dose groups, these were unrelated to dose. None of these effects was considered to be toxicologically significant. An increase in the incidence of hydronephrosis of the kidney was observed in high dose male rats at the end of exposure and at the end of the recovery period. These lesions were also present in the control, low and intermediate groups, albeit at lower incidence and it was concluded that the incidence was more likely to be spontaneous than treatment related.

Dalbey et al (1991) exposed rats to aerosols of three base oils used to formulate lubricating oils: a solvent-refined oil (SRO), a hydrotreated and acid-washed white oil (WTO) and a severely hydrotreated and hydrocracked oil (HBO). Exposures were for 6 hours per day, 5 days per week for 4 weeks at concentrations of about 0, 50, 210 and 1000 mgm^{-3} with a mass median aerodynamic diameter (MMAD) of about 1µm. The only treatment-related changes were observed in the lung and associated lymph nodes. Lungs showed a concentration dependent increase in wet weight and dry/wet weight ratio that was associated with accumulations of foamy alveolar macrophages, particularly in alveoli close to alveolar ducts. Mild infiltration by neutrophils was observed with WTO and SRO and thickened alveolar walls were noted with the highest concentration of HBO. In a 13 week study, Dalbey (2001) exposed rats, 6 hours/day, 5 days/week to aerosols of generic cutting oil, generic gear oil and generic commercial engine oil at concentrations of 0 and approximately 50, 150, or 400-520 mgm^{-3}. The main effects were the accumulation of foamy macrophages in pulmonary alveoli and alveolar walls, very mild thickening of alveolar walls due to foamy macrophages and a mixed cell infiltrate, and subtle epithelial hyperplasia in the lung. The foamy macrophages tended to group together in aggregates giving rise to visible plaques on the surface of the lung. These histological changes were accompanied by concentration-related increases in lung weight and pulmonary hydroxyproline, whereas pulmonary function tests were generally unaffected.

Skyberg et al (1990) exposed rats to mist and vapour of two mineral oils at aerosol concentrations of 70 mgm^{-3} and 700 mgm^{-3} for 2 weeks. Elevated numbers of pulmonary macrophages and increased macrophage vacuolization were observed. Deposition analysis for one of the oils showed an absence of oil in the brain whereas retroperitoneal fat tissue contained 541 (401-702) µg oil/g tissue of which half remained 2 weeks after the end of exposure. Stula and Kwon (1978) exposed dogs, rats, mice, and gerbils for 6 hours/day, 5 days/week, for up to 2 years, to a complex mineral oil-base mist at concentrations of 5 and 100 mgm^{-3} with a MMAD of approximately 1.0 µm and the test atmospheres also contained 1000 ppm acetone. Evidence of oil mist was detectable within lung macrophages of all species tested and at both concentrations. Dogs and rats exposed to 100 mgm^{-3} developed oil microgranulomas. Rats exposed for 12 months and allowed to recover for 10 months did not completely recover from the oil microgranuloma. Robledo et al (2000) exposed mice to JP-8 jet fuel aerosol for 1 hour/day for 7 days and reported increases in respiratory permeability paralleled by markers of cell injury at concentrations of 48 and 118 mgm^{-3}. Effects on bronchiolar epithelium included perivascular oedema, Clara cell vacuolization, and necrosis. Alveolar injury included sporadic pulmonary oedema, intra-alveolar haemorrhage, and alterations in type II epithelial cells. Herrin et al (2006) exposed mice to JP-8 jet fuel at average concentrations of 45, 267, and 406 mgm^{-3} for 1 hour/day for 7 days. No significant effects on respiratory function were observed at 45 or 267 mgm^{-3} and the only significant effect observed at 406 mgm^{-3} was a decrease in inspiratory dynamic lung compliance. Alveolar type II epithelial cells showed limited damage other than evidence of increased surfactant production, at 45 and 406 mgm^{-3} and there was some insignificant damage to the terminal bronchial epithelium.

In a review of the respiratory toxicity of mineral oils, Dalbey and Biles (2003) reported that subchronic exposures to aerosols of mineral base oils at concentrations >100 mgm^{-3} give rise concentration-dependent accumulations in the lung of alveolar macrophages laden with oil

droplets. The lowest reported effects levels were 50 mgm^{-3} for engine oil and 60 mgm^{-3} for gear oil. Higher aerosol concentrations were associated with increased numbers of inflammatory cells. These pulmonary changes were interpreted as a nonspecific response to the presence of deposited aerosol. Dalbey and Biles did not consider these as adverse effects and that the no adverse effects levels for oil aerosols were likely to be in the range 50-150 mgm^{-3} for a 13 week exposure (daily duration not stated, assumed to be 6 hours on basis of standard practice). They noted that additives in some formulated products and/or maintenance of mineral-based metalworking fluids may play a much more significant role in potential health effects.

Overall, exposure of animals to a mineral oil composed of simple C_9-C_{16} alkanes does not appear to give rise to adverse respiratory effects at exposure levels equivalent to exposure for 4 weeks for 30 hours/week to a concentration of 24 mgm^{-3}. It is possible that longer term exposure to this concentration or exposure for more than 6 hours/day might give rise to adverse effects. At higher concentrations, mild adverse effects may occur including the accumulation of oil-laden cells in the lung. The presence of other substances in oil is likely to have a substantial impact on toxicity.

6.3.2 Neurotoxicity

Extremely high levels of exposure to C_9-C_{16} hydrocarbons have been shown to cause neurotoxicity in animals. Nilsen et al (1988) reported gross ataxia, general and focal seizure and spasms in rats exposed to n-C_9 at concentrations of 3,560-5,280 ppm combined with severe cerebellar damage in animals that survived exposure to 4,438 ppm. No toxic effects were observed in animals exposed to 2,414 ppm of n-C_9 or to the nC_{10}-C_{13} alkanes. Studies reviewed by the IPCS (1996) indicate that high levels of exposure to white spirit (C_5-C_{13}) are associated with neurotoxicity in rats (Table 2).

Table 2: Studies in which rats were exposed to white spirits reviewed by IPCS (1996)

Inhalation exposure	Effects
4,800 mgm^{-3}, 8 hours/day, 26 weeks	Reduced nerve conduction velocity in the tail axon
2,290 and 4,580 mgm^{-3}, 6 h daily, for 3 weeks or 6 months	Changes in brain chemistry, no effects in neurobehavioural tests
6-month exposure to either 2,339 or 4,679 mgm^{-3} (400 or 800 ppm) of dearomatized white spirit	Changes in sensory evoked potentials in brain of rat detected 2 months after end of exposure

Myhre and Fonnum (2001) investigated the effects of C_7 and C_9 aliphatic (n-heptane, n-nonane), naphthenic (methylcyclohexane, TMCH) and aromatic (toluene, TMB) hydrocarbons on the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in rat brain synaptosome fraction. The generation of ROS and RNS in the brain may be an important factor leading to neurotoxic effects. Their results suggest that the naphthenic hydrocarbon TMCH showed the strongest potential for ROS and RNS formation in rat brain synaptosomes, followed by TMB, toluene, n-nonane, n-heptane, and methylcyclohexane, respectively.

The CNS effects of solvent exposure are thought to result from the incorporation of solvent molecules in the lipid membranes in nerve cells and subsequent effects on ion transport (SINTEF, 1984). The narcotic effects of the C_5-C_9 n-alkanes increases with increasing chain length due to increasing lipophilicity. Although the C_{10}-C_{15} alkanes may have a greater narcotic potential, this is offset by a greatly reduced uptake by inhalation because increasing of hydrophobicity (SINTEF, 1984).

6.3.3 Haematological effects

Inhalation of decane at a concentration of 540 ppm for 18 hours/day, 7 days/week for 123 days caused an increase in body weight and a reduced lymphocyte blood count in rats (SINTEF, 1984). The IUCLID chemical data sheet for kerosene indicates some haematological effects were detected in rats exposed to 100 mgm^{-3} in a four-week study.

6.4 TOXICITY IN ANIMALS FOLLOWING DERMAL EXPOSURE

6.4.1 Skin irritation

Kerosenes are known to cause skin irritation and inflammation under conditions of acute and repeated exposure but are not skin sensitizers (Koschier, 1999). The IUCLID chemical data sheet for hydrotreated light petroleum distillates (CAS no: 64742-47-8) indicates that in rabbits exposed 3 times a week for 4 weeks, significant reddening and swelling was observed at the application sites. The IUCLID chemical data sheet for kerosene indicates that reddening and swelling was associated with dermal exposure to 200 mg/kg/day in a 28 day study in rabbits. SINTEF (1984) reported that one study demonstrated that skin irritancy in rabbits increased in the order $C_{11}<C_{12}<C_{17}<C_{13}<C_{14}$ whereas another study reported that the skin irritancy of alkanes reduces with increasing chain length. Another study reported a maximum dermal toxicity with C_{14}-C_{19} alkanes with a transition to no dermal toxicity around C_{21}-C_{23} that might reflect a decreasing rate of skin penetration as chain length and molecular size increase. Other data suggests however that for smaller molecules, the severity of skin lesions increases for solvents of low water solubility and lower penetration. In a more recent study in hairless rats, Babu et al (2004) demonstrated that the potential for longer chain alkanes to cause dermal irritation appeared to reduce with increasing chain length with nonane>dodecane> tetradecane. Despite the uncertainty as to the relative importance of different compounds in causing irritation, however, there is no uncertainty that dermal contact with petroleum distillates, kerosene and similar fluids will give rise to skin irritation.

6.4.2 Systemic toxicity

The IUCLID chemical data sheet for hydrotreated light petroleum distillates (CAS no: 64742-47-8) indicates that dermal exposure of rabbits to 2000 mg/kg/day administered as 3 dose/ week for 4 weeks was associated with liver lesions and the no effects level was equivalent to 1000 mg/kg/day. The IUCLID chemical data sheet for kerosene indicates there was a significant increase in spleen weights in female rabbits exposed to dermal doses ≥200 mg/kg/day for 28 days and a significant increase in heart weights in male and female exposed to ≥1,000 mg/kg/day. At a dose of 2,000 mg/kg/day, animals showed a reduction in body weights, liver lesions and effects on bone marrow. Some treatment-related deaths occurred.

In a study of 13 refinery products, Feuston et al (1994) reported that toxicity in rats was correlated with concentrations of PAHs composed of 3, 4, 5, 6, and/or 7 rings. Effects included decreased thymus weight, increased liver weight and abnormal haematology and serum chemistry.

Upreti et al (1989) reported that exposure of male mice to kerosene by wrapping each of their hind feet with a muslin cloth wetted with kerosene for 15 to 60 minutes/day for 7 consecutive days led to histological changes in the foot pad skin and popliteal lymph nodes and systemic effects including abnormal haematology, significant decreases in relative weight of thymus, spleen and abdominal lymph nodes and altered histology.

6.4.3 Reproductive toxicity

Schreiner et al (1997) investigated the reproductive and dermal toxicity of diluted hydrodesulfurized kerosene (HDS kerosene) in female rats exposed for 7 weeks (premating, mating to day 19 of gestation) and male rats exposed for 8 weeks. Slight to moderate skin irritation was observed at the highest dose in both sexes but no apparent maternal, reproductive, or developmental toxicity. The NOAEL for HDS kerosene for reproductive and developmental toxicity in rats was reported as 494 mg/kg/day. Feuston et al (1994) reported an increased incidence of embryo resorption, and decreased foetal body weight in rats exposed to petroleum distillates.

6.4.4 Carcinogenicity

A large number of studies have investigated the carcinogenicity of different petroleum derived fractions following dermal exposure. The PAH content of petroleum derivatives is generally correlated with mutagenicity in bacterial tests of genotoxicity and has an important influence on carcinogenic potential. Roy et al (1988), for example, reported a significant correlation between 3-7 ring PAH content and both the mutagenic and carcinogenic potencies of a series of complex oil mixtures with higher boiling points than the petroleum distillate typically used in drilling fluids. Highly refined oils and oils from which PAH content has been largely removed by processing appear to have less potential to cause cancer in animal experiments. Halder et al (1984) reported that solvent refining at normally used severities appeared to eliminate carcinogenicity in mice whereas mild hydroprocessing only reduced carcinogenic potency. Carcinogenic activity could also be eliminated by following moderate solvent refining with mild hydroprocessing. McKee et al (1989) reported that unrefined light and heavy vacuum distillates from a naphthenic crude oil induced tumours and significantly reduced survival of exposed mice whereas none of the mice treated with severely hydrotreated oils developed skin tumours. Subsequently, McKee et al (1990) found no evidence of dermal carcinogenicity in mice exposed to cutting fluids produced from highly refined lubricant base oils including solvent-extracted lubricant base oils and fresh and used cutting fluids and related industrial oils. Nessel (1999) however highlighted that although middle distillate fuels do not generally contain appreciable levels of PAHs and give negative results in standard assays of genotoxicity, they have produced weak tumorigenic responses in mouse skin that are characterized by low tumour yield and long latency. Several investigators have suggested a role for chronic irritation and associated inflammation in giving rise to dermal cancers following exposure to petroleum fractions with low PAH contents.

The IUCLID chemical data sheet for kerosene, indicates that negative results were obtained in both in vitro and in vivo assays of genotoxicity. Mixed results were also obtained in long term experiments in which mice were exposed to kerosene via the skin. All the studies reported skin irritation at the site of application and it is suggested in the data summary that observed tumours may have been a consequence of repeated dermal irritation rather than a direct result of exposure to kerosene. In a 12 month study in which mice were exposed twice a week to 0.05 ml of kerosene (CAS 8008-20-6), one of 50 exposed animals developed a malignant tumour at the application site. In a two year study with a similar dosing regime with straight run kerosene (CAS 64741-54-4), 29 malignant tumours were reported in 50 animals. In a third study with JP-5 Navy fuel (CAS 8002-20-6), marked skin irritation, chronic dermatitis and ulceration was observed following 103 weeks exposure to 500 mg/kg/day in acetone but only one of 50 animals developed a malignant tumour. A further short term study in mice (28 days) with kerosene (8008-20-6) established that the test substance was a promoter but not an initiator of carcinogenesis. Biles et al (1988) reported that a series of middle distillates that varied with respect to boiling range, composition, and source of blending stocks, all showed evidence of weak tumorigenic activity characterized by low tumour yields and long median latencies. There

was evidence of non-neoplastic dermal changes including hyperplasia. There was no association of tumorigenic activity with aromatic carbon content. Grasso et al (1988) reported that thrice weekly applications of three middle distillates with low PAH contents gave rise to severe skin damage from week 1 onwards in mice with two of the distillates producing epidermal loss and ulceration. Marked epidermal hyperplasia was produced by all three substances. Nessel et al (1998, 1999) compared the effects of repeated skin application of undiluted and diluted forms of middle distillates in mice and reported that all the materials produced moderate irritation and a significant increase in tumour incidence when applied undiluted. When diluted with mineral oil, however, skin irritation was reduced and few, if any, tumours were produced for most of the materials. One material, however, gave rise to a significant increase in tumour incidence, even when applied diluted. Another substance gave rise to an increase in tumour frequency when applied in a dilute form despite only limited skin irritation, contained a significant (8.7%) proportion of three- to seven-ring PAHs. In contrast, Skisak (1991) reported that although tumour promotion by petroleum middle distillates was associated with the development of persistent hyperplasia it was only weakly associated with subacute inflammation and the association with hyperplasia was too weak to account for the observed tumour promotion. Similarly Broddle et al (1996) found that a range of middle distillates including straight run kerosene, hydrodesulfurized middle distillate, straight run middle distillate and light catalytic cracked distillate were carcinogenic giving rise to tumours in 16 to 67% of exposed animals, despite containing virtually no PAHs and showing no evidence of genotoxicity. There was no correlation between carcinogenic potency and the indices of irritation, alopecia, erythema, and scabbing.

In conclusion, the factors that govern the dermal carcinogenicity of oils are only partially understood. The hydro-treated distillate used in modern drilling fluids is likely to have a low PAH content and low potential to cause cancer following prolonged dermal exposure, provided that exposure levels are insufficient to cause chronic irritation and inflammation of the skin. It is not possible, however, to eliminate the possibility of an increased dermal cancer risk associated with some oil compositions or environmental conditions. There is more certainty that the use of less refined/processed petroleum products with higher PAH contents would be associated with a potential increased cancer risk for workers with prolonged dermal exposure.

6.5 HUMAN HEALTH DATA

6.5.1 Petroleum drilling fluids

There is a paucity of information about the health effects of workplace exposure to drilling fluids. Several studies have investigated cancer incidence. Aas et al (2009) reported that the cancer incidence in a cohort of >25,000 male Norwegian offshore oil workers who were employed at installations in the North Sea in the period 1965-1999 was not significantly different from that in the general Norwegian population but there were indications of excess risks of acute myeloid leukaemia (SIR=2.0, 95% confidence interval (CI) 1.0-3.7) and cancer of the pleura (SIR=2.2, 95% CI 0.9-4.6). It was concluded that an extended observation period was required before an in-depth analysis could be conducted. This study did not investigate the specific effects of exposure to oil-based drilling fluids. Kirkeleit et al (2010) reported an excess of oesophageal cancer, among male offshore upstream petroleum workers but this was largely associated with a fourfold increase in the risk of adenocarcinoma in upstream operators and unlikely to be related to exposure to oil drilling fluids. Kirkeleit et al (2008) undertook a cohort study of 27,919 offshore workers registered from 1981 to 2003 employed in Norway's upstream petroleum industry exposed to crude oil and other products containing benzene. They reported that workers in the job category "upstream operator offshore" with the greatest exposures to crude oil showed an excess risk of blood and bone marrow neoplasms (rate ratio: 1.90, 95% CI: 1.19-3.02). The authors attributed this increased risk to benzene exposure and the findings are of

limited relevance to understanding the potential carcinogenicity of drilling fluids. A US study of 24,124 US workers employed at petroleum production and pipeline locations sometime during 1946-94 with an average of 22 years of follow up, reported that overall mortality, and most cause specific mortalities were lower than or similar to those for the general US population (Divine and Hartman, 2000). There were significant deficits for all the leading causes of death in the US including all cancers, cancer of the lung, stroke, heart disease, respiratory disease, and accidents. Slightly increased mortality was found for cancer of the prostate, cancer of the brain and central nervous system, and cancer of other lymphatic tissue. There was a significant increase for acute myelogenous leukaemia that was restricted to people who were first employed before 1940 and who were employed in production and pipeline jobs for >30 years.

Gardner (2003) noted that dermatitis is a recognised risk associated with skin contact with drilling fluids but did not identify a specific link with oil-based drilling fluids.

Overall, published studies of petroleum workers provide little information about the potential risks to health associated with the use of drilling fluids.

6.5.2 Exposure to cutting fluids in other workplace environments

Introduction

Whereas relatively few investigators have examined the human health effects of exposure to vapours and aerosols associated with drilling fluids, there has been extensive investigation of the effects of exposure to oil mist generated from cutting fluids. In the absence of extensive information about the effects of drilling fluids, the exposures associated with the use of cutting fluids are analogous to those associated with drilling fluids and studies of cutting fluids may be informative about the potential health issues associated with drilling fluids. Cutting fluids are generally based on slightly heavier oils than those typically used in drilling fluids: C_{16}-C_{24} rather than C_9-C_{16} alkanes. Given that C_9-C_{24} alkanes are closely related compounds, it is anticipated that the toxicity of C_{16}-C_{24} alkanes would not be greatly dissimilar from that of shorter chain alkanes. Some modification of toxic potential would be expected to arise from the decreasing volatility and water solubility with increasing chain length and the increase in lipid solubility.

Non-malignant respiratory effects associated with exposure to oil mist generated from cutting fluids

A number of studies have demonstrated an association between exposure to metal working fluids and adverse effects on respiratory health. Rosenman (1997), for example, reported that metal working fluids were the second most common cause of work-related asthma reported in Michigan between 1988 and 1994 and found evidence of significant under-reporting of work-related asthma. Workers exposed to emulsified, semisynthetic, or synthetic machining coolants were more likely to have chronic bronchitis; to have visited a doctor for shortness of breath; to have visited a doctor for a sinus problem; to be bothered at work by nasal stuffiness, runny nose, or sore throat; and to have an increased prevalence of respiratory symptoms consistent with work-related asthma, compared to workers exposed to mineral oil metal working fluids. Robertson et al (1988) concluded that while occupational asthma due to oil mists is common, there are between worker differences in the provoking agent within oil.

Jaakkola et al (2009) reported that exposure to metal working fluids to aerosol levels above $\geq$0.17 mgm^{-3} (the median concentration in general workshop air) was associated with a doubling of nasal and throat symptoms, cough, wheezing, breathlessness, chronic bronchitis, and current asthma. There was an increase in throat symptoms, cough, and chronic bronchitis in machine workers with $\geq$15 years experience. Kennedy et al (1989) reported significant cross shift

reductions in lung function in car workers exposed to machining fluids at inhalable aerosol concentrations of >0.20 mgm^{-3}. An earlier study had found increased rates of cough and phlegm and a possible association with occupational asthma. Total aerosol concentrations for assembly workers ranged from 0.07 to 0.44 mgm^{-3}, and for machinists from 0.16 to 2.03 mgm^{-3}. After adjusting statistically for a history of childhood asthma, for smoking prior to lung function testing, and for race, the odds ratios (OR) for an FEV_1-response were 4.4 among workers exposed to aerosols of straight mineral oils, 5.8 for oil emulsions, and 6.9 for synthetic fluids. There was no progressive decline in FEV_1 over the working week. In a small study of textile workers, Kremer et al (1994) reported that exposure to oil mist and vapour (without simultaneous exposure to airborne dust) was associated with chronic respiratory symptoms and a significant reduction in lung function after 10 years exposure. It is unlikely, however, that the oils were similar to those used in drilling fluids.

In conclusion, there is substantial evidence linking exposure to oil mist generated from some cutting fluids to adverse effects on respiratory health. Reported levels of exposure giving rise to adverse effects are much lower than might be inferred from inhalation studies conducted in animals (section 6.3.1). This may be partly because the endpoints that have been examined in humans are more sensitive than those examined in animals, for example, respiratory symptoms versus pathological changes. Another important factor that may contribute to an apparently greater potency, is the presence of various additives in cutting fluids. The human data suggest that the risks to health are greater for cutting fluids based on synthetic mixes and emulsions than for straight mineral oil. It seems likely that the toxicity of aerosols generated from some cutting fluids would be considerably greater than that associated with aerosols generated from C_9-C_{16} petroleum distillates. However, given that drilling fluids are also likely to contain a range of additives that will lead to a modification of the toxicity of associated aerosols, it would be prudent to take note of the relatively low levels of exposure associated with adverse respiratory effects for some cutting fluid compositions.

Other non cancer effects associated with exposure to oil mist from cutting fluids

The results of two studies suggest a possible association between exposure to oil mist or petroleum distillate aerosol and rheumatoid arthritis. In a Swedish study, Sverdrup et al (2005) reported a possible association between exposure to oil mist and an increased risk of developing rheumatoid factor positive rheumatoid arthritis or anticitrulline-positive rheumatoid arthritis. A case control study undertaken in women from Michigan and Ohio (Lacey et al, 1999) reported an association between undifferentiated connective tissue disease (a precursor to a range of autoimmune disorders such as rheumatoid arthritis) and self-reported exposure to ten specific solvents, paint thinners or removers (OR = 2.73, 95 percent CI 1.80-4.16) and mineral spirits (OR = 1.81, 95% CI 1.09-3.02). The authors concluded that exposure to petroleum distillates increases the risk of developing for undifferentiated connective tissue disease.

In a study of workers employed by a Norwegian cable manufacturing company, Skyberg et al (1989) reported a decrease in the lymphocyte counts in the most heavily exposed subgroup but no other significant differences were found between exposed workers and referents.

Carcinogenicity of oil mists from cutting fluids in humans

IARC last reviewed the carcinogenicity of mineral oils (CAS no 8002-05-9; petroleum) in 1987. They concluded that untreated and mildly-treated oils are carcinogenic to humans (Group 1) whereas highly-refined oils are not classifiable as to their carcinogenicity to humans (Group 3). Tolbert (1997) reviewed epidemiological studies of mineral oil exposure for metal machining, print press operating, and cotton and jute spinning. The composition of mineral oils depends on the source of the oil and the method of refinement and workers are also exposed to a variety of

additives and contaminants. The data suggest that early formulations of mineral oils used in cotton and jute spinning and in metal machining were carcinogenic to the skin. This would be consistent with the presence of carcinogenic PAHs in some historical formulations that would not be present in modern mineral oil formulations. There was evidence of a possible association of mineral oil exposure with laryngeal and rectal cancer, particularly with respect to straight oils. There was suggestive evidence that grinding operations (which can entail either mineral oil-based or ethanolamine-based fluids) are associated with excess risk of cancer of the oesophagus, stomach, and pancreas and that bladder cancer may be associated with work as a machinist. There was limited evidence of an association with cancer of the colon, prostate, and sinonasal region. Studies in metal machinists have generally not found an association with lung cancer. In a study of automobile workers exposed to metal working fluids, exposure to mineral oils appeared to be associated with almost a two-fold excess in larynx cancer risk which may have been linked to PAHs (Eisen et al, 1994). Friesen et al (2009) investigated bladder cancer incidence in 21,999 car workers, followed from 1985 through 2004. The hazard ratio increased with cumulative exposure to a maximum of 2-fold observed at 75 mgm^{-3}.year straight oil MWF exposure (lagged 20 years) strengthening the evidence that mineral oils are bladder carcinogens, although the authors were unable to separate the effects of mineral oil from those of PAHs. No association was observed between any exposure and incident lung cancer, suggesting that smoking was unlikely to confound the reported associations. In a study of the incidence of malignant melanoma in the same cohort, Costello et al (2011) reported that a hazard ratio of 1.99 (95% confidence interval = 1.00-3.96) for the highest category of exposure to straight oil MWFs. Their analysis suggested a linear exposure-response over the full range of exposure. The change in hazard ratio for malignant melanoma per mgm^{-3}.year of straight mineral oil increased monotonically from 1.01 to 1.04, when the date-of-birth restriction increased from 1925 to 1945 in 5-year intervals. A weaker association was found between exposure to soluble MWFs and no association was reported with synthetic fluid. Friesen et al (2011) derived constituent-based exposure metrics of polycyclic aromatic hydrocarbons (PAHs), water-based MWF, biocides, and nitrosamines in order to investigate the potential carcinogenicity of different components of MWFs in a cohort of 30,000 carworkers. They observed that for most cancer sites, the constituent-based metrics resulted in stronger exposure-disease associations than the MWF classes alone. Laryngeal and bladder cancer were most strongly associated with PAH. In contrast, protective effects for stomach and lung cancer were observed with biocide, a component that may be a surrogate for endotoxin.

Overall, the data suggest an association between exposure to some mineral oils and increased cancer risk which is likely to be linked to the presence of carcinogenic PAHs in some oil formulations, particularly those used in the past. The PAH content of drilling fluids is typically negligible suggesting that the potential for carcinogenicity is very much lower.

Dermatitis

In a European study (Mirabelli et al, 2009), 10% of metalworkers reported current skin symptoms were that were associated with frequent use (≥ 4 days per week) of oil-based metal working fluids [prevalence ratio (PR): 1.76, 95% CI: 1.25-2.49] and organic solvent/degreasing agents (PR: 2.06, 95% CI: 1.21-3.50).

Sprince et al (1996) reported that the prevalence of dermatitis (definite plus possible) among machine operators exposed to metal working fluids in a large car transmission plant was greater than for unexposed assemblers (27.2% vs. 13.7). Significant risk factors were subjective assessment of wetness of the work, exposure to semisynthetic as opposed to soluble oil metal working fluids, current cigarette smoking, and increasing worker age.

6.5.3 Exposure to white spirits and other solvents

White spirit is a widely used solvent that comprises a mixture of paraffins (C_5 to C_{13}) that overlaps with the more volatile components of petroleum distillate that are typically used in drilling fluids. The IPCS (1996) indicate that the odour of white spirits can be detected at levels of 0.5-5 mgm^{-3}.

One of the key adverse effects associated with both short and long term exposure to solvents including white spirit is neurotoxicity (Dick, 2006). Acute exposures to high concentrations give rise to headache, dizziness and light-headedness (with potential progression to unconsciousness, seizures and death). Short term exposure to relatively low concentrations may give rise to effects including impaired memory, poor concentration, fatigue and reduced motivation that resolve on cessation of exposure. In volunteer experiments, a 7-hour exposure to white spirit at a concentration of ≥600 mgm^{-3} resulted in impaired balance during walking and to an increased reaction time. Exposure to 4,000 mgm^{-3} for 50 minutes resulted in impaired performance in tests for perceptual speed and short-term memory (IPCS, 1996). Longer term exposure may give rise to irreversible effects on cognition affecting attention/concentration, visuospatial skills and verbal memory and/or give rise to effects on mood and personality including lowered mood, anxiety and irritability. A range of adverse effects have been identified in epidemiological studies of painters who are presumed to have long-term exposure to white spirit but are also likely to have variable levels of exposure to other hazardous substances. These studies have shown increased incidences of complaints of memory impairment, fatigue, impaired concentration, irritability, dizziness, headache, anxiety and apathy and dose-related impaired performance in neuropsychological tests (IPCS, 1996). At still higher levels of exposure dementia may develop. Some solvents including styrene are associated with sub-clinical changes in colour vision. Solvent exposure may also be associated with hearing loss, particularly if combined with exposure to noise (Dick, 2006).

Other effects associated with white spirit include eye irritation, reported at concentrations of 600 mgm^{-3} (100 ppm) and respiratory irritation reported at higher concentrations. Skin contact with white spirit over several hours may lead to irritation and dermatitis. Haematological effects have been reported in workers long term exposure to white spirits including decreased erythrocyte, leukocyte and platelet counts, and increased mean corpuscular volume (IPCS, 1996). In addition, several case-control studies have shown a high risk of glomerulonephritis among painters. In a study of workers at a major car manufacturing plant in England, Yagoob et al (1993) found evidence of an increased incidence of early markers of kidney dysfunction in workers with chronic hydrocarbon exposure. The most marked effects were observed in workers exposed to paint-based hydrocarbons and effects were also observed in workers exposed to petroleum-based mineral oils.

6.5.4 Conclusions

Based on the human data short term exposure to extremely high concentrations of oil vapour such as arising from the use of petroleum distillate in drilling could give rise to irritation of the nose, throat and eyes and might be associated with CNS symptoms such as dizziness and headache. In contrast to the findings of animal inhalation experiments with oil vapours and aerosols, experience with cutting fluids (in the absence of data for drilling fluids) indicates that even low exposures to oil mist (≥ 0.2 mgm^{-3}) may give rise to adverse respiratory effects in humans. The apparently greater potency of cutting fluids than the oils tested in animal experiments may partly reflect the presence of additional components or contaminants in drilling fluids, not present in the experiment oils. The hydrocarbon content and additives present in cutting fluids are likely to differ from those in drilling fluids with cutting fluids generally employing slightly less volatile hydrocarbons. This is likely to lead to some differences in

toxicity, but it seems likely that the effects associated with drilling fluids would not be dissimilar to those reported with cutting fluids.

Long term exposure to oil aerosol/vapour arising from the use of petroleum distillate in drilling fluids is likely to be associated with increased risks of respiratory illness and dermatitis. Other potential impacts include possible increased risks of haematological abnormalities and kidney disease. Human data provide very limited evidence of an increased cancer risk associated with exposure to petroleum vapours may be related to PAHs present in older formulations and have little relevance to current exposures.

6.6 EXPOSURE LIMITS FOR HYDROCARBON AEROSOLS AND VAPOURS

The GESTIS database contained no limits for petroleum distillate however Belgium have set a limit of 200 mgm^{-3} for kerosene and NIOSH have set a recommended exposure limit of 100 mgm^{-3} for kerosene based on the results of animal studies that had shown no indications of adverse effects at concentrations below 100 mgm^{-3}. The NIOSH recommendation was made in 1977 and workplace exposure limits for other substances have substantially reduced over the last 3 decades, suggesting that more precautionary recommendation might be made, if NIOSH were to review kerosene in the near future.

The ACGIH have set threshold limit values (TLVs) for nonane and for shorter chain alkanes. The ACGIH TLV-time weighted average (TWA) of 200 ppm for nonane was derived by analogy with octane and the belief that the toxicity of n-alkanes increased with chain length (ACGIH, 2005). The ACGIH TLV-TWA of 300 ppm for octane was based on analogy with other paraffins. Possible neurotoxic effects were believed to be associated with a metabolite of the n-octane isomer. Mucous membrane irritation and narcosis have been observed in animals exposed to very high concentrations of octane (ACGIH, 2005). The ACGIH TLV-TWA of 400 ppm for heptane was based on limited information that suggested that the toxicity of heptane is greater than that of n-hexane in relation to acute effects such as narcosis and respiratory irritation (ACGIH, 2005). The ACGH set a specific TLV of 50 ppm for n-hexane because of its neurotoxicity which is not displayed by other hexane isomers. Workplace exposure to hexane concentrations of 500 ppm had been reported to give rise to occupational polyneuropathy and near continuous exposure of animals to 250 ppm also caused neurotoxic effects (ACGIH, 2005).

6.7 CONCLUSIONS

The petroleum derived fluids that comprise a major component of oil-based drilling fluids have variable compositions. They are predominantly composed of C_9-C_{16} alkanes which have relatively low toxicities but may also contain a range of aromatic compounds, naphthenes and small quantities of alkenes. These other components may give rise to significantly greater risks of neurotoxicity and also of carcinogenicity. The toxicity of different compounds in each class varied according to molecular size and structure.

Acute inhalation exposure to high concentrations of hydrocarbon vapour is likely to give rise to irritation of the eyes and respiratory system, respiratory symptoms and possible CNS effects such as dizziness, drowsiness or headache. Acute exposure to high aerosol concentrations is also likely to cause irritation of the mucous membranes and respiratory symptoms. People with asthma or other pre-existing respiratory conditions are likely to be most susceptible to effects following short term exposure to either aerosol or vapour.

Long term inhalation exposure to hydrocarbon vapours can give rise to neurotoxicity including adverse effects on cognitive function. Differences in uptake by the brain are likely to give rise to greater neurotoxic effects with nonane than shorter or longer chain alkanes and neurotoxicity is

also likely to be greater for aromatic and naphthenic compounds and possibly alkenes than for alkanes containing a similar number of carbon atoms. The neurotoxic effects of long term exposure to hydrocarbon aerosols (as opposed to vapour) are unclear. It seems likely that aerosol compositions would be dominated by a larger proportion of longer chain hydrocarbons than would be present in vapour. This combined with lower absorption from the respiratory system of oil droplets than oil vapour would give rise to a lower degree of hazard relative to that associated with vapour. Long term exposure to either vapour or aerosol giving rise to chronic respiratory irritation would be expected to give rise to more serious chronic respiratory illness. It is possible that the deposition of aerosol in the lungs would give rise to a higher risk of chronic bronchitis and other chronic lung disease than would be associated with exposure to vapour.

Long term inhalation exposure to hydrocarbon vapours or aerosol may be associated with a very small increase in the risk of respiratory cancer risk due to the presence of extremely small quantities of aromatic compounds.

Dermal exposure to hydrocarbon vapours and liquids is likely to cause dermal irritation and dermatitis. Repeated long term exposure and the associated chronic skin irritation might give rise to an increased cancer risk, but there are no human data indicative of raised skin cancer risks in drilling workers. It seems likely that measures taken to minimise skin irritation would also be protective against the more serious consequences of repeated dermal irritation.

7 WET WORKING

Water (H_2O) is an important constituent of some of the drilling fluid compositions used in the industry (Appendix 1). Aqueous based drilling fluids may have water contents between 60 and 80%. Water is not regarded as a toxic substance, although repeated wetting of the skin may give rise to "wet hand" dermatitis. About 30% of reported work-related dermatitis in the UK is associated with wet work (Cherrie et al, 2007). In a recently reported German study, Apfelbacher et al (2011) reported an association between having wet hands for ≥2 hours/day and current irritant hand eczema.

Water vapour/mist would not normally be expected to be hazardous to health, but there is some evidence that exposure to water vapour/mist does have a measurable effect on the airways of some people with asthma that could give rise to a short term exacerbation of symptoms. During the 1980s and early 1990s, water vapour was widely used to induce constriction of the airways in asthmatics in experimental investigations of the effectiveness of different medications.

Although is unlikely that inhalation of pure water would adversely affect respiratory health, water is a carrier of microbial infections (eg legionella) and endotoxin (a component of bacteria) and these agents have been associated with adverse respiratory effects in. Other waterborne infections such as those associated with gastrointestinal illness may be an issue where dermal contact is possible in combination with inadvertent hand to mouth contact.

Under most circumstances human pathogens have a limited lifetime in water unless conditions are close to those prevalent in the human body and the potential for microbial infections can be greatly reduced by how fluids are stored and managed, as well as the use of appropriate biocides.

In conclusion, the key health issues associated with water in drilling fluids is the potential for dermatitis to arise as a consequence of repeated wetting of the skin, the potential for infections such as legionella to arise and the potential for fever and other symptoms to arise as a result of exposure to endotoxin. Provided that adequate measures are employed to prevent microbial growth in drilling fluids, then neither exposure to waterborne infections or endotoxin should arise.

8 COMPOUNDS OF ALKALI AND ALKALI EARTH METALS

8.1 EXPOSURE

No peer reviewed published particle size information is available and while these compounds are likely to be added to drilling fluids as fine powders, it is unclear how much of the powder is likely to be respirable. It is also not known whether these compounds are present in air within oil droplets, within water droplets, as discrete particles or as a mix of two or more of these. Galea et al (2010) completed a study for Statoil which aimed to investigate the effect of temperature on the particle size distribution (PSD) of aerosols generated from drilling fluids at a shale shaker in a purpose built onshore test centre. The peak of the first mode for the mass-based PSD was observed around 2 to 3.5 μm, depending on the drilling fluid temperature, with the second mode occurring at around 18 μm., Comparing the average particle concentrations at a drilling fluid temperature of 70˚C with that at 70˚C showed that the highest increase in particle concentration occurred for particles with a aerodynamic diameter between 1.1 and 1.7μm. Scanning Electron Microscopy (SEM) results showed a range of liquid droplets (3-30 μm), some of which containing smaller solid particles inside including silicon, calcium and barium.

8.2 CALCIUM OXIDE AND CALCIUM HYDROXIDE

The drilling fluids composition information provided in Appendix 1 indicates that drilling fluids may contain between 1 and 3% lime (calcium oxide (CaO)) or between 1 and 5% calcium hydroxide (CaH_2O_2).

8.2.1 Effects arising from alkalinity

Calcium oxide (CAS no: 1305-78-8) is corrosive to the eyes, skin and respiratory tract. The effects of acute exposure may be delayed. Repeated or prolonged contact with skin may cause dermatitis. Long term or repeated exposure to airborne lime may cause ulceration and perforation of the nasal septum and give rise to chronic respiratory illness. Calcium hydroxide (CAS no: 1305-62-0) can cause irritation of the skin, eyes and respiratory system. Both compounds are hygroscopic and would therefore be anticipated to be damaging to tissue at high levels of exposure to the dust.

The ACGIH TLV for calcium oxide is 2 mgm^{-3} (8 hour-TWA). The documentation indicates that industrial experience has demonstrated that calcium oxide is very irritating to mucous membranes and moist skin. Strong nasal irritation had been reported in workers exposed to mixed dusts containing calcium oxide at concentrations of about 25 mgm^{-3} although no observable effects were associated with exposure to 9 to 10 $mgm^{-3.}$ The TLV was set by analogy with that for calcium hydroxide (5 mgm^{-3}, ACGIH, 2005). The TLV for calcium hydroxide was set by analogy with sodium hydroxide but taking account of its lower alkalinity. Long term exposure to either compound in workplace air would be expected to give rise to increased risks of chronic respiratory illnesses such as bronchitis, although there are no published data.

8.2.2 Calcium intake

The median lethal oral dose of calcium oxide in rats and mice respectively is reported as 7,340 and 7,300 mg/kg respectively suggesting a relatively low acute toxicity following ingestion. The oral median lethal dose of calcium hydroxide in rats is 7,340 mg/kg.

Calcium is an essential element that plays a key role in skeletal growth and maintenance, maintaining cellular membranes and in the regulation of a wide range of enzyme functions and intracellular signalling with effects on a wide range of body processes such as blood clotting.

The UK Expert Group on Vitamins and Minerals (2002) record a Reference Nutrient Intake of 700 mg/day and Acceptable Intake 1,000 mg/day (elderly 1,200 mg). The US office of Dietary Supplements, National Institutes of Health Recommended Daily Allowance for men (19-70 years) and women (19-50 years) is 1,000 mg increasing to 1,200 mg for women over 50 and men over 70 (ODS, 2011).

Plasma calcium concentrations are normally maintained at constant levels with a balance between calcium absorption from the diet and excretion (homeostasis). Extreme over-exposure to calcium is rare but may occur if an individual consumes large quantities of calcium and other alkalis, for example, taking antacid tablets, calcium supplements and drinking milk. Acute calcium excess leads to nausea, vomiting, diarrhoea, weakness, elevated plasma calcium levels, metabolic alkalosis and renal failure. Long term ingestion of excess calcium has been found to increase the risks of hypercalcaemia (increased plasma calcium blood levels) in women taking a daily supplement of 2,000 mg during pregnancy. Effects of hypercalcaemia include renal insufficiency, vascular and soft tissue calcification, hypercalciuria (high levels of calcium in the urine), kidney stones and neurotoxicity. However, hypercalcaemia rarely results from increased calcium intake and is more commonly associated with primary hyperparathyroidism or malignancy. The risks of hypercalcaemia are increased by certain medications such as thiazide drugs, kidney failure and hyperparathyroidism.

The US office of Dietary Supplements tolerable upper intake for adults (19-50 years in age) is 2,500 mg/day, reducing to 2,000 mg/day in adults over 50. These levels are based on the risk of developing kidney stones. The equivalent intake by inhalation over an 8 hour shift would correspond to a concentration of 200-250 mgm^{-3} as an 8 hour TWA. The difference between the recommended intake and tolerable upper intake corresponds to a concentration of 80-150 mgm^{-3} as an 8 hour TWA with adults over 50, particularly females being more sensitive to both calcium deficiency and excess than younger adults.

8.2.3 Evaluation

The corrosive effects of calcium oxide or calcium hydroxide in drilling fluids will be greatly reduced by dilution to 1-5% in fluids and their impact on the alkalinity/acidity of drilling fluids will depend on the overall fluid composition. The presence of these substances in a strongly alkaline fluid would contribute to skin irritation, dermatitis, irritation of the eyes and nose and long term adverse effects on respiratory health. Conversely, if these substances are used as an acidity regulator within drilling fluids, then they are likely to reduce the potential for adverse effects that might arise from over-exposure to those fluids. Increased exposure to calcium resulting from the use of calcium oxide or hydroxide in drilling fluids is likely to be small in relation to dietary uptake and would not be expected to lead to adverse effects.

8.3 CALCIUM CHLORIDE AND CALCIUM HYDROXIDE

8.3.1 Substances

The drilling fluid composition information provided in Appendix 1 indicates that calcium chloride ($CaCl_2$; CAS no: 10043-52-4) is used in the petroleum distillate/kerosene based drilling fluids at concentrations of between 1 and 5%.

8.3.2 Effects

Calcium chloride is hydroscopic and can cause irritation of the skin, eyes and respiratory system. It has a low systemic toxicity as calcium and chloride are naturally present in human tissue and the intake of calcium associated with the presence of these substances in drilling

fluids is likely to be insignificant in comparison to dietary sources (see discussion of calcium hydroxide). The IUCLID chemical data sheet for calcium chloride indicates that it has a relatively low acute toxicity following ingestion which is attributed to irritation of the digestive tract. The reported median lethal dose is 1,940-2,045 mg/kg in mice, 3,798-4,179 mg/kg in rats and 500-1,000 mg/kg in rabbits. Large single doses in humans induce nausea and vomiting. The dermal median lethal dose in rabbits is greater than 5,000 mg/kg. No significant adverse effects were observed in rats fed 1,000-2,000 mg/kg/day for 12 months.

There is a dearth of information about the inhalation toxicology of calcium chloride. Prolonged exposure by inhalation could give rise to chronic respiratory illness such as bronchitis resulting from repeated irritation of the airways. Prolonged dermal irritation arising from exposure to calcium chloride is likely to cause dermatitis and may lead to irreversible damage to skin resulting in permanent lesions.

8.4 SODIUM HYDROXIDE

Sodium hydroxide (NaOH; CAS no: 95077-05-7) is present in some drilling fluid compositions at concentrations of up to 1% (Appendix 1).

Pure sodium hydroxide is very corrosive and can cause severe burns. Inhalation of low concentrations of sodium hydroxide as dusts, mists or aerosols may cause irritation of the nose, throat, and respiratory airways. Higher levels of exposure can produce swelling or spasms of the upper airways leading to obstruction and loss of measurable pulse; inflammation of the lungs and accumulation of fluid in the lungs may also occur. Long-term exposure to sodium hydroxide in the air may lead to ulceration of the nasal passages and chronic skin irritation

Ingestion of solid or liquid sodium hydroxide can cause spontaneous vomiting, chest and abdominal pain, and difficulty swallowing. Corrosive injury to the mouth, throat, oesophagus, and stomach is very rapid and may result in perforation, haemorrhage, and narrowing of the gastrointestinal tract. Death results from shock, infection of the corroded tissues, lung damage, or loss of measurable pulse. RTECS records the lowest report lethal dose in humans as equivalent to 110 mg in a 70 kg adult.

Skin contact with sodium hydroxide can cause severe burns with deep ulcerations. Pain and irritation are evident within 3 minutes, but contact with dilute solutions may not cause symptoms for several hours. Contact with the eye may produce pain and irritation, and in severe cases, clouding of the eye and blindness.

The ACGIH TLV and UK WEL for sodium hydroxide is set at 2 mgm^{-3}, although the supporting documentation in both cases notes reports of irritation to the eyes and respiratory system at much lower levels of exposure (ACGIH, 2005; HSE, 2002).

Given that the mean intake of sodium in the UK's average diet was 8.6 g in 2008 compared with 9.5g in 2000/01 and that the UK has a target to reduce average salt intakes across the population from 9.5g to 6g per day (UK Food Standards Agency, 2008), any increase in systemic exposure to sodium as a result of the presence of sodium hydroxide in drilling fluids is likely to be negligible. No adverse impacts on health would be anticipated.

It seems likely that sodium hydroxide is added to drilling fluids as an acidity regulator or to otherwise modify drilling fluid composition, perhaps through interaction with some of the organic substances present in fluids. It is unlikely that the concentrations of sodium hydroxide present in drilling fluid would add significantly to any risks of dermatitis or other skin effects, irritation of the eyes and respiratory system or longer term respiratory illness.

8.5 POTASSIUM HYDROXIDE

The drilling fluid information provided in Appendix 1 indicates that small quantities (<1%) of potassium hydroxide (KOH; CAS no: 71769-53-4) is present in some drilling fluid compositions.

8.5.1 Effects associated with exposure to a strong alkali

The Screening Information Data Set (SIDS) dossier (available from URL:www.inchem.org) indicates that potassium hydroxide has a relatively low toxicity and that adverse effects from exposure arise from its highly caustic nature. Aqueous solutions of potassium hydroxide may be irritating to the skin at concentrations of about 0.5 to 2% and more concentrated solutions are corrosive. Mist containing potassium hydroxide is irritating to the eyes and respiratory system. The SIDS dossier indicates that potassium hydroxide is unlikely to form airborne dust because of its hydroscopic nature and reactivity with atmospheric carbon dioxide. There is little information about the effects of inhaled potassium hydroxide and the ACGIH TLV of 2 mgm^{-3} is set by analogy with sodium hydroxide (ACGIH, 2005).

8.5.2 Systemic effects of increased potassium exposure

The mean daily dietary potassium intake in the UK is 2800 mg/day with a 97.5th percentile of 4700 mg/day. The recommended nutritional intake is 3500 mg/day (UK Expert Group of Vitamins and Minerals, 2003). The equivalent intake by inhalation over an 8 hour shift would equate to an exposure concentration of 350 mgm^{-3}. Ingestion of high doses of potassium chloride has been reported to result in heart failure, cyanosis and cardiac arrest. Chronic ingestion of potassium chloride has reported to result in abdominal pain, nausea and vomiting, diarrhoea, and ulceration of the oesophagus, stomach and duodenum and ileum. Toxicity resulting from high doses of salt substitutes have been associated with chest tightness, nausea and vomiting, diarrhoea, raised potassium levels, shortness of breath and heart failure. One set of studies in which subjects received 3,700 mg/day potassium supplements for 2 years found no increased incidence of side effects compared with placebo whereas other studies have reported that this level of intake can lead to gastrointestinal erosions with only mild symptoms being apparent. The Expert Group concluded that supplemental doses of up to 3,700 mg potassium/day appear to be without overt adverse effects. In the US, the adequate intake of potassium is considered to be 4,700 mg/day.

8.5.3 Evaluation

The health effects of potassium hydroxide are similar to those of sodium or calcium hydroxide. The caustic nature of potassium hydroxide is neutralised by other substances present in drilling fluids and its presence at concentrations of up to 1% is unlikely to have a substantial impact on the potential harmfulness of drilling fluids. Any increase in systemic exposure to potassium arising from the use of potassium hydroxide in drilling fluids will be negligible in comparison to dietary intake.

8.6 FORMATE SALTS OF ALKALI AND ALKALI EARTH METALS

Caesium, potassium or sodium formate brines are present in drilling fluids in concentrations of 1-100% (Appendix 1). The actual quantity of salt present is unclear.

8.6.1 Specific information about toxicity of metal formates

There is little information on the toxicity of metal formate salts. The limited available information suggests that they have relatively low toxicities. Both sodium and potassium are naturally present in body fluids and ingested in the diet. Inhalation of aqueous droplets containing these metals would not be expected to lead to a significant increase in exposure.

The median lethal concentration of sodium formate (CAS no: 84050-17-9) is listed in RTECS as 670 mgm^{-3} (4 hour exposure). The median lethal oral dose in rats is >3,000 mg/kg and in mice is 4,700 mg/kg.

The international chemical safety card indicates that sodium formate is irritating to the eyes and respiratory system. It also indicates that sodium formate decomposes in acids to release formic acid (which would also cause irritation to the eyes and respiratory system).

The median lethal dose of potassium formate (CAS no: 64-18-6) in mice is 5500 mg/kg.

There is no information about the toxicity of caesium formate (CAS no: 3495-36-1).

Calcium formate has been evaluated for use as a dietary supplement in humans. Although not reported to be used in drilling fluids, calcium formate would be anticipated to be chemically very similar to sodium formate. In a 14 day study, 12 healthy women ingested calcium formate (1,300 mg) three times a day giving a daily intake of 3900 mg (Altaweel et al, 2009). The equivalent intake by inhalation over an 8 hour shift would equate to workplace exposure concentration of 390 mgm^{-3} as an 8 hour TWA. Peak and final serum levels of formate did not differ significantly from baseline levels measured prior to supplementation. There was no evidence of accumulation of serum formate or toxicity and there was no evidence of effects on the function of the optic nerve or retina. This study provides reassurance that short term exposure to formate salts of essential metals is unlikely to be harmful but is not informative about any potential long term effects. Given however, that workplace exposure to airborne particles are likely to be controlled to levels that are a small fraction of equivalent concentration of calcium formate in workplace air, it seems unlikely that exposures to sodium or potassium formate in the workplace would lead to any detectable adverse health effects.

Sodium, potassium and caesium

Intakes of sodium and potassium associated with the use of their formate salts in drilling fluids will be negligible in comparison to dietary intakes and would therefore not have adverse impacts on health.

Most studies of the effects of caesium have focussed on its radioactive isotope and reported effects are largely due to radiation exposure rather than caesium toxicity (ATSDR, 2004). There is very little information about the toxicity of the stable isotope of caesium. A human volunteer who ingested 34 mg/kg of caesium chloride reported that he suffered loss of appetite, diarrhoea and experienced feelings of euphoria. The effects were, however, self-reported and do not therefore provide strong evidence that caesium is associated with relatively mild effects.

8.6.2 Formate

Formate forms endogeneously in the body as a metabolite of other substances and small amounts of formate are also present in the diet. Formate has been identified as the metabolite of methanol that is responsible for many of its toxic effects (IPCS, 1997). The toxicity of methanol is governed by the conversion of methanol to formic acid and the subsequent metabolism of

formate to carbon dioxide in the folate pathway. Toxicity arises if formate generation continues at a rate that exceeds its rate of metabolism. The IPCS indicates that humans (and other primates) are particularly sensitive to methanol poisoning. Effects include formic acidaemia, metabolic acidosis, ocular toxicity, nervous system depression, blindness, coma and death. Most of the information about the effects of methanol in humans relates to acute rather than long term exposure. The IPCS (1997) indicates that acute inhalation of methanol vapour concentrations below 260 mgm^{-3} or ingestion of up to 20 mg methanol/kg by healthy or moderately folate-deficient humans should not result in formate accumulation above endogenous levels. This implies that the intake of formate from inhalation of mists generated from drilling fluids containing formate salts is likely to be negligible in comparison to endogenous levels of formate and will not give rise to any toxic effects.

8.6.3 Formic acid (CH_2O_2)

Formic acid (CAS no: 992-98-3) is irritating to the skin, respiratory system and eyes. It would be anticipated that the effects of "formate" associated with an alkali metal might be less severe than those of formic acid as some of the irritative effects is likely to be due to acidity whereas the alkali metal formats are weak alkalis. There is relatively little information linking exposure concentrations to effects. The effects of formic acid would be expected to be related to, but greater than those of acetic acid, for which a little more information is available.

The ACGIH have set a TLV for formic acid is 5 ppm as an 8 hour TWA with a short term limit of 10 ppm. The TLV appears to have been set to reflect achievable concentrations and took account of the perceived greater toxicity of formic acid than acetic acid. The TLV for acetic acid is 10 ppm (25 mgm^{-3}) as an 8 hour TWA with a short term limit of 15 ppm and was set to prevent "undue irritation" despite reports of conjunctive irritation in workers exposed to less than 10 ppm (ACGIH, 2005).

RTECS records that effects on the eyes, nose and lungs have been reported following 3 minutes exposure to acetic acid at a concentration of 816 ppm and effects on the nose have been reported following 2 hours exposure to 10 ppm. Effects on urine composition were reported following exposure to formic acid at a concentration of 7.3 mgm^{-3} for 8 hours.

RTECS indicates that exposure of mice to formic acid at a concentration of 64 ppm for 6 hours/day for 13 weeks gave rise to changes in liver and bladder weight and weight loss/reduced weight gain. Exposure of rats under the same conditions gave rise to changes in lung and liver weights and effects on phosphatase activity and exposure to 50 mgm^{-3} for 16 weeks gave rise to effects on the brain, impaired liver function and raised urinary protein levels. Exposure of rats or mice to 500 ppm for 6 hours/day gave rise to effects on the nose and respiratory system and death after 12 days of exposure.

Formic acid is used as a flavouring in food. JECFA (1999) determined that there was no safety concern at current levels of intake. The group average daily intake (ADI) of 3 mg/kg bw that was established for formic acid and ethyl formate is equivalent to an intake of 21 mg/day for a 70 kg adult (equivalent to an intake by inhalation of 2.1 mgm^{-3} over an 8 hour shift).

8.6.4 Dermal uptake

No specific toxicity due to sodium, potassium or caesium formate in fluids would be expected although excessive exposure to any aqueous fluid may lead to wet hand dermatitis.

8.6.5 Conclusions

Potassium, sodium and formate are all naturally present in body tissues and no systemic toxicity is expected to arise as a result of inhaling mists containing these substances in aqueous solution. Intakes of potassium and sodium would be small (<2%) compared to intake from dietary sources and the impact on formate levels would be indistinguishable against endogeneous levels. There is no evidence that caesium formate would be substantially more toxic than sodium or potassium formate, but there is a paucity of information about caesium toxicity as opposed to the adverse effects associated with its radioactive isotope.

Potassium, sodium and caesium formate powders are all likely to cause irritation to skin and mucous membranes and it is possible that highly concentrated brines based on these substances would also be irritants. Excessive dermal contact with drilling fluids based on these brines is more likely, however, to give rise to dermatitis as a result of repeated skin wetness, rather than as a specific reaction to these salts.

Potassium, sodium and caesium formate will decompose in acids to release formic acid which is irritating to the mucous membranes and skin. Long term over-exposure would be anticipated to give rise to increased risks of respiratory disease.

8.7 SODIUM CARBONATE

Sodium carbonate (Na_2CO_3; CAS no: 7542-12-3) is present in some drilling fluid compositions at concentrations of up to 5% (Appendix 1). It is an alkaline substance that causes irritation to the eyes and respiratory system when present as airborne dust in workplace air. A single entry in RTECS indicates that human exposure to 40 mgm^{-3} for one month (presumably in workplace air) was associated with eye irritation. The SIDS dossier indicates that sodium carbonate has a relatively low potential to cause skin irritation.

Sodium carbonate has a low toxicity. Both sodium and carbonate are naturally present in the body. The median lethal concentration (for 2 hours exposure) for guinea pig, mouse and rat is 800, 1200 and 2300 mgm^{-3} respectively. The SIDS dossier indicates that there are no valid repeated dose toxicity data and refers to a poorly reported repeated dose inhalation study that reported local effects on the lungs consistent with the alkaline nature of sodium carbonate. RTECS indicates that rats exposed to 16.2 mgm^{-3} for 16 weeks showed adverse effects on the sense of smell, emphysema and respiratory depression and a decreased cellular immune response.

The SIDS dossier indicates that sodium carbonate has no adverse reproductive or developmental effects, gave negative results in a bacterial mutagenicity assay and is not expected to be genotoxic.

Repeated exposure to high concentrations of sodium carbonate in workplace air might give rise to lasting adverse effects on the eyes and the development of chronic respiratory illness as a result of repeated irritation of the respiratory tract. The potential of sodium carbonate to cause adverse effects would be anticipated to be less than the more caustic material sodium hydroxide. It is probable that sodium carbonate is added to drilling fluids as an acidity regulatory or to otherwise modify drilling fluid composition, perhaps through interaction with some of the organic substances present in fluids. It is unlikely that the concentrations of sodium carbonate present in drilling fluid would add significantly to any risks of dermatitis or other skin effects, irritation of the eyes and respiratory system or longer term respiratory illness.

8.8 POTASSIUM CARBONATE

The drilling fluid information provided in Appendix 1 indicates that potassium carbonate (K_2CO_3; CAS no: 584-08-7) is present in some drilling fluid compositions at concentrations of up to 3%. It is an alkaline substance that would be expected to cause irritation to the eyes and respiratory system when present as airborne dust in workplace air. Repeated exposure to high concentrations might give rise to more lasting adverse effects on the eyes and the development of chronic respiratory illness. The potential of potassium carbonate to cause adverse effects would be anticipated to be less than the more caustic material potassium hydroxide. It would also be anticipated to have a lower alkalinity and less potential to cause respiratory and ocular irritation than sodium carbonate. RTECS indicates that the median lethal oral dose in rats is 1,870 mg/kg, the lethal concentration is >500 mgm^{-3} and rats exposed to 43 mgm^{-3} for 17 weeks showed non-specific changes in electrocardiogram (EKG), effects on urine composition and changes in potassium metabolism.

It is probable that potassium carbonate is added to drilling fluids as an acidity regulatory or to otherwise modify drilling fluid composition. It is unlikely that the concentrations of potassium carbonate present in drilling fluid would add significantly to any risks of dermatitis or other skin effects, irritation of the eyes and respiratory system or longer term respiratory illness.

8.9 CALCIUM CARBONATE

The drilling fluid composition information provided in Appendix 1 indicates that calcium carbonate ($CaCO_3$; CAS no: 72608-12-9) may be present in drilling fluids at concentrations of up to 30%. Calcium carbonate is weakly alkaline and regarded as a low toxicity dust. High levels of exposure to airborne dust may cause symptoms of irritation to the eyes and respiratory system at high levels of exposure as the result of a non-specific reaction to dust rather than any irritancy specific to calcium carbonate. Long term inhalation exposure to high concentrations of calcium carbonate may be associated with increased risks of reduced lung function and the development of chronic respiratory illnesses such as bronchitis. Extreme over-exposure might lead to the development of pneumoconiosis.

RTECS indicates that rats exposed to 84 mgm^{-3} for 4 hours/day for 40 weeks developed interstitial fibrosis of the lung and showed evidence of kidney damage. Rats exposed to 250 mgm^{-3} for 2 hours/day for 24 weeks developed focal fibrosis of the lung (pneumoconiosis).

Any increment in calcium exposure due to exposure to the presence of calcium carbonate in drilling fluids would be small in relation to daily intakes in food (see discussion of calcium oxide) and would not be expected to lead to calcium intakes exceeding tolerable levels.

The presence of calcium carbonate in drilling fluids would not be expected to give rise to adverse health effects, provided that overall levels of exposure to airborne particles are adequately controlled. The UK WEL for calcium carbonate are 10 and 4 mgm^{-3} for inhalable and respirable dust, respectively. The ACGIH TLV is 10 mgm^{-3}.

8.10 SODIUM BICARBONATE

Some drilling fluids contain small quantities (<1%) of sodium bicarbonate ($NaHCO_3$; CAS no: 7542-12-3) (Appendix 1). The SIDS dossier (available from www.inchem.org) indicates that sodium bicarbonate has a low toxicity and has a long history of use in foodstuff, feed and industrial processes. Bicarbonate and sodium ions are normally present in tissue and any excess is readily excreted in urine. The reported median lethal oral dose in a variety of species is >4,000 mg/kg. No deaths were reported in rats exposed by inhalation to a concentration of

4,740 mgm^{-3}. Excessive exposure to sodium bicarbonate by ingestion may lead to metabolic alkalosis, cyanosis and raised sodium levels. RTECS indicates that the lowest reported toxic dose in humans is equivalent to ingestion of 280 mg/day for 5 days (for a 70 kg adult). This gave rise to nausea and vomiting, changes in potassium metabolism and metabolic acidosis. Sodium bicarbonate is a mild skin irritant and may be mildly irritating to the eyes and respiratory system. There is no evidence of genotoxic activity and no indication that sodium bicarbonate is likely to be carcinogenic. Oral administration of aqueous solutions of sodium bicarbonate at doses ranging from 5.8 to 580 mg/kg/day to pregnant mice, 3.4-340 mg/kg/day to pregnant rats and 3.3-330 mg/kg/day to pregnant rabbits did not give rise to any adverse effects on foetal development.

In conclusion, exposure to small quantities of sodium bicarbonate in oil drilling fluids would not be expected to give rise to adverse effects on health.

8.11 POTASSIUM BICARBONATE

The drilling fluid composition information provided in Appendix 1 indicates that some drilling fluids contain small quantities (<1%) of potassium bicarbonate (K_2CO_3; CAS no: 298-14-60). Potassium bicarbonate would be expected to have a low toxicity by analogy with sodium bicarbonate and because both potassium and bicarbonate are present in tissues. RTECS records the lowest reported toxic dose in rats following oral administration in a number of studies (Table 3). The data indicate that extremely high levels of exposure to potassium bicarbonate may adversely affect kidney function and the urinary tract and may also have adverse effects on the adrenal cortex hyperplasia. By analogy with sodium bicarbonate, it is likely that potassium bicarbonate is a mild skin irritant and may be mildly irritating to the eyes and respiratory system.

Table 3: Lowest reported toxic dose in rats following oral administration of potassium bicarbonate

Duration	Dose mg/kg/day	Effects
6 weeks	1,200	Increased urine volume
4 weeks	1,200	Changes in adrenal weight, reduced weight gain/weight loss
13 weeks	2,400	Adrenal cortex hyperplasia, Kidney effects (including acute renal failure, acute tubular necrosis)
1 week	1,000	Metabolic alkalosis
13 weeks	1,000	Reduced weight gain/weight loss
6 weeks	2,000	Changes in urine composition
13 weeks	2,000	Kidney effects (including acute renal failure, acute tubular necrosis)
78 weeks	2,586	Adrenal cortex hyperplasia
130 weeks	2,421	Bladder tumours

Exposure to small quantities of potassium bicarbonate in oil drilling fluids would not be expected to give rise to a significant increase in potassium intake or give rise to adverse effects on health. It is also is unlikely to make a significant contribution to the potential of drilling fluids to cause irritation to the eyes, respiratory system or skin.

8.12 SODIUM SILICATE

The drilling fluid composition information provided in Appendix 1 suggests that sodium silicate (Na_2SiO_3; CAS no: 84992-49-4) is not widely used in drilling fluids but can be present at concentrations of 30-60% in some formulations.

Sodium silicate covers a range of substances with differing sodium to silicate ratios. They are not strictly stoichiometric and their structures include variable quantities of bound water. The SIDS dossier (www.inchem.org) provides information about monosodium and disodium silicate, disodium silicate pentahydrate and disodium silicate nonahydrate.

Sodium silicates are irritants. They range from irritating to corrosive to rabbit skin. Effects reduce with increasing SiO_2 to NaO_2 ratio and increase with increasing concentration. Sodium silicates are likely to be mildly irritating to the eye on the basis of comparison with potassium silicate. Disodium silicate was not sensitising in the mouse local lymph node assay. One case of contact allergic rash associated with sodium silicate has been reported in humans.

Sodium silicates have a low toxicity. The median lethal dose of sodium silicates following oral administration in rats ranges from 1,152 to 5,700 mg/kg with toxicity decreasing with increasing molar SiO_2 to NaO_2 ratio. Effects include apathy, staggering gait, tonic cramps, breathlessness, piloerection and signs of abdominal discomfort. The reported oral median lethal dose for disodium silicate in mice is 770-8,210 mg/kg/day.

In repeated dose experiments, no adverse effects were reported in rats exposed to an oral dose of monosodium silicate of 159 mg/kg/day for 180 days. In mice exposed to disodium silicate by oral administration for 90 days, the lowest observed adverse effect level was 716-892 mg/kg/day which gave rise to a reduction of pituitary gland weight in females. At doses greater than 1,000 mg/kg/day, rats and dogs showed polydipsia, poluria, soft stools, reduction of blood plasma calcium and magnesium levels and liver zinc concentrations, gross cortical lesions of the kidneys and increased plasma concentrations of P and reduced plasma concentrations of zinc.

Sodium silicates have given negative results for in vitro tests and limited in vivo tests. They are not anticipated to be genotoxic. No carcinogenicity data are available.

Studies with the monosodium silicate in rats showed no dose-related effects on litter size at doses up to 159 mg/kg/day, although reduced numbers of offspring were reported at 79 mg/kg/day. No developmental effects were observed in mice exposed to up to 200 mg/kg/day.

It is likely that skin contact with drilling fluids containing concentrations of sodium silicate of 30-60% would be associated with increased risks of dermatitis. Exposure to aerosols generated from these fluids would be associated with increased risks of respiratory irritation and smaller risks of irritation to the eyes. Repeated inhalation exposure giving rise to repeated irritation of respiratory system would be expected to give rise to increased risks of longer term respiratory illness such as chronic bronchitis. Because of the potential for respiratory irritation to occur, it would be desirable to control aerosol concentrations to levels well below the limits set for low toxicity dusts.

8.13 BARIUM SULPHATE

The drilling fluid information provided in Appendix 1 indicates that the barium sulphate ($BaSO_4$; CAS no: 8054-35-1) content of drilling fluids may be as high as 30%. Barium sulphate is generally regarded as a low toxicity dust and exposure to barium sulphate is likely to give rise to similar effects as observed with other low toxicity dusts such as calcium carbonate (Tran et al, 2000). The health effects of barium compounds have been reviewed by the US ATSDR (2007) and the US EPA (review updated 2005). The information below is largely summarised from these sources as there are no more recent data available.

There are no reported animal inhalation experiments with barium sulphate, but Tarasenko et al. (1977) reported a range of adverse effects in rats exposed to 5.2 mgm^{-3} of the closely related substance barium carbonate for 4 hours/day, 6 days/week for 4 months. Reported effects included alterations in some haematological and serum chemistry parameters, perivascular and peribronchial sclerosis with collagenation in the lungs, and increases in arterial pressure. No adverse effects were observed in the rats exposed to 1.15 mgm^{-3} barium carbonate (0.80 mgm^{-3} barium). Uchiyama et al. (1995) reported adverse pulmonary effects (bronchopneumonia, bronchitis, or bronchiolitis) in rabbits exposed by intratracheal administration to a suspension containing 85% barium sulphate, but it is difficult to extrapolate from the findings of this experiments to exposure by inhalation in workplace air.

There is no evidence that skin contact with barium sulphate is likely to give rise to adverse effects and the low solubility of barium sulphate means that absorption through the skin will be negligible.

The toxicity of ingested barium compounds increases with increasing solubility. Barium sulphate being relatively insoluble would be expected to have a low toxicity following ingestion. Animals that drank barium over long periods had damage to the kidneys, decreases in body weight, and some died. The lower bound estimate of the barium intake associated with a 5% increase in kidney toxicity in mice exposed to barium in drinking water is 63 m/kg/day. Both the US ATSDR and the US EPA have derived a reference dose for ingested barium of 0.2 mg/kg/day based on this study. The equivalent intake by inhalation over an 8 hour shift would be equivalent to a concentration of barium in workplace air of 1.4 mgm^{-3}, although the systemic barium uptake resulting from exposure to inhaled barium sulphate would be much lower than that following ingestion of soluble barium.

In a series of subchronic and chronic drinking water studies, Perry et al. (1989, 1985) observed a hypertensive effect in rats receiving as little as 6 mg/kg/day. However, the NTP (1994) found no association between subchronic barium exposure and cardiovascular toxicity in rats at the highest level tested (200 mg/kg/day). Likewise, McCauley et al. (1985) observed no adverse effect on blood pressure following subchronic exposure to barium in drinking water at the highest level tested (150 mg/kg/day). It has been suggested that the hypertension observed by Perry et al. (1989, 1985) may have been the result of calcium deficiency arising from the maintenance of the rats on a low metals diet.

Long term human exposure to high concentrations of barium sulphate in workplace air results in baritosis, a relatively benign type of pneumoconiosis (Seaton et al, 1986; Doig, 1976; Pendergrass and Greening, 1953). Although baritosis has been identified in chest X-rays, it is not associated with alterations in lung function, abnormal physical findings, or increases in the incidence of subjective symptoms. It appears that barium sulphate is cleared form the lungs after the cessation of exposure. The exposure levels leading to the development of baritosis are unknown, but the age of the studies would be consistent with exposure to much higher dust concentrations than would be anticipated in workplaces meeting currently regulatory exposure limits for low toxicity dusts (eg 10 mgm^{-3} for inhalable dust and 4 mgm^{-3} for respirable dust in the UK).

NIOSH (1982) reported an increased incidence of hypertension in workers involved in grinding and mixing several grades of barium-containing zinc ores exposed to an unspecified concentration of barium sulphate, consistent with findings of hypertension following oral exposure to barium compounds. The workers, however, were also exposed to other metals, including lead, which has a known hypertensive effect. In the 7 personal samples collected from the bayrite area, the levels of soluble barium ranged from 0.09 to 1.9 mgm^{-3} (mean: 1.07 mgm^{-}

^{3}). In a small scale study, Zschiesche et al. (1992) found no evidence of adverse effects in arc welders exposed to barium concentrations ranging from 0.1-6 mgm^{-3}.

Exposure to barium in drinking water at concentrations greater than 2 mg/litre (US drinking water standard) can cause gastrointestinal disturbances and muscular weakness within a relatively short period. Increased exposure to barium in food or water for a short period may lead to vomiting, abdominal cramps, diarrhoea, difficulties in breathing, increased or decreased blood pressure, numbness around the face, and muscle weakness (ATSDR, 2007). Eating or drinking very large amounts of barium compounds that easily dissolve can cause changes in heart rhythm or paralysis and possibly death.

There is conflicting evidence as to whether or not ingested barium may induce hypertensive effects in humans. Acute hypertension has been observed following accidental or intentional ingestion of soluble barium salts (CDC, 2003; Downs et al., 1995). Two human studies that investigated the effects of long-term barium ingestion in drinking water on blood pressure (Brenniman et al., 1981; Wones et al., 1990) and found no hypertensive effect with their highest exposure concentrations. Both studies identified a NOAEL of 0.21 mg/kg/day. Given that hypertension may develop in response to a number of interacting factors, it is very possible that the effect of chronic barium exposure on blood pressure is relatively small compared to other determinates such as diet and exercise.

In conclusion, the presence of barium sulphate in drilling fluids would not be expected to give rise to adverse health effects, provided that overall levels of exposure to airborne particles are adequately controlled. The UK WELs for barium sulphate are 10 and 4 mgm^{-3} for inhalable and respirable dust, respectively, whereas the limit for soluble barium compounds is 0.5 mgm^{-3}.

9 OTHER MINERALS

9.1 BENTONITE

The drilling fluid composition information provided in Appendix 1 indicates that drilling fluids may contain between 5 and 10% bentonite (CAS no: 1302-78-9). The toxicity of bentonite was reviewed by IPCS (2005). Bentonite is composed mainly of montmorillonite, a clay mineral of the smectite group, and forms through the devitrification of volcanic ash. In addition to montmorillonite, bentonite may contain feldspar, cristobalite, and crystalline quartz. Bentonite has the ability to form thixotrophic gels with water, an ability to absorb large quantities of water, and a high cation exchange capacity. The term bentonite is applied commercially to any clay with similar properties such as Fullers Earth. The crystalline silica content of bentonite has an important influence on its potential to cause adverse respiratory effects.

Long-term workplace exposure to bentonite dust may cause lung damage. The limited data available from studies of bentonite-exposed workers suggest exposure is associated with mild nonspecific tissue changes, similar to those that have been described "small airways mineral dust disease" (nodular peribronchiolar dust accumulations containing refractile material [montmorillonite] in association with limited interstitial fibrosis). In some of the studies, radiological abnormalities have also been reported. There are insufficient data to establish a dose–response relationship and there is no evidence of a marked diffuse/nodular pulmonary tissue fibrotic reaction to montmorillonite in the absence of free silica. Statistically significant increases in the incidence of or mortality from chronic bronchitis and pulmonary emphysema in workers exposed to clays in workplace air may result from exposure to quartz rather than the clay minerals.

There are few animal data for bentonite. The deposition and kinetics of inhaled radio labelled fused montmorillonite have been studied in mice, rats, dogs, and humans. Deposition in the nasopharynx increases with particle size whereas tracheobronchial deposition is independent of particle size and pulmonary deposition decreases with increasing particle size. The removal of particles from the lungs took place by solubilization in situ and by physical clearance. The clearance by mechanical removal was slow, especially in dogs: the half-time was initially 140 days and increased to 6,900 days by day 200 post-exposure.

Single intratracheal injection into rodents of bentonite and montmorillonite with low content of quartz has been reported to cause dose- and particle size-dependent cytotoxic effects, as well as transient local inflammation, oedema and, consequently, increased lung weight. Single intratracheal exposures of rats to bentonite produced storage foci in the lungs 3–12 months later. After intratracheal exposure of rats to bentonite with a high quartz content, fibrosis was also observed. Bentonite increased the susceptibility of mice to pulmonary infection.

There are limited data on the effects of multiple exposures of experimental animals to montmorillonite or bentonite. Mice fed diets containing 10% or 25% bentonite displayed slightly reduced growth rates, whereas mice fed a diet with 50% bentonite showed minimal growth, developed fatty livers and eventually fibrosis of the liver and benign hepatomas.

The results of in vitro studies of the effects of bentonite on a variety of mammalian cell types indicate dose-dependent cytotoxicity characterised by membrane damage, cell lysis and functional changes in several types of cells. No adequate studies are available on the carcinogenicity of bentonite or the genotoxicity of clays.

Single, very limited studies did not demonstrate developmental toxicity in rats after oral exposure to bentonite.

The biological effects of clay minerals are influenced by their mineral composition and particle size. The decreasing rank order of the potencies of quartz, kaolinite, and montmorillonite to produce lung damage is consistent with their known relative active surface areas and surface chemistry.

In conclusion the toxicity of bentonite is heavily dependent on its crystalline silica content. In the absence of silica, montmorillonite (the main clay mineral in bentonite) appears to have a relatively low toxicity and would not be expected to give rise to adverse respiratory effects, provided that overall levels of exposure to airborne particles are adequately controlled.

9.2 KAOLIN

Drilling fluids may contain up to 1% kaolin, a low toxicity aluminosilicate, presumably present as a contaminant of bentonite or other mineral component of drilling fluids.

The UK HSE summary criteria document for an occupational exposure standard (OES) (most recent revision, 1997) indicates kaolin would not be anticipated to cause irritation to the eyes and respiratory system or to be associated with sensitisation. In rats exposed to 10 mgm^{-3} for 12 months, minimal fibrosis was observed at 24 months post exposure. Pneumoconiosis has been reported in workers exposed to high concentrations of kaolin. Only one study has reported dose-response information. It was established from extrapolation from an extremely limited data set that 40 years exposure to concentrations between 2.5 and 5 mgm^{-3} is associated to increased risks of category 1 pneumoconiosis, although this would not be associated with discernable symptoms or loss of lung function. Working lifetime exposure to concentrations of between 0.2 and 1 mgm^{-3} is unlikely to give rise to radiological evidence of pneumoconiosis. The UK OES is 2 mgm^{-3}. The ACGIH TLV for kaolin is also 2 mgm^{-3}. This is based on studies in which pneumoconiosis was reported in kaolin processing workers (milling, bagging and loading) with exposures to 2 to 5 mgm^{-3}, although historical exposures (that would have contributed substantially to pneumoconiosis risk) were likely to have been much higher (potentially >300 mgm^{-3}). Pneumoconiosis was relatively uncommon in extraction workers exposed to dust concentrations of between 0.2 and 1 mgm^{-3} (ACGIH, 2005)

Some kaolin preparations may be contaminated with crystalline silica which would lead to a greatly enhanced level of toxicity relative to pure kaolin, but given the small quantity of kaolin expected to be present in drilling fluids, the issue of silica contamination is likely to be of minimal significance.

In conclusion, repeated exposure to elevated concentrations of kaolin is associated with increased risks of developing chronic respiratory illness including pneumoconiosis. Given the low concentrations of kaolin expected to be present in drilling fluids, however, the associated risk of adverse respiratory effects is anticipated to be negligible, provided that overall exposures to airborne particles are adequately controlled.

9.3 CRYSTALLINE SILICA

Drilling fluids contain variable quantities of crystalline silica (SiO_2; CAS no: 99439-28-8) but where respirable silica is specifically identified, the content is less than 2%. The silica is presumably present as a contaminant of bentonite or other mineral product added to drilling fluids. Exposure to respirable crystalline silica (RCS) in workplace air has the potential to cause silicosis, an irreversible, slowly progressing lung disease that can take years to develop. The

main symptoms are breathing difficulties and a chronic cough. In severe cases, silicosis can be extremely disabling and can lead to premature mortality. Long term exposure to RCS is also associated with an increased risk of lung cancer and the International Agency for Research on Cancer (IARC, 1997) have classified RCS as a Category 1 Carcinogen (ie a proven human carcinogen).

There have been many studies of the relationship between differing levels of workplace exposure to crystalline silica and the risks of developing respiratory illness. Both the intensity of exposure to silica (mean personal exposure concentrations over a typical working shift) and the number of years over which workers are exposed appear to be important. The severity of silicosis is categorised on the basis of x-ray response with 1/1 being the least severe category considered in epidemiological studies. Even in the absence of workplace exposure to crystalline silica or other dusts, many individuals do develop mild changes in chest x-rays during life, particularly if they smoke. Reported dose response relationships linking workplace exposure to crystalline silica to the risk of developing silicosis are very variable (Figure 1). There are a number of factors that contribute to this variability including:

- Differences in the potency of crystalline silica in different workplaces;
- Uncertainties in the estimation of exposures used in the calculation of exposure-response relationships;
- Differences in the length of follow-up (changes in chest x-ray responses may only become apparent years after cessation of exposure); and
- Differences in the smoking habits of different populations.

A number of the studies did not follow subjects beyond retirement and report significantly lower risks than those with more complete follow up (Finkelstein, 2000). Finkelstein (2000) suggests that the exposure-response function for silicosis is nonlinear with risks becoming disproportionately greater as cumulative exposure increases.

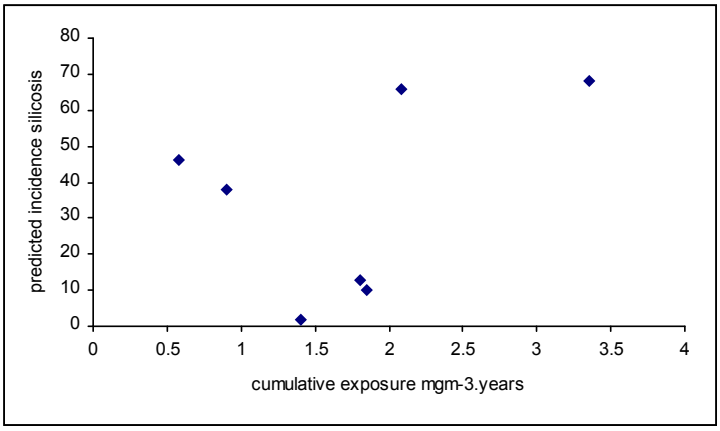

Figure 1: Relationship between cumulative exposure to crystalline silica and the risk (percent) of developing silicosis category 1/1 or greater in workers exposed to airborne dust containing crystalline silica (NIOSH, 2002)

Particles of crystalline silica in different workplace environments may be either quartz or cristobalite and may have very different surface characteristics that affect their toxicity. Other particles present in workplace air such as clay minerals may either increase or reduce the toxicity of quartz or cristobalite. The studies reviewed by NIOSH (2002) suggest that the risk of developing the early radiographic symptoms of silicosis (ILO category 1/1+) are about 20% per mgm^{-3}.year of cumulative exposure. This implies that 40 years exposure to 0.1 mgm^{-3} at work

would be associated with a 2% risk of developing silicosis. A more recent Scottish study (Buchanan et al, 2003) in which coalminers had unusually high exposures to freshly shattered RCS reported that only 15 years exposure to a concentration of 0.1 mgm^{-3} would be associated with a 2.5% risk of developing silicosis of sufficient severity to give rise to discernable respirable symptoms. It is likely that quartz particles within drilling fluids would have aged surfaces that may be coated by aluminosilicate clays or other substances that would reduce their surface reactivity. The silicosis risk associated with 40 years exposure to 0.1 mgm^{-3} RCS in drilling fluids is more likely to be similar to the level of risk reported in the studies reviewed by NIOSH (2002) than the much higher levels of risk reported in the Scottish study. The cancer risk is very much smaller than the risk of silicosis. Steenland et al (2001) estimated that excess lifetime risk (through age 75) of lung cancer for a worker exposed from age 20 to 65 at 0.1 mgm^{-3} RCS was 1.1-1.7%, above background risks of 3-6%. Other studies have failed to find an excess risk of lung cancer (eg Mundt et al, 2011).

9.4 TITANIUM DIOXIDE

9.4.1 Exposure

The drilling fluid information provided in Appendix 1 indicates that drilling fluids may contain between 1 and 5% titanium dioxide (TiO_2) (CAS no: 98084-96-9).

9.4.2 Effects in humans

TiO_2 dust is not specifically irritating to eyes, respiratory system or skin but may cause symptoms of irritation at high levels of exposure.

Long-term exposure to airborne TiO_2 in the workplace has been associated with a decline in lung function, pleural disease with plaques and pleural thickening, and mild fibrotic changes. However, the workers in studies reporting these effects were also exposed to asbestos and/or silica (IARC, 2006). It is likely, however, prolonged high levels of exposure would give rise to a reduction in lung function and increased risks of respiratory illness such chronic bronchitis and potentially pneumoconiosis, similar to effects seen in other workers with prolonged heavy exposure to airborne dust.

Studies on the application of sunscreens containing ultrafine TiO_2 to healthy skin of human volunteers revealed that TiO_2 particles only penetrate into the outermost layers of the stratum corneum, suggesting that healthy skin is an effective barrier to TiO_2 (IARC, 2006). There are no studies on penetration of TiO_2 in compromised skin.

IARC (2006) reviewed three epidemiological cohort studies and one population-based case–control study that investigated cancer risk. The largest of the cohort studies was in TiO_2 production workers in six European countries. The study indicated a slightly increased risk for lung cancer compared with the general population but found no evidence of an exposure–response relationship. There was no increase in the mortality rates for kidney cancer in comparisons with the general population, but there was a suggestion of an exposure–response relationship in internal analyses. The other cohort studies were conducted in the USA and did not report an increased risk for lung cancer or cancer at any other site. The population-based case–control study conducted in Montreal did not indicate an increased risk for lung or kidney cancer. All four studies had methodological limitations and none were designed to assess the impact of particle size (fine or ultrafine) or the potential effect of the coating compounds on the risk for lung cancer. The increasing use of nano-sized TiO_2 materials may lead to different findings in future studies.

9.4.3 Effects in animals

Studies of the deposition, retention and clearance of inhaled TiO_2 in experimental animals have demonstrated dose-dependent impairment of alveolar macrophage-mediated clearance that are species and strain (rat) dependent. Ultrafine primary particles of TiO_2 are more slowly cleared than their fine counterparts (IARC, 2006). Bermudez et al (2004), for example, demonstrated that mice and rats exposed to 10 mgm^{-3} ultrafine TiO_2 for 6 hours/day, 5 days/week, for 13 weeks showed reduced levels of pulmonary clearance on cessation of exposure reflecting overload that was accompanied by markers of lung inflammation and cellular damage. There was some reduction in lung inflammation in mice following cessation of exposure, but not in rats. Rats developed pulmonary lesions that consisted of foci of alveolar epithelial proliferation of metaplastic epithelial cells around aggregated foci of heavily particle-laden macrophages.

The results of long term inhalation studies in animals are mixed (IARC, 2006). The incidence of benign and malignant lung tumours was increased in female rats in one study whereas in another study, the incidences of lung adenomas were increased in the high-dose groups of male and female rats. Cystic keratinizing lesions that were diagnosed as squamous-cell carcinomas but re-evaluated as non-neoplastic pulmonary keratinizing cysts were also observed in the high-dose groups of female rats. These keratin cysts are a species-specific lesion that is unique to the rat lung under conditions of particle overload exposure (Warheit and Frame, 2006). No tumours were reported in two other inhalation studies in rats and one in female mice.

Rats exposed to TiO_2 by intratracheal instillation showed an increased incidence of both benign and malignant lung tumours following treatment with two types of TiO_2. Tumour incidence was not increased in intratracheally instilled hamsters and female mice.

There is little evidence that TiO_2 is genotoxic.

9.4.4 Conclusions

IARC concluded that there is sufficient evidence in experimental animals for the carcinogenicity of TiO_2 and classified TiO_2 as possibly carcinogenic to humans (Group 2B). The IARC evaluation was controversial as there has been considerable debate as to whether the cancers observed in animals exposed to high concentrations of TiO_2 are attributable to some intrinsic property of TiO_2. It has been widely argued that the observed tumours were a secondary consequence of exposure to excessive dust concentrations giving rise to lung overload accompanied by chronic alveolar inflammation. The inflammatory response may result in cell injury, cell proliferation, fibrosis, induction of mutations, and, ultimately, cancer. Since many of these steps also occur in dust-exposed workers, IARC considered that data on cancer in animals obtained under conditions of impaired lung clearance were relevant to humans, particularly as animal experiments have demonstrated that overload with ultrafine particles occurs at much lower mass concentrations than with fine particles.

In terms of considering the toxicity of oil drilling fluids, it is unlikely that workers would be repeatedly exposed to concentrations of airborne particles sufficient to cause overloading of the lung's clearance systems and the possible carcinogenicity of TiO_2 is unlikely to be of relevance. Excessive exposure, however, may give rise to an increased risk of chronic respiratory illnesses such as bronchitis and potentially pneumoconiosis.

10 SOLVENTS, EMULSIFIERS AND DETERGENTS

10.1 2-(2-BUTOXYETHOXY)ETHANOL

2-(2-butoxyethoxy)ethanol ($C_8H_{18}O_3$) (also known as Diglycol monobutyl ether or DEGBE) (CAS no: 210818-08-9) is present in some drilling fluids used by Statoil at concentrations of up to 1% (Appendix 1).

There is little readily available information about 2-(2-butoxythoxy)ethanol. The International Chemical Safety Card (www.inchem.org) indicates that exposure can lead to dry skin and redness and pain of the eyes.

There is considerably more information about the related but simpler molecule 2-butoxyethanol ($C_6H_{14}O_2$; CAS no: 9004-77-7). The CICAD (2005) indicates that 2-butoxyethanol is readily absorbed following inhalation, oral, and dermal exposure and is mostly metabolised to 2-butoxyacetaldehyde and 2-butoxyacetic acid. 2-butoxyethanol has moderate acute toxicity and is irritating to the eyes and skin; it is not a skin sensitizer. Both 2-butoxyethanol and its metabolite 2-butoxyacetic acid are toxic to red blood cells, with the rat being the most sensitive species. It seems likely that the metabolites of 2-(2-butoxyethoxy)ethanol would include also include 2-butoxyacetic acid such that similar adverse effects on blood cells might arise.

The CICAD indicates that in rats, 2-butoxyethanol also causes adverse effects on the central nervous system, kidneys, and liver but at higher levels of exposure than haemolytic effects. The lower bound estimate of the dose associated with a 5% incidence of haematological effects in rats in a long term study was 5.3 mgm^{-3}

There is no evidence that 2-butoxyethanol is mutagenic. In a two year study in rats, exposure to 2-butoxyethanol at 153 mgm^{-3} (the lowest concentration tested) or greater resulted in haemolytic effects but no evidence of carcinogenicity. In a two year study in mice, however, there were increased incidences of tumours of the fore-stomach which were statistically significant in females exposed to 1,230 mgm^{-3} and in males at 614 and 1,230 mgm^{-3}. The incidence of hyperplasia of the epithelium of the fore-stomach was significantly increased in a concentration-related manner in all exposed groups, which was accompanied by a concentration-related trend in the incidence of ulcers of the fore-stomach in female mice. The severity of the epithelial hyperplasia in females also increased with exposure level. There was also a concentration-related increase in the incidence of haemangiosarcomas of the liver in male mice (significant at 1,230 mgm^{-3}). The lowest concentration at which non-neoplastic effects (haematotoxicity and fore-stomach lesions) were reported was 308 mgm^{-3} in both sexes. The predicted concentration associated with a 5% increase in the incidence of hyperplasia of the fore-stomach epithelium was 4.3 mgm^{-3}.

Information on human health effects associated with exposure to 2-butoxyethanol are limited to a few case reports, a clinical investigation, and a cross-sectional survey. The principal human health effects attributed to 2-butoxyethanol exposure have involved the central nervous system, the blood, and the kidneys. In a cross-sectional survey, slight, but statistically significant, changes in some haematological parameters were observed in a group of 31 men occupationally exposed to average concentrations of 2-butoxyethanol of 3.64 or 2.20 mgm^{-3} compared with unexposed workers. However, there was no correlation with urinary levels of a marker of exposure to 2-butoxyethanol, and information on exposure was limited. Another report indicated that the exposure of two males to 2-butoxyethanol at 560 mgm^{-3} for 4 hours produced nose and eye irritation as well as disturbed taste. Similar effects were observed among two males and one female exposed to 2-butoxyethanol at 960 mgm^{-3} for two 4 hour periods,

separated by a 30 minute period of no exposure. When two males and two females were exposed to 2-butoxyethanol at 490 mgm^{-3} for 8 hours, the effects included vomiting and headache.

The CICAD (2005) derived a tolerable human dose of 11 mgm^{-3} based on haematological disturbances in rats and 0.4 mgm^{-3} based on fore-stomach tumours in mice.

It seems possible that high levels of exposure to 2-(2-butoxyethoxy)ethanol would cause haematoxic effects. Given the low concentrations present in drilling fluids, it is likely that exposure levels would be well below levels that might be harmful to human health. It is possible that 2-(2-butoxyethoxy)ethanol would augment haematoxicity associated with other substances present in drilling fluids.

10.2 QUATERNARY AMMONIUM SALTS

Drilling fluids may contain up to 1% quaternary amine. Quaternary amines include a wide range of compounds used as emulsifiers, detergents and disinfectants. The IPCS (1999) Poison Information Monograph (PIM) indicates that quaternary amines are associated with various health effects ranging from mild skin and respiratory irritation at low levels of exposure to severe caustic burns on skin at higher levels of exposure. Repeated exposure to lower concentrations may cause dermatitis. Systemic absorption of quaternary ammonium salts following contact with intact skin is small and no systemic effects would be anticipated following accidental splashes. Some systemic absorption would be likely if fluid came into contact with broken skin. Ingestion causes gastro-intestinal symptoms (e.g., nausea and vomiting), more severe damage to the gastrointestinal tract, coma, convulsions, hypotension and death.

Repeated dermal application of benzalkonium chloride, a widely used quaternary ammonium compound, induced skin irritation in several species of laboratory animal (EMEA, 1997). Skin irritation was not observed in rabbits repeatedly exposed to a 0.1% solution but was observed in rats exposed to a 1% solution. Very slight irritation of the eye was reported in rabbits exposed to concentrations as low as 0.01 and 0.03% and minimal irritation of the rabbit eye at a concentration of 0.1% (SCCP, 2002). Eye irritation has also been reported in humans and animals exposed to concentrations of benzalkonium chloride of between 0.01 and 0.3%. In humans, exposed to various concentrations of benzethonium chloride, the lowest concentration associated with skin irritation was 0.63% (under an occlusive dressing) and no irritation was observed at 0.31% (SCCP, 2002).

Rats exposed to a dermal dose of benzalkonium chloride of 10 mg/kg, 5 times a week for 3 months showed changes in blood cell counts, liver and kidney damage, increased body temperature and increased weight of adrenals, kidneys and testes. In long term experiments in rats in mice repeated exposed to benzethonium chloride via the skin, the no effects level for systemic toxicity was greater than 12.5 mg/kg/day. No adverse effects were observed in rats exposed to 300 mg/kg/day of benzalkonium chloride in their diet for 4 to 5 weeks. Rabbits exposed to 50 mg/kg/day for 2 weeks showed an accumulation of blood and fibrous material in their lungs (EMEA, 1997). In repeated dose experiments in which animals were exposed to benzethonium chloride in food, the no effects level in dogs was greater than 40 mg/kg/day and in rats it was greater than 80 mg/kg/day. Effects on male reproductive organs were observed in rats at 200 and 400 mg/kg/day and increased mortality was also observed in rats at 400 mg/day.

The PIM indicates that repeated exposure to dilute solutions or infrequent exposure to a high concentration may give rise to sensitisation. Other sources suggest that the potential for sensitisation is very low. Uter et al (2008) found some weak clinical evidence indicating that in

benzalkonium chloride is a contact allergen. The EMEA summary of benzalkonium chloride toxicity also indicates that there is evidence linking exposure to benzalkonium chloride at concentrations of between 0.01 and 0.3% to sensitisation. In contrast, negative results were obtained in a sensitisation test in humans exposed to benzethonium chloride at a concentration of 0.12% under closed patches. Negative results were also obtained in an assay in guinea pigs at concentrations of 0.2 or 0.5% (SCCP, 2002). In a study of the cumulative irritation and/or sensitisation potential of benzethonium chloride in humans exposed to a 0.3% aqueous solution, 6 of 152 subjects showed evidence of mild skin irritation and one individual showed evidence of sensitisation. It was concluded that benzethonium chloride at 0.3% did not elicit dermal irritation and/or sensitisation (SCCP, 2002).

The concentration of quaternary amine that is present in drilling fluids is likely to be sufficient to cause skin irritation, particularly in susceptible individuals, and repeated exposure may be associated with a small risk of sensitisation.

11 THICKENING AGENTS

11.1 POLYALKYLENE GLYCOL

Polyalkylene glycol (CAS no: 9003-13-8) may be present at concentrations of up to 5% in some drilling fluid compositions. Polyalkylene glycols span a wide range of compounds but information is most readily available for polyethylene glycol (PEG) (CAS no: 25322-68-3) and polypropylene glycol (PPG) (CAS no: 57-55-6) which are both used as food additives and in cosmetics and medications.

A review of the use of PEG derivatives in cosmetics (Fruijtier-Pölloth, 2005) indicated that PEGs produce little or no ocular or dermal irritation, have extremely low acute and chronic toxicities, and are highly unlikely to give rise to reproductive and developmental toxicity, genotoxicty or cancers. They do not readily penetrate intact skin and have little potential to cause sensitisation.

The JECFA (1979) review of PEG indicates that they appear to be slow-acting parasympathomimetic-like compounds (i.e. substances that stimulate or mimic the parasympathetic system which controls activities such as sexual arousal, salivation, lacrimation (tears), urination, digestion and defecation). Intravenous administration can cause blood to clot and if given rapidly causes clumping of the cells leading to death from embolism. Inhalation exposure to exceedingly high concentrations (>>>10 mgm^{-3}) of PEGs might conceivably give rise to similar effects. PEGs have a low toxicity following oral administration (Table 4) and their toxicity reduces with increasing molecular weight.

Table 4: Median lethal dose following oral administration of PEGs of differing molecular mass.

Molecular weight	Median lethal dose mg/kg	
	Rats	Mice
PEG 200	28,900	33,900
PEG 300	29,900	31,000
PEG 400	43,600	35,600
PEG 600	32,600	35,600
PEG 1000	32,000 – 44,700	>50,000
PEG 4000	>50,000	>50,000
PEG 6000	>50,000	>50,000
PEG 9000	>50,000	>50,000

In two year repeated dose experiments in rats, an oral dose 60 mg/kg/day of PEG 1500 or 20 mg/kg/day of PEG 4000 did not cause any significant adverse effects (mortality, frequency of infection, life-span, fluid consumption, body weight gain, kidney and liver weights, litter size, blood cytology, urinary albumen and sugars, occurrence of neoplasm, and micropathology). In another 2 year study in rats, the no effects level for PEG 1540 and 4000 was 4% diet and for PEG 400, the NOEAL was 2%. At higher exposures, PEGs produced small, nonspecific effects upon growth or minor cloudy swelling of the liver. The NOEAL for PEG 200 was 4.0%.

PEGs have a low potential to cause skin irritation or sensitisation, although a small number of individuals have become sensitised to lower molecular weight liquid polyethylene glycols in topical medications. Prolonged skin contact of PEG 1500 and 4000 upon the skin of rabbits in dosages of 10 g/kg gave rise to no adverse effects and little, if any, absorption through the skin.

JECFA concluded that the NOAEL in rats is 20,000 ppm (2%) in the diet, equivalent to 1,000 mg/kg. The ADI for man was estimated as 10 mg/kg (700 mg), or an intake equivalent to that associated with inhalation of a concentration of 70 mgm^{-3} over an 8 hour shift.

JECFA reported that PPG has many properties in common with PEG but is considered to be less toxic. PPG has an irritant effect on direct contact with eyes, mucous membranes and possibly after prolonged contact with skin. The toxicity of PPG is mainly due to the parent compound and not to its metabolites. PPG causes CNS depression similar to that caused by ethanol but is only one-third as potent. PPG is also associated with cardiotoxic effects including arrhythmias and cardiac arrest and liver and kidney damage. The SIDS dossier, however, indicates that propylene glycol has an extremely low toxicity. The lowest median lethal oral doses range between 18 and 23.9 g/kg (5 different species) and the reported median lethal dermal dose is 20.8 g/kg. Propylene glycol does not cause skin irritation, causes mild eye irritation and is not a skin sensitizer. Exposures of rats to PPG in drinking water at a dose of 10 g/kg/day or feed at a dose of 2500 mg/kg/day for 2 years did not cause adverse effects. PPG is not genotoxic or carcinogenic and does not cause reproductive or developmental toxicity in experimental animals. JECFA determined that the ADI for PPG is up to 25 mg/kg/day.

In conclusion, although excessive exposure to polyalkylene glycols may cause adverse effects on health, it is unlikely that their presence in drilling fluids is likely to give rise to toxicity or irritation of the eyes, respiratory system or skin.

11.2 POLYETHYLENE GLYCOL ETHER/ POLYALKYLENE GLYCOL ETHER

Polyethylene glycol ether may be present in drilling fluids at concentrations of up to 5%. Small quantities (<1%) of polyalkylene glycol ether may be present in some drilling fluid compositions. It is not clear whether polyalkylene glycol ether refers to a specific compound or a class of compounds or what the nature of polyalkylene glycol ether might be. There is virtually no information on the toxicity of polyethylene glycol ethers and the limited information available suggests that derivatives of polyethylene glycol (PEG) typically have relatively low levels of toxicity. These compounds are widely used in cosmetic products and may also be used as food additives because of their solubility and viscosity properties, and because of their low toxicity.

A review of the use of PEG derivatives in cosmetics (Fruijtier-Pölloth, 2005) indicated that PEGs, their ethers, and their fatty acid esters produce little or no ocular or dermal irritation, have extremely low acute and chronic toxicities and have a negligible potential to cause sensitisation. Based on information for some of these compounds, it was concluded that they are highly unlikely to give rise to reproductive and developmental toxicity, genotoxicty or cancers. Fruijtier-Pölloth (2005) concluded that PEGs of a wide molecular weight range (200 to over 10,000), their ethers, and fatty acid esters are safe for use in cosmetics, provided that these products are not applied to damaged skin. It seems unlikely that the toxicity of other polyalkylene glycol ethers would be significantly different from that of PEG derivatives.

It seems highly unlikely that the presence of polyethylene glycol ether(s) or polyalkylene glycol ether in drilling fluids represents a significant risk to health provided that overall exposure to airborne particles are adequately controlled and dermal contact is minimised/prevented. Adverse effects may arise if fluids are in contact with broken skin.

11.3 POLYAMIDE

Polyamide (CAS no: 63428-83-1) is present in some drilling fluids at concentrations of less than 5%. The term polyamide covers a wide range of substances including naturally occurring

proteins and man-made polymers such as nylon. In the absence of information about the nature of the polyamide, it is difficult to comment on its potential toxicity.

11.4 AMPS-NA / ALKYLACRYLAMIDE POLYMER BLEND

AMPS-NA / Alkylacrylamide polymer blend is recorded as being present at concentrations of up to 1% in drilling fluids. There is no readily available toxicity information for this substance which appears to be regarded as having a relatively low toxicity (based on suppliers' information).

Given the relatively low levels of exposure to this substance that are likely to occur and the absence of information indicating that this substance is likely to be particularly harmful to health, it is anticipated that its presence in drilling fluids is associated with a negligible risk to human health.

11.5 POLYANIONIC CELLULOSE POLYMER

Polyanionic cellulose polymer is recorded as being present at concentrations of up to 1%. There is no readily available toxicity information for this substance which appears to be regarded as having a relatively low toxicity (based on suppliers' information).

Given the relatively low levels of exposure to this substance that are likely to occur and the absence of information indicating that this substance is likely to be particularly harmful to health, it is anticipated that its presence in drilling fluids is associated with a negligible risk to human health

11.6 STARCH

Small quantities (<1%) of starch ($C_{27}H_{48}O_{20}$) (CAS no: 9057-07-2) may be present in some drilling fluids. Starch is an important dietary component and has a low toxicity following ingestion. The ACGIH TLV is set up 10 mgm^{-3} and the documentation notes that the only known adverse health effect of workplace exposure to starch is mild dermatitis associated with the handling of starch products. Workplace exposure to airborne starch may aggravate existing respiratory illness, but it is not believed to have other adverse effects on respiratory health (ACGIH, 2005). By comparison with other low toxicity dusts, it seems likely that excessive exposure to airborne starch as powder or in a mist would result in irritation of the airways in the short term and increased risks of chronic respiratory illness following repeated exposure. Workplace exposures to airborne starch are often combined with exposure to endotoxin or other bioaerosol components that could give rise to adverse effect. This would only be of relevance to drilling fluids, if controls on microbial growth were inadequate.

In conclusion, the presence of low concentrations of starch in drilling fluids would have a negligible impact on the potential of these fluids to cause dermatitis or respiratory illness.

11.7 COLLOIDAL CELLULOSE FIBRE

Small quantities (<1%) of colloidal cellulose fibre may be present in some drilling fluids. Cellulose is an important dietary component and has a low toxicity following ingestion. Although there are limited animal data suggesting that the inhalation of high concentrations of respirable cellulose fibre is likely to be damaging to health (eg Cullen et al, 2000), it seems unlikely that the use of colloidal cellulose in small quantities in drilling fluids would give rise to an increase in airborne fibre concentrations. The presence of low concentrations of colloidal cellulose in drilling fluids would have a negligible impact on the potential for dermatitis.

11.8 XANTHIUM GUM

Small quantities (<1%) of xanthium gum may be present in some drilling fluid compositions. Xanthium gum appears to be used as a thickener in some food preparations and is therefore assumed to be of low toxicity, but no specific information was found by an internet search using Google. Given the low concentration that is present in drilling fluids, any contribution of xanthium to potential adverse health effects would be anticipated to be negligible.

11.9 ORGANIC CLAY

Organic clay is clay coated with fatty acids (wetting agents) in order that the clay is oil-wettable (Appendix 1). Organic clay is an efficient viscosifier in oil-based drilling fluids. The wetting agent is usually added while grinding the clay. It is difficult to predict the impact of the wetting agent on the toxicity of clay (or vice versa). It is likely to reduce the likelihood of the formation of respirable dust and, therefore, inhalation exposure. The wetting agent may, however, increase the potential of any respirable dust that is formed to cause respiratory irritation.

12 BIOCIDES

12.1 CITRIC ACID

Citric acid ($C_6H_8O_7$; CAS no: 77-92-9) may be present at concentrations of between 1 and 5% in some drilling fluids.

The SIDS dossier (available from www.inchem.org) indicates that citric acid has a low toxicity and that there were no adverse effects levels in rats following repeated oral exposure is 1,200 mg/kg/day. The main adverse effect associated with exposure to citric acid is irritation to the eyes, respiratory system and skin. A concentration of 0.3% is sufficient to cause "stinging" in intact skin. Repeated exposure may cause some changes in blood chemistry and metal desorption/excretion kinetics (which may be of relevance in the context of drilling fluids). The SIDS dossier indicates that citrate acid is not expected to be carcinogenic or genotoxic and the no effects level for reproductive toxicity in rats is 2,500 mg/kg/day.

Citric acid is unlikely to have an important influence on the toxicity of oil drilling fluids, although it may have a small influence on the toxicity of other substances present in drilling fluids, particularly metals. The presence of citric acid in drilling fluids may contribute to the potential of these fluids to cause irritation to the eyes, respiratory system and skin, although the irritative impacts of citric acid may be reduced by neutralisation of its acidity by other substances in drilling fluids.

12.2 GLUTARALDEHYDE

Glutaraldehyde ($C_5H_8O_2$; CAS no: 90045-36-6) is used as a biocide and may be present in drilling fluids at concentrations of between 1 and 5%. Exposure to glutaraldehyde is associated with irritation of the skin, eye and respiratory tract, skin sensitisation and occupational asthma.

12.2.1 Human data

The HSE summary criteria document (HSE, 2002), the combined Dutch Expert Committee on Occupational Exposure Standards (DECOS) and Nordic Expert Group (NEG) 1997 criteria document for an OEL and the SIDS dossier indicates that glutaraldehdye is an irritant to human skin at a concentration of 2-10% but not 0.5%. The DECOS-NEG criteria document, however, reviewed a volunteer study in which 16/109 individuals exposed to concentrations of 0.5% developed reddening of the skin, but no effects were observed at 0.1%. The HSE reported that a number of studies have shown that exposure to gluteraldehyde vapour at concentrations of 0.02 ppm gives rise to irritation of the eyes and respiratory system. No evidence of irritation has been reported at concentrations of 0.005-0.008 ppm. Concentrations as low as 0.13% have been reported to induce allergic dermatitis in humans and the no effects level has not been established for either dermal nor respiratory sensitisation. The SIDS dossier indicates that the use of glutaraldehyde as a preservative in cosmetics is permitted in Europe at concentrations of up to 0.1%, implying that this is an anticipated no effects level.

The SIDS dossier indicates that occupational exposure to glutaraldehyde solutions with concentrations of ≥1% is associated with significant risks of dermatitis, eye irritation and skin sensitisation where appropriate risk management measures are not employed.

12.2.2 Animal data

The HSE Criteria document indicates that glutaraldehyde is corrosive to skin and a severe eye irritant at concentrations of 1% and 0.1% respectively in rabbits (the SIDS dossier indicates 2

and 0.2 %). Respiratory irritation was observed in rats and mice following a single exposure by inhalation. The reported median lethal oral dose in rats ranges from 123-2,000 mg/kg, the dermal median lethal dose is 2,500 mg/kg and the inhalation median lethal concentration (4 hours) is 24-40 ppm (96-160 mgm^{-3}) with other unpublished industry data indicating values of 280-800 mgm^{-3}. The median lethal oral dose in mice is between 100 and 352 mg/kg. A number of repeated dose studies have been undertaken and these are summarised in the SIDS, UK HSE Criteria for an Occupational Exposure Limit, and the DECOS-NEG evaluation of Glutaraldehyde. Repeated dermal exposure of mice to glutaraldehyde solutions with concentrations of 25-50% led to deaths of all exposed animals within 9 days and exposure to a 5% solution caused weight loss for the first 4 to 6 days of a 10 day experiment. No signs of toxicity were observed at concentrations of 2.5% or less. Mice exposed for 28 days to doses of 50 - 150 mg/kg/day by dermal application showed reddening of the skin, oedema and a dose related increase in skin lesions. Inhalation exposure of rats for 6 hours/day for 9 days to varying concentrations of glutaldehyde gave rise to respiratory irritation and lesions of the nasal cavity at concentrations ≥ 1.1 ppm. A small increase in lung weight was observed in males at 0.3 ppm. Most animals exposed to 2.1 ppm (9/10 males, 7/10 females) and one animal exposed to 0.63 ppm died (1/20). Exposure of rats and mice for 6 hours/day, 5 days/week for two weeks led to the deaths of all rats exposed to 5 and 16 ppm and mice exposed to 1.6 ppm due to respiratory distress. Damage to the nasal cavity and larynx was observed in both species at ≥ 0.5 ppm. The NOEAL in both species was established as 0.16 ppm. Dose-related lesions of the nasal cavity were reported in rats and mice exposed for 13 weeks 6 hours/day 5 days/ week. A NOAEL of 0.125 ppm and a Lowest Adverse Effects Level (LOAEL) 0.25 ppm was reported in rats and a LOAEL of 0.0625 ppm was reported in mice. The NOAEL in mice was not established. Lesions were stated to be different from those associated with formaldehyde.

Conclusions

Glutaraldehyde is relatively toxic and can cause occupational asthma and/or allergic dermatitis at extremely low levels of workplace exposure.

12.2.3 Quaternary ammonium salts

Quaternary ammonium salts are both emulsifiers and disinfectants. Their toxicity is discussed above in section 10.2.

13 MIXED EXPOSURES

13.1 INHALED MIXTURES

13.1.1 Overview

The toxicology of mixtures is not well understood. There are a number of potential types of interaction that may lead to toxic effects being less than, equivalent to or greater than the sum of the component parts. A number of types of interaction are possible with airborne mixtures:

1. Respirable particles may transport adsorbed toxic substances to parts of the respiratory system in much greater quantities than would have been predicted from the concentration of those substances in air.

2. Adsorption of low toxicity substances onto the surfaces of toxic particles may mask their toxicity.

3. Interactions between substances in air could lead to the formation of new compounds that are more or less toxic than the original substances.

4. Following uptake of inhaled substances, modification or saturation of a metabolic route or physiological function by one substance may either reduce or increase the toxicity of other substances.

5. Competition for particular binding sites in enzymes may delay the metabolism of hydrocarbon species to more or less harmful metabolites (depending on substance and metabolic fate) whereas induction of particular enzymes may lead to increased metabolic rates. The resultant changes in maximum plasma concentrations and overall systemic exposure to the parent substance or metabolites will impact on the overall potential for toxicity to occur.

6. Competition between metals for binding sites in enzymes will impact on potential effects on haemoglobin, cellular function and musculosketal structure, as well as the extent to which metals are absorbed in different tissues.

7. The carcinogenic potential of inhaled substances may be greatly enhanced by other substances in the mix that would not normally be associated with an increased cancer risk in the absence of co-exposure to genotoxic carcinogens.

In risk assessment for workplace exposures, it is conventional to treat exposures to agents that have similar effects as being additive unless there is specific information to indicate that a greater level of control is appropriate (HSE, 2005). For example, when considering solvents, it is common practice to sum the ratio of measured concentration to the exposure limit for each individual sum and the overall exposure would be considered adequately controlled if the sum of the ratios is less than one. Where exposures are to unrelated substances with unrelated effects, it is not considered appropriate to sum up their effect. In contrast, for environmental exposures, a more precautionary approach is normally taken by summing the ratios of the concentration to environmental guidelines across all substances, regardless of whether effects are related or unrelated. If the sum of the ratios exceeds unity, then risks would normally be considered unacceptably high (eg US EPA, 1989; Department of Environment, 1995). The difference in approach reflects the more precautionary approach taken to managing environmental exposures which are involuntary in contrast to workplace exposures which

although voluntary, are associated with some benefit to the individual being exposed (i.e. payment).

13.1.2 Interactions between particles and other components in workplace air

Although there are many environments in which people are exposed to a mixture of particle types, there has been relatively little investigation of the effects of exposure to mixtures versus those associated with the component parts. The limited evidence is not consistent with the harmfulness for some mixed exposures greater than the sum of the parts whereas the converse is true for other mixtures.

Zhou et al (2003) reported a synergistic interaction between soot and ultrafine iron in healthy adult rats exposed for 6 hours/day for 3 days. No adverse respiratory effects were observed in animals exposed to soot particles at 0.25 mgm^{-3} or ultrafine iron at 0.057 mgm^{-3} but the addition of 0.045 mgm^{-3} of iron to soot with a combined total mass concentration of 0.25 mgm^{-3} gave rise to markers of pulmonary inflammation and oxidative stress. Transition metals are believed to play an important role in the toxicity of particles in ambient air because of their ability to participate in redox reactions leading to oxidative stress (Donaldson et al, 2005) and this may partly explain the enhancement of toxicity in the iron-soot mixture. Wilson et al (2002) reported that co-exposure to iron chloride led to a significant enhancement of the adverse pulmonary effects of ultrafine carbon black in rats. The clays used in drilling fluids generally have low transition metal contents in their pure form, although they may contain small quantities iron minerals as contaminants. It seems unlikely that significant synergistic interactions similar to that described by Zhou et al (2003) in the absence of readily available transition metals.

The reduction in the apparent toxicity of crystalline silica by co-exposure to aluminium containing compounds is well documented (NIOSH, 2002) and is thought to arise from deactivation of the surface properties of silica that are associated with toxicity. Conversely, the clearance of TiO_2 from the lungs is affected by pre-exposure to gaseous pollutants or co-exposure to cytotoxic aerosols indicating a potential increase in the toxicity of titanium dioxide arising from the resultant impact on lung burden (IARC, 2006).

It has been suggested that the toxicity of particles in ambient air is greatly enhanced by the presence of absorbed toxic substances such as PAHs and the potential increase in transfer of these substances to the deep lung as a result of absorption on particles. There is an absence of other data describing the effects of vapour particle mixtures that are directly relevant to drilling fluids. There are, however, data that show how mixed exposure to acid vapours or ozone and particles can give rise to greater effects than would have been predicted from the toxicity of the individual substances. A number of animal studies have shown that exposure to a range of particulate materials including ammonium sulphate, sulphuric acid, soot and carbon black, causes increased airways reactivity to ozone and other oxidants (COMEAP, 1995). Similarly, Oehme et al (2006) reported that nitrogen dioxide is synergistic with ozone and ammonium sulphate giving rise to a response that was 340% of the summed effects. Co-exposure to ozone and aerosols of neutral salts such as sodium sulphate or chloride does not however, give rise to synergistic effects (Last et al, 1984; 1991) suggesting that the acidity of the aerosol, rather than sulphate content potentiates the effects of ozone. Jakab et al (1996) found evidence that exposure of rats to sulphuric acid coated carbon black caused a decrease in the phagocytic activity of macrophages not seen in rats exposed to the same concentration of uncoated carbon black. Similarly exposure to metals may potentiate the response to sulphuric acid with sulphuric acid adsorbed on fine metal oxides being a more effective irritant than free sulphuric acid (Amdur, 1996).

It is possible that particles present in workplace atmospheres could enhance the toxicity of the volatile components of drilling fluids, but unlikely that this is a particularly significant effect as it has not been extensively described for other workplace atmospheres where mixtures exist. It seems likely that the harmfulness of respirable crystalline silica in drilling fluids is likely to be reduced by the presence of adsorbed clays and other substances.

13.1.3 Formation of toxic substances as reaction products in workplace air

Several studies have demonstrated how reactions of chemicals in airborne mixtures can give rise to products that are associated with a greater potential to cause irritation than the parent substances. For example, Clausen et al (2001) demonstrated how the reaction products of limonene (a common contaminant of indoor air) and ozone caused a greater degree of respiratory irritation in mice than would have been predicted from the concentrations of the known reaction products. No examples of the formation of irritant compounds in workplace air of direct relevance to drilling fluids were found during the literature search, but such reactions are a feature of complex mixtures that may contribute to the difficulty of predicting toxic effects.

13.1.4 Metabolic interactions

Metabolic interactions are likely to be important in determining the dose of toxic substances or their metabolites that reach target organs with resultant impacts on toxicity. They are likely to be of particular significance for hydrocarbon molecules, particularly those metabolised by the liver.

There is some evidence that the combined effects of exposure to toluene and benzene may be less than the summed effects of each individual agent. Gradiski et al (1981) reported the long term inhalation exposure of rats to benzene at a concentration of 50 ppm gave rise to leucopenia (lowered white blood cell count) with benzene alone but not when exposure was combined with toluene. Observed metabolic effects associated with the combined exposure relative to those associated with benzene alone included a decrease in the phenol urinary rate versus time, particularly from the third month of exposure on. Purcell et al (1990) investigated the metabolic interactions of benzene and toluene co-exposure in male rats and reported mutual suppression of metabolism with toluene inhibiting benzene metabolism to a greater extent than benzene inhibited toluene metabolism.

Kosak et al (1994) exposed rats to m-xylene and n-butyl alcohol at concentrations of 50 and 100 ppm and their 1:1 mixture at concentrations of 50 + 50 ppm and 100 + 100 ppm for 6 hours/day, 5 days/week for 3 months. Whereas exposure to n-butyl alcohol alone caused an increase of lipid peroxidation in hepatic microsomes without any induction of cytochrome P-450 monooxygenases, exposure to m-xylene alone or the mixture did not affect the activity of monooxygenase and lipid peroxidation rate in hepatic microsomes. Overall the effects of combined exposure to m-xylene and n-butyl alcohol were clearly less than additive.

Tardiff et al (1996) exposed rats by inhalation for 4 hours to various binary and tertiary mixtures containing ethylbenzene, toluene or xylene. They reported that exposures to binary and ternary mixtures resulted in significantly higher blood concentrations of unchanged solvents as a result of metabolic interaction between these solvents. Exposure to the ternary mixture resulted in greater interactive effects (3.17-fold increase) than exposures to binary mixtures (1.97-fold increase), whereas four out of six binary mixtures produced higher total levels of unchanged solvents in blood compared to the ternary mixture. The authors concluded that the greater risk of toxicity associated with exposures to complex mixtures may not only be related to the magnitude of interactive effects among components (i.e., degree of mutual metabolic

interaction) but might also reflect the impacts on the internal total dose of toxic chemicals in target organs/tissues.

Eide and Zahlsen (1996) exposed rats to mixtures of three C9 n-paraffinic, naphthenic and aromatic hydrocarbons (n-nonane, trimethylcyclohexane and trimethylbenzene, respectively) for 12 hours at four vapour levels (75, 150, 300 and 450 ppm). Measured concentrations of each compound in blood, brain, liver, kidneys and perirenal fat showed no evidence of any interactions on uptake. Their data was consistent with very rapid metabolism of the aromate compared with the other hydrocarbons and they suggested this might explain the apparent lack of interaction with the uptake of the other hydrocarbons. An alternative possibility considered by the authors is that the three hydrocarbons are metabolised by different P450 isozymes and are not competing with each other although it had previously been reported that C6-C10 n-alkanes may affect P450 activity towards benzo(a)pyrene in vitro depending on the pre-exposure history of the animal (Rabovsky et al, 1986).

Mortensen et al (1998) tested the 12 most frequent occurring binary combinations of volatile organic chemicals reported in Norwegian workplace air for mutual inhibition or enhancement of metabolism in an in vitro system with liver S9 cells obtained from rats that were either untreated or pre-treated with the binary mixture being tested. The in vitro system responded to in vivo pre-treatment by increasing the metabolic rate of several potentially toxic organic chemicals such as toluene, xylene, styrene, and dichloromethane. In untreated liver S9 cells, the in vitro metabolism of several of the tested binary pairs was inhibited as shown for instance when ethanol exposure was followed by exposure to ethyl acetate, dichloromethane was followed by styrene and mutually between toluene and xylene. This inhibitory effect disappeared, however, for several of the solvent pairs when tests were conducted with the in vivo induced liver S9 cells recovered from pre-treated rats, a situation which may be the most relevant for occupational exposure. It was concluded that several metabolic interactions occur between low-molecular weight volatile chemicals found in workplace air causing both induction and inhibition of metabolism with potential implications for toxicity.

13.1.5 Respiratory irritation

Studies of the potential of mixtures to cause respiratory irritation have shown mixed results with some studies indicating that co-exposure to several irritants gives rise to irritation at lower levels of exposure than would have been expected from experience with the individual substances while the results of other studies show the reverse. It might be anticipated that the airways response to one irritant would increase sensitivity to other irritants and this is borne out by the results of several studies. Korpi et al (1999), for example, investigated the potencies of 3 microbial volatile organic compounds (VOCs) and a mixture of 5 microbial VOCs to cause eye and upper respiratory tract irritation in mice. The concentration capable of decreasing the respiratory frequency by 50% (RD_{50}) for a mixture of 5 microbial VOCs was found to be 3.6 times lower than estimated from the fractional concentrations and the respective RD_{50}s of the individual components suggesting some synergistic effects for sensory irritation response. There was also evidence that the most potent component of a mixture may dominate the sensory irritation effect, if it is significantly more potent than the other substances present. Gagnaire et al (2002) exposed mice to acetic acid, hydrogen peroxide and peroxyacetic acid vapours for 60 minutes and found that a mixture containing 53% acetic acid, 11% hydrogen peroxide and 36% peroxyacetic acid had an RD_{50} of 10.6 ppm, which is 1.4 times lower than the theoretical value estimated from the fractional concentrations and the respective RD_{50}s of the individual components implying a synergistic response.

The results of other studies suggest that there may be some saturation of irritant effect as irritants compete for common receptors. Cassee et al (1996), for example, investigated the

sensory irritation associated with co-exposure to formaldehyde, acrolein and acetaldehyde as measured by the decrease in breathing frequency in male rats. Each substance caused a reduction in breathing frequency which wore off through time for formaldehyde and acrolein and increased for acetaldehyde. The effects of mixtures of the three substances were less than would have been predicted on the basis of the individual substance results and it was concluded that the less than additive combined effect of these aldehydes was the result of competition for a common receptor (trigeminal nerve). Previously, Korsak et al (1993) investigated the effects of combined exposure to m-xylene and n-butyl alcohol on respiratory rate in mice and reported RD_{50} values of 3,010 ppm, 1,360 ppm and 3,140 ppm for n-butyl alcohol, m-xylene and their 1:1 mixture, consistent with a less than additive effect.

Other studies have failed to demonstrate any interaction between potential irritations. Poon et al (1994) reported that inhalation exposure to methanol, toluene, or a mixture of both produced mild biochemical effects and histological changes in the thyroid and nasal passage with no interactive effects.

In the absence of a consistent pattern of response to mixtures of irritants, it would be prudent to assume that the additive effects would be greater than anticipated from experience with the individual substances alone.

13.1.6 Neurotoxicity

Experiments that have investigated the neurotoxic effects of solvent mixtures have reported mixed results. Korsak et al (1994) exposed rats to m-xylene and n-butyl alcohol for 6 hours/day, 5 days/week for 3 months. The motor coordination disturbances caused by mixture of m-xylene and n-butyl alcohol at concentrations of 100 + 100 ppm were identical as those caused by n-butyl alcohol at concentration of 100 ppm. In contrast n-butyl appeared to reduce the significant increase in sensitivity to pain observed in animals exposed to m-xylene alone. Overall the effects of combined exposure to m-xylene and n-butyl alcohol were clearly less than additive and this may be due to metabolic interaction between the two substances in the liver (see above). Previously Korsak et al (1993) had determined that the median effective concentration (EC_{50}) for effects on rotarod performance following acute exposure was 6,530 ppm, 1,980 ppm and 3,080 ppm for n-butyl alcohol, m-xylene and their mixture, respectively, suggesting a greater than additive effect. Korsak et al (1992) exposed rats to vapours of toluene, m-xylene and a 1:1 mixture for 6 hours/day, 5 days/week, for 3 or 6 months. All exposures gave rise to statistically significant impacts on performance in the rotarod test and decreased spontaneous motor activity. In animals exposed to mixtures (1:1) of toluene and m-xylene, changes were more pronounced when compared to single solvent groups but the difference was not statistically significant. It was concluded that the effects of co-exposure to toluene and m-xylene were more than additive. Korsak and Rydzyński (1994) investigated the effects of combined exposure to n-butyl alcohol and n-butyl acetate in rats. Both solvents and their mixture caused concentration-dependent disturbances of rotarod performance in rat. The EC_{50}s were reported as 7,559 ppm, 8,339 ppm and 10,672 ppm for n-butyl alcohol, n-butyl acetate and their mixture, respectively. Both solvents and their mixture also decreased sensitivity to the pain and changes were concentration-dependent. The results of both assays were consistent with the summation of individual solvent effects. Rebert et al (1990) examined the effects on brain electrophysiology in rats of exposure to toluene and dichloromethane at concentrations of 10,700 and 16,000 ppm individually and 16,000 ppm as a combined mixture. Both solvents prolonged the latencies of components of the brainstem auditory-evoked response whereas toluene caused mean electroencephalograph (EEG) frequency to increase, dichloromethane had the opposite effect. Overall, although there were several variables exhibiting synergistic relationships, independent or additive interactions were the most common.

In conclusion, the neurotoxic effects of exposure to a solvent mixture may be more or less than the combined effects of the individual components. Different types of interaction may arise for the same combined exposure depending on the endpoint which is assessed.

13.1.7 Haematological effects

A number of hydrocarbons are associated with adverse haematological effects and there is extremely limited evidence that the haematoxicity of some mixtures is greater than the effects that would be predicted on the basis of exposure to the individual substances. Exposure of rats to a 1:1 mixture toluene and m-xylene at concentrations of 1,000 ppm or 100 ppm, 6 hours/day, 5 days/week, for 3 or 6 months gave rise to a decrease of red blood cells count and increase of rod neutrophil cell counts not observed with either solvent alone (Korsak et al, 1992).

13.1.8 Potential interactions affecting genotoxicity of mixtures

Metabolic interactions may lead to modification of the genotoxic potential of substances by either increasing or reducing the exposure of target organs to genotoxic substances or metabolites. In addition, substances such as kerosene that are not considered to be genotoxic carcinogens could promote and enhance the carcinogenic response to another substance

Leavens et al (1997) investigated the genotoxicty of 1,3-butadiene and styrene which are both oxidized, in part, by cytochrome P450 2E1 and metabolic interactions have been demonstrated in rodents exposed by inhalation to mixtures of both compounds (Leavens, 1996). The genotoxic effects of mixtures of butadiene and styrene were not significantly different from those of butadiene alone. The toxicity of both butadiene and styrene is associated with their metabolites and metabolic interactions may alter the response in animals exposed to mixtures of butadiene and styrene compared with the response in animals exposed to butadiene alone or styrene alone. While not directly relevant to petroleum drilling fluids, their results are illustrative of the potential interactions that may occur on mixed exposures to small levels of carcinogens that may be present in drilling fluids.

13.1.9 Implications for inhalation exposure to oil drilling fluids

Oil drilling fluids give rise to complex mixtures of vapour and particles in air and this is likely to lead to some modification of the toxicological properties of individual substances. Some likely effects include:

- A reduction in the toxicity of RCS due to the presence of alumino-silicates;
- An increase in the relative harmfulness of trace levels of substances such as PAHs that may be transported more effectively into the deep lung by adsorption onto particles;
- Possible greater effects for respiratory irritation than anticipated from experience with the individual substances alone.
- Possible additive risks of neurotoxicity arising from exposure to a solvent mixture; and
- Small effects on the absorption, metabolism and elimination of different hydrocarbon species that may have some minor toxicological consequences.

Levels of exposure to airborne alkali and alkali earth metals are likely to be low in relation to dietary intakes of sodium, potassium and calcium and insufficient for important interactions to occur. Levels of exposure to heavy metals are also likely to be too small to impact substantially on iron, zinc, manganese and calcium homeostasis (the normal processes by which the body maintains appropriate levels of essential metals).

Overall, it is likely that there is some modification of the toxicological properties of individual substances by other components present in drilling fluids. There is no evidence from other workplaces, however, that would suggest that the overall impact of exposure to the mixture is likely to be substantially different from predictions based on the sum of the toxicological impacts of each individual component. The only substance for which there is some evidence that workplace exposure to different mixtures may confer some differences in effect is respirable silica. It is however, difficult to separate the potential modification of effects of respirable silica due to co-exposure to other substances in airborne dust from differences in effect due to intrinsic differences in the silica (whether freshly shattered, particle size, crystal structure) in different environments. It is also clear, that regardless of the other components that may be present in workplace air, exposure to crystalline silica causes irreversible lung damage at extremely low exposures.

13.2 DERMAL EXPOSURE TO MIXTURES

13.2.1 Overview

The skin is a good barrier against a wide range of substances with some important exceptions. Some components of mixtures, however, can increase the dermal absorption of substances that would not normally be absorbed to any significant effect. The enhanced absorption may be due to damage to the skin that makes it more permeable to foreign substances or it may arise because a substance capable of permeating the skin acts as a carrier for other components of the mixture. For example, oils can defat the skin making them more vulnerable to other substances and both oil and water can act as carriers for substances that would not otherwise penetrate the skin. In addition, nano-sized particles (<0.1 μm) may penetrate the skin and act as carriers for other substances. The physical damage to skin arising from the abrasive effects of mineral particles or irritation associated with acids, alkalis or solvents may also increase its permeability to foreign substances.

13.2.2 Effects of oil and other components of drilling fluids on skin permeability

The results of some studies suggest that dermal exposure to kerosene can lead to significantly increased absorption of other substances. In a study of the dermal absorption of kerosene in rats, Tsujino et al (2003) reported that absorption could be detected soon after the start of exposure. Whereas absorption of the trimethylbenzenes present in kerosene was influenced by the total amount of kerosene rather than area of exposure, the quantity of aliphatic hydrocarbons remaining in the skin at significant levels was a function of the amount of kerosene per unit area exposed. Fujihara et al (2004) applied kerosene to rat skin for 1 hour/day for up to 5 days and found weak evidence that aliphatic components appeared to accumulate in blood following daily exposure whereas trimethylbenzene did not.

Baynes et al (2005) examined the effects of trichloroethylene (TCE), a solvent used for cleaning meaning components on the dermal absorption of triazine, a biocide widely used in cutting fluids, in an *in vitro* flow-through diffusion cell system. Their results suggested that TCE pre-treatment almost doubled triazine permeability, but this pre-treatment had no effect on triazine diffusivity. The pre-treatment effects of TCE on triazine permeability appear to be more important in PEG-based mixtures than in the mineral oil-based mixtures. TCE absorption was significantly less than triazine absorption; however, other cutting fluid additives had a more significant effect on TCE absorption than on triazine absorption. These results suggest that the various solvent species that may be present in oil drilling fluids or solvents that may be used in conjunction with exposure to oil drilling fluids, may greatly increase skin permeability to biocides or other substances in drilling fluids. Similarly the extent of solvent penetration of the

skin is likely to be significantly modified in response to other components of the drilling fluid mix.

Van der Merwe and Riviere (2006) investigated the effects of sodium lauryl sulphate (SLS), a widely used anionic surfactant, on the stratum corneum (outermost layer of the skin) partitioning and permeability of a range of chemicals: phenol, p-nitrophenol, pentachlorophenol, methyl parathion, ethyl parathion, chlorpyrifos, fenthion, simazine, atrazine and propazine in water, ethanol and propylene glycol. SLS decreased partitioning into stratum corneum from water for lipophilic compounds, decreased partitioning from propylene glycol and did not alter partitioning from ethanol. SLS effects on permeability were less consistent, but generally decreased permeability from water, increased permeability from ethanol and had an inconsistent effect on permeability from propylene glycol. The authors concluded that, for the compounds tested, partitioning into the stratum corneum was determined by the relative solubility of the solute in the donor solvent and the stratum corneum lipids. Permeability, however, reflected the result of successive, complex processes and was not predictable from stratum corneum partitioning alone. The findings of this study indicate that small quantities of surfactant/detergent in drilling fluids can have a significant impact on dermal absorption and penetration of biocides and other substances present in drilling fluid and that the impacts of surfactants on the dermal availability of biocides are likely to be different for aqueous or oil-based fluids and in the presence of PEG.

13.2.3 Aqueous or oil carriers of other species

The results of several studies suggest that water may be a more effective carrier for transdermal penetration than oil for substances such as pesticides and PAHs that may be present at low concentrations in drilling fluids. Microemulsions, thermodynamically stable colloidal dispersions of water and oil stabilized by a surfactant and, often, also a cosurfactant, are used as drug carriers for percutaneous, ocular, oral and parenteral administration (Santos et al, 2008).

In a study of 6 male volunteers, Jakasa et al (2004) reported that the dermal absorption of 2-butoxyethanol from aqueous solutions was markedly higher than that of neat 2-butoxyethanol. Sartorelli et al (1999) examined the dermal penetration of PAHs using an in vitro static diffusion cell system and full-thickness monkey skin. Comparison of the penetration of 13 PAHs from a lubricating oil and from acetone solution with artificial sweat showed a significantly slower passage from the oil matrix for acenaphthene, anthracene, phenanthrene, fluoranthene, naphthalene, pyrene and fluorine. For benzo[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, and benzo[a]pyrene it was only possible to demonstrate passage through the skin when compounds were applied in acetone solution with artificial sweat.

Vijay et al (2009) investigated the dermal permeation of biocides and other aromatic chemicals in water and in three generic soluble oil, semi-synthetic, and synthetic metal working fluid types using an in vitro flow-through diffusion cell. In general, the permeation of chemicals was highest in aqueous solution, followed by synthetic, semi-synthetic, and soluble oil metal working fluid. The absorption profiles of most of the chemicals including six biocides were statistically different among the synthetic and soluble oil metal working fluid formulations, with reduced permeation occurring in oily formulations. Permeation of almost all chemicals was statistically different between aqueous and three metal working fluid formulation types. Data from this study show that permeation of chemicals is higher in a generic synthetic metal working fluid when compared to a soluble oil metal working fluid. The dilution of these metal working fluid formulations with water appeared to increase dermal permeability of biocides giving rise to an enhanced risk for systemic toxicological effects and dermatitis.

In experiments with mice, Lee et al (2000) and Lee and Talska (1999) report that the use of kerosene to remove dermally applied used gasoline engine oil (UGEO) led to a significant decrease in skin DNA adduct levels relative to no washing but increased lung adduct levels after 8 hours. The authors suggested that reflects greater UGEO skin penetration and absorption in the presence of kerosene cleanser.

Oil composition and physical properties have an important impact on transdermal penetration and the impact on the transdermal transport of other substances. Potter et al (1999) reported that the uptake of radiolabelled benzo(a)pyrene into blood following application to the skin in mice reduced 5 fold as viscosity increased in the range ca. 30 to 5000 cSt (base oil to residual aromatic extract). Further increases in viscosity from ca. 5000 to 69 x 10^6 cSt (i.e. residual aromatic extract to bitumen) resulted in a further but smaller (ca. twofold) reduction in uptake. Similar findings were reported for the bioavailability of benzo(a)pyrene in experiments with viable human skin in vitro.

13.2.4 Particle mediated enhancement of dermal absorption of other substances

Several groups have investigated the impact of nanoparticles (particles <0.1 μm in diameter) used in sunscreen on the skin permeability of pesticides and other substances. The results of these studies suggest that nanosized particles can enhance transdermal transfer of other substances.

In a study of the in vitro penetration of benzene through freshly prepared human skin Nakai et al (1997), reported that application of baby oil, moisturizer, or insect repellent to the skin before exposure did not affect the flux of benzene, whereas a significant increase was observed when the skin was pre-treated with sunscreen. Brand et al (2003) investigated whether commercially available sunscreens containing the physical UV absorbers TiO_2 or zinc oxide (ZnO) enhance the transdermal absorption of pesticides in hairless mice and in an in vitro assay. Pre-treatment with five of the nine tested sunscreens significantly increased the transdermal absorption of 2,4-D and the transdermal penetraton of paraquat, parathion and malathion was significantly increased by pre-treatment with a representative sunscreen. Investigation of individual UV absorbers formulated in phenyl trimethicone showed that that ZnO can impede 2,4-D penetration whereas TiO_2 had no effect and it was possible to combine UV absorbers in the presence of trimethicone to create a 'sunscreen' that could inhibit 2,4-D penetration.

Although most of the particles present in oil drilling fluids will have larger diameters than those present in sunscreens or used as nanoparticle carriers of drugs, it seems likely that the finest particles could act as carriers that would increase the dermal absorption of the small quantities of pesticides and other toxic substances present in drilling fluids.

13.2.5 Modification of the dermal toxicity of substances in mixtures

There is limited information that suggests that the dermal toxicity of substances is significantly modified by the presence of other components of a mixture and such effects are not necessarily due to changes in dermal permeability or absorption. Monteiro-Riviere et al (2006) assessed the potential of additives to cutting fluids to cause irritant contact dermatitis in pigs. Pigs were exposed to 5% mineral oil or 5% PEG aqueous mixtures containing various combinations of 2% triazine (TRI), 5% triethanolamine (TEA), 5% linear alkylbenzene sulfonate (LAS), or 5% sulfurized ricinoleic acid (SRA). The only significant effect observed in the in vitro assay was with sulfurized ricinoleic acid and mineral oil that caused an increase in IL-8 release (an indicator of inflammation) after 1 or 2 hours' exposure. In vivo exposure to traizine appeared to increase erythema, oedema, and dermal inflammation while sulfurized ricinoleic acid alone was least likely to initiate a dermal inflammatory response. In 2-component mixture exposures, the

presence of traizine appeared to increase the dermal inflammatory response at 4 and 8 hours especially with the PEG mixtures. In the 3- and 4-component mixtures, mineral oil mixtures were more likely to incite an inflammatory response than PEG mixtures.

13.2.6 Summary

Dermal exposure to mixtures such as drilling fluids may lead to relatively greater systemic absorption of components such as pesticides than would have occurred as a result of a similar level exposure to the substance alone, as well as local irritant effects.

14 DISCUSSION

There have been substantial changes in the nature of drilling fluids, some advances in knowledge and some changes in attitude towards different types of health risks since Eide published his review of drilling fluid toxicity in 1990. At the time Eide undertook his review, respiratory irritation was not viewed as a potentially serious health issue and exposure limits were set to prevent "severe irritation" whereas in recent years limits have been set for various substances that are intended to prevent any irritation of the mucous membranes. This may be partly due to the recognition of the potential role of repeated and/or severe respiratory irritation in giving rise to chronic respiratory illness including Reactive Airways Dysfunction Syndrome (RADS, a type of occupational asthma) and even respiratory cancers. Concern about dermatitis, including "wet hand" dermatitis is also likely to have increased since the early 1990s. It also seems likely from the limited discussion in Eide's paper that exposure levels have reduced substantially over the last two decades.

Eide (1990) focussed on the toxic effects of inhaled C9-C15 aliphatic and naphthenic hydrocarbons present in oil-based drilling fluids. He identified nervous system toxicity and possibly pulmonary fibrosis as potentially important and indicated more investigation was needed of both pulmonary fibrosis and carcinogenicity. He also discussed nephropathy but concluded that although renal effects had been observed in rats exposed to hydrocarbons, these effects were species specific. The results of more recent studies do not indicate that renal toxicity is likely to be a concern. Eide's conclusions imply that control of hydrocarbon concentrations to less than 100 mgm^{-3} would prevent neurotoxic effects occurring.

The main risks to health associated with inhalation of aerosol and vapour associated with oil-based drilling fluids identified by our review are irritation of the mucous membranes and neurotoxicity. The exact nature of potential effects will vary with oil composition and the other substances present in specific drilling fluid and exposure levels. The saturation of specific metabolic pathways by oil components may increase systemic exposures to other substances. The potential of oil vapour to cause respiratory irritation is likely to be greater than the summed impacts of the individual substances present in oils. It is also likely that the oil vapour also increases the potential for other components in drilling fluids to cause irritation, although there are some limited data that suggest a saturation effect for respiratory irritation. Long term inhalation exposure to oil vapours and aerosol is likely to be associated with increased risks of developing chronic respiratory illness including bronchitis, even at relatively low exposure concentrations (<1 mgm^{-3}). Long term exposure may also be associated with the risk of permanent neurological impairment leading to memory loss, impaired cognition and, at very high levels of exposure, dementia. It is unclear whether the potential of oil vapour to cause neurotoxic effects may be more or less than the summed impacts of the individual components. Although Eide (1990) indicated that the carcinogenicity of oil drilling fluids is of potential concern, concentrations of carcinogens present in typical drilling fluids are negligible. It seems unlikely that the carcinogens are present at levels that would give rise to a significant increased cancer risk, although there are limited data that may link exposure to oils to an increased risk of cancers of the upper airways. The absence of a clear increased cancer risk suggests that the level of risk is relatively small. In conclusion, Eide (1990) implies that exposures to combined aerosol/vapour concentrations of less than 50 mgm^{-3} are unlikely to be harmful to health whereas more recent studies have identified adverse respiratory effects in humans associated with exposure to oil mists generated from cutting fluids at concentrations of only 0.2 mgm^{-3}.

The effects of dermal exposure were outwith the scope of Eide (1990) original review. Skin contact with oil-based drilling fluids is likely to cause irritation. Long term exposure of the skin is likely to lead to dermatitis and potentially more serious skin problems. There are some animal

data that link chronic skin irritation arising from repeated application of kerosene to a slight increase in skin tumour incidence. The oils may increase the bioavailability of other substances, including toxic biocides, in drilling fluid compositions through their impact on skin permeability and/or metabolism. The saturation of specific metabolic pathways by oil components may increase systemic exposures to other substances.

Eide (1990) did not discuss water-based drilling fluids. The main risk to health that is specifically associated with water-based fluids is probably wet hand dermatitis. There will be a range of other risks to health that vary depending on the substances present within the fluids. Given the very wide range of different fluid compositions in use, it is unlikely that aqueous based fluids are consistently more or less toxic that oil-based fluids.

The brines that are used in drilling fluids are typically low toxicity salts such as sodium, potassium or caesium formate. Levels of exposure to sodium, potassium or formate are highly unlikely to lead to uptakes of these salts that exceed endogenous levels. Similarly other salts added to drilling fluids such as sodium or potassium bicarbonate are highly unlikely to lead to uptakes of these salts that exceed endogenous levels. There is no evidence that low level exposure to caesium in aqueous solution is likely to be harmful to health.

Eide (1990) did not consider the potential risks to health associated with minor components of drilling fluids.

The pH adjusters added to drilling fluids such as sodium, potassium or calcium hydroxide are highly corrosive in pure form and would be expected to cause skin irritation or irritation of the mucous membranes at relatively low concentrations in water or in an aqueous mist. The presence of other substances within drilling fluids is likely to substantially modify the potential of these substances to cause irritation, providing that the pH of fluids is maintained at near neutral levels.

The emulsifiers and surfactants used in drilling fluids may cause irritation of the skin or mucous membranes at relatively low levels of exposure, although there is little information about the specific substances used or the toxicity of these types of substance. There is limited evidence that some quaternary ammonium salts, for example, may potentially be dermal or respiratory sensitisers.

The mineral powders that may be added to drilling fluids are generally of low toxicity (calcium carbonate, barium sulphate, bentonite, titanium dioxide). Their presence in fluids may however lead to enhanced uptake of other more toxic substances through the skin or via inhalation. Short term exposure to elevated concentrations of these substances may cause respiratory irritation (as a non-specific response to inhaling aerosols) and long term over exposure to respirable mineral dusts may lead to increased risks of chronic respiratory illnesses including bronchitis and potentially fibrotic lung disease such as pneumoconiosis. Respirable crystalline silica (RCS), which may be present in small quantities in drilling fluids, is considerably more toxic than the other mineral dusts likely to be present. Long term exposure to even low concentrations (0.1 mgm^{-3}) of RCS is associated with the development of silicosis (a fibrotic lung disease specific to silica) which causes impairment of respiratory function and may contribute significantly to premature mortality (for example, through the associated impacts on cardiovascular health). RCS is also a confirmed human carcinogen, although the lung cancer risks are considerably smaller than those of silicosis. Sodium silicate which was reported to be present in one drilling fluid composition would be expected to be associated with irritation or the skin and mucous membranes.

The biocides that are added to drilling fluids may significantly enhance the fluids toxicity. Glutaraldehyde is highly toxic following dermal or inhalation exposure, causes dermal and mucous membrane irritation at low levels of exposure and is a potent sensitiser. The bioavailability of biocides in drilling fluids may be significantly enhanced by other substances within the fluids that may act to increase skin permeability or as carriers.

The various thickeners that are added to drilling fluids such as PEGs and PEG derivatives, cellulose and starch, are generally of low toxicity and would not be expected to contribute significantly to the toxicity of the mixture.

15 CONCLUSIONS

In conclusion, the main health effects that are likely to arise from exposure to drilling fluids of any composition are irritation of the skin, eyes and respiratory system with long term exposure leading potentially to dermatitis and chronic respiratory illness. Long term exposure to oil-based fluids may be associated with increased risks of neurotoxicity. A range of other more serious health effects including occupational asthma, allergic dermatitis, pneumoconiosis or even cancer are possible although neither pneumoconiosis or cancers are likely, provided exposures are controlled to levels below those associated with irritation of the skin or respiratory system.

The more recent guidance on the health effects of exposure to oil drilling fluids published by IPIECA (2009) identifies more or less the same health issues as identified in this review. The IPIECA provides a good practical guide as to the health effects that could result from exposure to oil drilling fluids. It also provides a useful overview of the nature of the exposures.

The health hazards identified by our review are consistent with those highlighted by IPIECA/OGA (2009). This review is however supported by an account of the relevant literature which is not provided by IPIECA/OGA. We have indicated how published studies may be informative as to the effects of oil drilling fluids and examined both the potential role of the individual components of drilling fluids and of the mixture in giving rise to adverse effects.

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APPENDIX 1

Table A1: Drilling fluids reported to be used by Statoil, December 2010

Drilling system	Ingredient, labelling required	Weight
Oil-based 1	Distillates (petroleum), hydrogen treated, light; kerosene – unspecified	30-60%
	Calcium chloride	1-5%
	Calcium hydroxide	1-5%
	Organic clay	Unknown
Oil-based 2	Distillates (petroleum), hydrogen treated light	30-60%
	Calcium hydroxide	1-5%
Oil-based 3	Paraffins (petroleum), normal C5-C20	10-30%
	Calcium chloride	1-5%
	Calcium hydroxide	1-5%
	Polyamide	<1%
Oil-based 4	No information provided	No information provided
Oil-based 5	Cesium/Potassium formate Brine	60-100%
	Distillates (petroleum), hydrogen treated mildly	10-30%
Oil-based 6	Distillates (Petroleum)	30-60%
	Emulsifier	5-10%
	Calcium chloride	1-5%
	Lime	1-3%
Oil-based 7	Distillates (petroleum), hydrogen treated mildly Calcium	10-30%
	chloride	1-5%
	Polyamide	1-5%
	Calcium hydroxide	<1%
Oil-based 8	Paraffins, petroleum, normal C>10	40-60%
	Titanium oxide	5-10%
	Calcium chloride	3-5%
	Sodium hydroxide	<1%
	2-(2-butoxyethoxy)ethanol	<0.5%
	2-butoxyethanol	<0.2%
	Modified amide amine	<0.2%
	Distillates (petroleum), hydro treated light	<0.1%
	a-quartz, total dust	3-5%
	a-quartz, respirable dust	<0.2%
Oil-based 9	Calcium chloride	0-5%
	Cristobalite	<1%
	Sodium hydroxide	<1%
	2-(2-butoxyethoxy)ethanol	<1%
	2-butoxyethanol	<1%
	Distillates (petroleum), hydro treated light	20-60%
	Quarts	<1%
	Kaolin	<1%
	Calcium hydroxide	<1%
	Quarternary amine	<1%

Drilling system	Ingredient, labelling required	Weight
Water-based 1	Poly ethylene glycol ether	1-5%
	Crystalline silica	<1%
	Calcium carbonate	0-30%
	Barium sulphonate	0-30%
Water-based 2	Barite (Ba(SO4))	30-60%
	Bentonite	5-10%
	Sodium carbonate	<0.1%
Water-based 3	Sodium formate	1-53%
	Caesium Formicate	1-84%
	Potassium Formicate	1-76%
	Water	>13%
	Calcium carbonate	<9%
	Sodium carbonate	<3%
	Carbonic acid, dipotassium salt	<3%
	Sodium bicarbonate	<3%
	AMPS-NA / Alkylacrylamide polymer blend	<1%
	Potassium bicarbonate	<3%
	Polyanionic cellulose polymer	<1%
	Starch	<1%
	Cellulose, Colloidal Fibre	<1%
	Xanthium Gum	<1%
	Potassium hydroxide	<1%
Water-based 4	No information provided	No information provided
Water-based 5	Citric acid	1-6%
	Distillates (petroleum), hydro treated light	<0.1%
Water-based 6	Sodium carbonate	1-5%
	Polyalkylene glycol	<0.1%
Water-based 7	Sodium hydroxide	0-0.1%
	a-quartz, total dust	0-100%
	a-quartz, not respirable	<1%
Water-based 8	Sodium carbonate	1-5%
	2-(2-butoxyethoxy)ethanol	<0.1%
	Distillates (petroleum), hydro treated light	<1%
	Alkanolether	<1%
Water-based 9	Glutaraldehyde	1-5%
	Polyalkylene glycol ether	<1%
Water-based 10	A-quartz, total dust	0-100%
	Polyalkylene glycol	0-5%
	A-quartz, non respirable	<1%
	Sodium carbonate	0.1%
Water-based 11	No information provided	No information provided
Water-based 12	Sodium silicate, MR>3,3	30-60%
	Water	60-100%

Table A2: Oil-based base oils used by Statoil 2007- 2010

Base oil	Viscosity [cSt at 40°C]
BO1	3.4
BO2	3.3 – 3.7
BO3	2.3
BO4	<2
BO5	3.4-4.5
BO6	1.7

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