AN INVESTIGATION INTO VISUAL PROBLEMS OF CRANE OPERATORS AT A PETROCHEMICAL FACTORY AND THE POSSIBLE LINK WITH EXPOSURE TO HYDROCARBONS

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ABSTRACT

The aim of this investigation was to determine the exposure to total hydrocarbons including toluene and to determine if there are any relation between exposure to toluene and visual problems experienced by crane operators. Exposure to industrial chemicals can affect a number of sensory capacities including colour perception. The nature of a crane operator's duties does not allow for any error in judgement since this can have disastrous consequences. Colour vision and contrast sensitivity tests were performed on all 30 operators and on the control group. The results obtained from analysing air samples using OVM badges revealed levels of toluene ranging from 0 to 0.477 ppm. These levels are well below the threshold limit value (TLV) for toluene which is 50ppm. Hydrocarbon levels were also determined by biological monitoring. The levels of hippuric acid/ g creatinine and ortho-cresol/ g creatinine in the urine were also lower than the threshold values. Some subjects of the experimental group did have problems with colour and contrast discrimination. Evident from the results is the fact that more problems regarding contrast sensitivity and colour discrimination were observed on the Friday than on the Monday but not statistically significantly so. Considering the findings, recommendations are made regarding minimum risk levels (MRLs) for toluene.

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CHAPTER 1

INTRODUCTION

Petrochemical research started during the First World War and the first petrochemical product was produced in 1919 – 1920. The petrochemical industry now supplies over half of the world's chemicals which are all important consumer goods such as plastics, detergents and soaps, synthetic fibers, synthetic rubbers, solvents and many more (Barhad 1985). At a petrochemical plant, workers are exposed to a mixture of volatile organic compounds and not only to specific individual gases (ATSDR 1999).

Exposure to a mixture of volatile organic compounds can lead to different health effects from that of exposure to an individual compound. In order to get an accurate account of the effect of these mixtures on the body, it is important to determine the total hydrocarbon concentration that the workers are exposed to. A single organic compound can be used as a reference marker which can provide more information about the health impact of a mixture of compounds *versus* the impact of a single compound.

For this study, toluene was chosen as reference marker since it has already been identified to be linked to visual problems (Zavalic *et al.* 1998, Campagna *et al.* 2001 and Vrca *et al.* 1997). These visual problems include difficulty with colour discrimination and contrast sensitivity. Results obtained from eye examinations of the crane operators indicated that some did experience trouble with colour discrimination and contrast sensitivity. The employees of this petrochemical factory are medically examined annually by professional occupational health practitioners. The plant has its own medical facilities on site where routine physical examinations are performed. The crane operators were then advised to have their eyes tested off- site and before they start with a working day. Test results from independent optometrists revealed no signs of colour deficiency or vision problems.

Question: Does exposure to hydrocarbons especially toluene lead to visual problems in crane operators of the petrochemical plant?

Aims and objectives:

The goal of this study is to determine the exposure to total hydrocarbons including toluene and to determine if there are any relation between exposure to toluene and visual problems experienced by the crane operators under investigation.

Difficulty with colour discrimination is one of the first indications of the adverse health effects of toluene exposure, it is therefore essential to include tests on colour discrimination. In order for a crane operator to successfully complete his/her duties, it is essential that nothing impairs their sensory input and clear vision is of the utmost importance.

Hypothesis: Exposure to hydrocarbons including toluene does result in visual problems in crane operators at this petrochemical plant.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

A petrochemical plant is characterized by different chemical processes that ultimately lead to the production of oil from coal. During these processes, several by-products are formed which are further processed in the coal-tar plant. At these plants, workers are exposed to a mixture of volatile organic substances and not only to specific individual gases. Petrochemicals are characterized by raw materials such as 1) *gaseous hydrocarbons* which include saturated hydrocarbons with 1 – 4 carbon atoms, natural gas for its methane content, and refinery gas for its olefin content; 2) *liquid hydrocarbons* (gasoline fractions which contain aromatic hydrocarbons and 3) *solid hydrocarbons* (paraffin wax) (Barhad 1985).

Hydrocarbons are formed when hydrogen and carbon monoxide react under pressure in the presence of a catalyst. Aromatic hydrocarbons include benzene, toluene and xylene which are very volatile (Gossel and Bricker 1994). Volatile organic substances to which workers at a petrochemical plant, are exposed to include benzene, toluene, heptane, hexane, octane, xylene, Stoddards solvent and methyl ethyl ketone . The crane operators under investigation are exposed to a number of different hydrocarbons.

2.1.1 Hydrocarbons:

Aromatic hydrocarbons possess the special properties associated with the benzene nucleus or ring in which six carbon-hydrogen groups are arranged at the corners of a hexagon (Parmeggiani 1985).The characteristic reaction of benzene is one of substitution, in which a hydrogen is replaced by a substituent, univalent element or group. Aromatic hydrocarbons and their derivatives are compounds of one or more stable ring structures and can be considered as derivatives of benzene according to three basic processes: 1) Replacement of a hydrogen atom with an aliphatic hydrocarbon radical gives rise to toluene and derivatives eg. ethylbenzene, styrene, xylene; 2) Linkage of two or more benzene rings directly eg. diphenylmethane, or linking by intermediate aliphatic chains or

radicals eg. triphenylmethane and 3) Condensation of benzene rings eg. naphthalene, benz(a)pyrene (Parmeggiani 1985).

The main sources of aromatic hydrocarbons are the distillation of coal and a number of petrochemical operations. The main uses of aromatic compounds as pure products are the chemical synthesis of plastics, synthetic rubber, paints, dyes, explosives, pesticides, detergents, perfumes and drugs (Parmeggiani 1985).

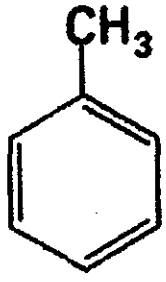
Absorption takes place by inhalation and in small quantities through the skin. Aromatic hydrocarbons are metabolized through the bio-oxidation of the ring (Parmeggiani 1985). Exposure to a mixture of volatile organic substances can lead to different health effects from that of exposure to an individual compound. Several studies have indicated that colour discrimination is especially sensitive to exposure to industrial chemicals (Iregren *et al.* 2002). Semple and co-workers (2000) have also found that an increase in annual exposure to organic solvents is significantly associated with increasing annual exposure. Even short-term, experimental exposure to toluene resulted in reduced colour discrimination (Baelum *et al.* 1985).

In order to get an accurate account of the effect of these mixtures on the body, it is important to determine the total hydrocarbon concentration that the workers are exposed to. A single organic compound can be used as a reference marker which can provide more information about the health impact of a mixture of substances *versus* the impact of a single substance. Toluene was chosen as reference marker because; 1) it is widely used at this plant and is definitely one of the substances found in the mixture of hydrocarbons and 2) research has shown that toluene does have harmful effects on the central nervous system and can also lead to visual problems (Vrca *et al.* 1996).

2.1.2 Toluene ($C_6H_5CH_3$):

Toluene (methyl benzene), (see Figure 2.1) is a clear, colourless liquid which is a good solvent and it has a distinctive smell reminiscent to that of benzene. It is produced in the process of making fuel from oil by the process of dehydrogenation of cycloparaffin fractions followed by the aromatisation of saturated aromatic hydrocarbons (Lob 1985). It

occurs naturally in crude oil and the tolu tree. It is employed as a solvent for oils, resins, natural and synthetic rubber, coal tar, asphalt, pitch and acetyl celluloses and diluent for cellulose paints and varnishes, photogravure inks. It is also found in mixtures used as cleaning products (Lob 1985). According to the South African Regulations for Hazardous Chemical Substances, the time-weighted average (TWA) Occupational Exposure Limit - Recommended Limit (OEL-RL) for toluene is 50ppm or 188mg/m ^{3}. The short-term OEL-RL for toluene is 150 ppm (Occupational Health and Safety Act No. 85 of 1993). The Occupational Safety and Health Administration (OSHA) in the USA has set a limit of 200 ppm of toluene for air in the workplace, averaged for an 8 hour exposure over a 40 hour work week and the American Conference of Governmental Industrial Hygienists (ACGIH) recommends that toluene in the workplace air should not exceed 50 ppm (Kamrin 1988 and Dorsey *et al.* 2000).



toluene

Figure 2.1: Structure of Toluene

From: Hart and Schuetz (1978).

2.2 Toxicokinetics:

Toluene is readily absorbed from the respiratory and gastrointestinal tracts and to a lesser degree, through the skin (Lob 1985, Lof *et al.* 1993). Studies in animals have shown high concentrations of toluene in the adipose tissue, brain and bone marrow and moderately high concentrations of toluene and its metabolites in liver and kidney in case of oral administration of toluene orally or by inhalation (Dorsey *et al.* 2000). The first steps in

toluene metabolism in humans and laboratory animals are side-chain hydroxylation, catalyzed by the cytochrome P450 (CYP) isozyme, CYP2E1, follwed by oxidation to benzoic acid. Most of the benzoic acid is then conjugated with glycine to form hippuric acid. A small portion can be conjugated with UDP-glucuronate to form acyl-glucuronide. A very small portion of absorbed toluene can be converted to CYP1A2, CYP2B2 or CYP2E1 to ortho- or para-cresol, which are excreted in the urine as sulfate or glucuronate conjugates (Lob 1985).

2.2.1 Absorption and distribution:

Toluene appears in the blood of humans exposed to 80 ppm, within 10-15 min after exposure (Hjelm *et al.* 1988) and Lof *et al.* (1993) found about 50% of toluene was absorbed from the lungs in volunteers exposed to 53 ppm toluene for 2 hours during a period of light exercise. A positive correlation was found between the levels of toluene in alveolar air and the levels in blood in both humans and animals (Lof *et al.* 1990). Toluene is distributed in a 1:1 ratio between the plasma and red blood cells of humans and it appears that it associates with the haemoglobin rather than the cell membrane. The mechanism is not clear but it is hypothesized that toluene interacts with the hydrophobic core of the heme protein. This interaction increases the amount of toluene that can be accommodated by the aqueous blood medium and facilitates transport of toluene to all areas of the body. Transport of toluene in the blood takes place at a much faster rate than if toluene was transported only in the plasma. Following exposure to toluene in humans, it has been identified in the brain, liver, lung and blood (Takeichi *et al.* 1986). Toluene has a greater affinity for the lipid-rich white matter of the brain such as the brain stem (Ameno *et al.* 1992).

The brain stem controls many involuntary aspects of cardiac, respiratory and vasomotor function. Autopsies on humans exposed to toluene indicated that toluene is distributed to lipid-rich and highly vascular tissues such as the brain. Toluene levels in the brain and liver of a 16 year old male who died after an episode of glue sniffing were 297 and 89 μg/mg, respectively (Paterson and Sarvesvaran 1983). The rate of perfusion of the tissue with blood will also influence transfer of toluene from blood to a tissue.

2.2.2 Metabolism:

The first steps in toluene metabolism are methyl and ring hydroxylations that are catalysed by cytochrome P450 (CYP) isozymes. Benzyl alcohol is formed after methyl hydroxylation of toluene in liver microsomes. Ortho- and para-cresols are formed through ring hydroxylation and only represents 5% of total metabolite formation. Results form several studies have indicated that CYP2E1 is the most active isozyme in forming benzyl alcohol and CYP1A2 is most active in the formation of ortho- and para-cresols.

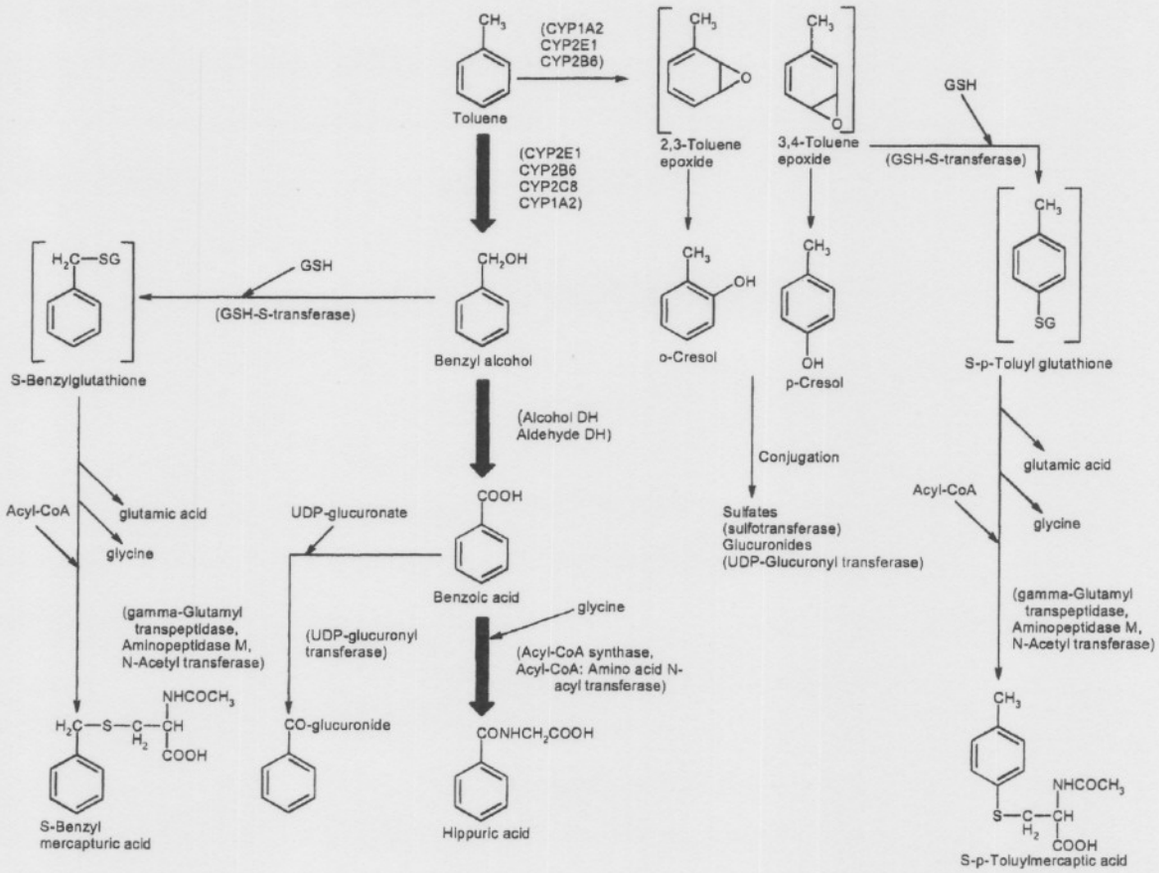


Figure 2.2. Scheme for Toluene metabolism in Humans and Animals.

Proposed enzymes in parentheses.

Sources: IARC 1999. Nakajima and Wang 1994, Nakajima *et al.* 1997.

CoA = coenzyme A; CYP = cytochrome P-450; DH = dehydrogenase; GSH = glutathione; UPD = uridine 5'-diphosphate

Benzyl alcohol is then converted to benzoic acid by alcohol dehydrogenase and aldehyde dehydrogenase. Hippuric acid is formed after conjugation with glycine and this represents 80 – 90 % of urinary metabolites in rats (Nakajima and Wang 1994). (see Figure 2.2).

Another minor human urinary metabolite, S-p-toluylmercapturic acid, is formed by a series of reactions from the proposed intermediate, 3,4- toluene epoxide. The prime site of toluene metabolism is probably the liver based on the high concentration of CYP isozymes (Nakajima and Wang 1994).

2.2. 3 Excretion:

Approximately 75 – 80% of inhaled toluene that is absorbed can be accounted for by urinary excretion of hippuric acid which is the principal metabolite of toluene (Lof *et al.* 1993). The biological half-life of hippuric acid is in the order of 1 – 2 h and the normal level of hippuric acid expected in the urine is 0.5 – 2.5 g/24h (which represents 0.8 g hippuric acid/ g creatinine) (Lob 1985). Other metabolites that are also excreted include S-benzyl mercapturic acid, S-p-tolulyl mercapturic acid and conjugates of ortho- and para-cresol and account for less than 5 % of absorbed toluene. Within exhaled air, non-metabolized toluene are excreted and this can contain 7 – 20% of absorbed toluene (Lof *et al.* 1993).

2.3 Toxicological action of toluene:

Acute exposure to toluene: Evidence suggest that interactions between toluene and components (lipids or proteins) of nervous system membranes lead to neurological effects such as central nervous system depression and narcosis. These interactions involve toluene itself and not its metabolites. From studies involving rats, synaptosomes showed decreased phosphatidylethanolamine content, altered phospholipid methylation activities, altered outer membrane fluiditity and increased Na^+-K^+–ATPase activities (Lebel and Schatz 1990). It has been postulated that the acute anaesthetic actions of toluene involve intercalation of toluene into the lipid bilayer of nerve membranes and/or reversible interactions with proteins in the membrane (Franks and Lieb 1987).

Magnetic resonance imaging (MRI) of the brain of solvent abusers suggest preferential atrophy in lipid-rich regions of the brain (Rosenberg *et al.* 1988). They found evidence of diffuse central nervous system demyelination in toluene abusers with obvious neurological impairment. The results of Rosenberg *et al.* (1988), indicate that chronic exposure to high concentrations of toluene brings about structural changes in the brain related to lipid compositional changes.

Intermediate to chronic exposure: It is more difficult to understand the mechanisms involved relating to intermediate to chronic exposure to toluene in the workplace. These include symptoms such as mild neurological impairment, performance deficits on neurobehavioral tests, hearing loss and changes in brainstem auditory-evoked potentials and colour vision impairment and changes in brainstem visual-evoked potentials (Dorsey *et al.* 2000).

2.4 Chemical interaction:

Interaction with other hydrocarbons:

Interaction between toluene and other chemicals are very important since alteration of toluene metabolism may influence the toxicity of toluene. Substances that stimulate or inhibit metabolism of toluene may respectively decrease or increase toluene toxicity. Campo and co-workers (1998) found that rats that were exposed to large doses of ethanol (4g/kg/day) and daily inhalation exposure to toluene concentrations of 1750 ppm, 6 hours/day, 5 days/week for 4 weeks, showed significantly greater changes in auditory – evoked brainstem potentials and outer hair cell loss in the ear than rats only exposed to toluene. They also found that co-exposure to ethanol caused a significant decrease in hippuric acid urinary excretion rates compared with exposure to toluene alone. These results indicate that large doses of ethanol inhibited the metabolism of toluene (Campo *et al.* 1998).

Intake of alcohol will exacerbate the effect of toluene and can result in more damage to the liver than either substance alone (Dorsey *et al.* 2000). Results also indicate that exposure to toluene causes hearing loss and that workers exposed to toluene who regularly drink

alcohol are at a greater risk of developing toluene-related neurological problems than non-drinkers.

The interaction of toluene and other hydrocarbons have also been investigated. Cytochrome P-450 oxidation is responsible for the metabolism of benzene, xylene and toluene.' Studies by Purcell *et al.* (1990) indicated that toluene has a greater inhibitory effect on benzene metabolism than benzene has on toluene metabolism. Research suggests that the interaction of benzene and toluene are non-competitive and data from studies of this interaction may indicate that workers exposed to mixtures of both solvents have a lower risk of benzene-induced leukopenia than workers exposed to benzene alone (Purcell *et al.* 1990).

In the case of interaction between toluene and xylene, results have shown that both solvents were increased compared to controls exposed to one solvent alone, indicating that metabolism of both was decreased by co-exposure (Tardif *et al.* 1992). The level of exposure was high (80 – 150 ppm xylene, 95 or 150 ppm toluene). Several studies investigating the interaction of toluene and n-hexane suggest that toluene is a more effective inhibitor of n-hexane metabolism than *vice versa* (Dorsey *et al.* 2000).

The interaction of toluene and n-hexane are both neurotoxic chemicals and act by different modes at different sites. The result from co-exposure to these two chemicals in rats indicated that toluene is a more effective inhibitor of n-hexane metabolism than n-hexane is of toluene metabolism (Ali and Tardiff 1999).

Interaction with other drugs:

Results from several studies have indicated that high doses of aspirin (salicylic acid) may potentiate toluene effects on hearing by inhibiting toluene mechanism. Benzoyl coenzyme A, a metabolite of toluene and aspirin are conjugated with glycine. Glycine pools may be depleted by competition for glycine by aspirin metabolism which may inhibit toluene metabolism (Dorsey *et al.* 2000). Co-exposure to acetaminophen (paracetamol) prolonged the concentration of toluene in the blood, consistent with inhibition of toluene metabolism.

2.5 Health effects related to toluene:

A serious health concern of toluene is the effect that it has on the central nervous system of humans. According to Lob (1985), the toxicity of toluene is more intense than that of benzene. After exposure to 1000ppm toluene it result in vertigo, difficulty in maintaining equilibrium and intense frontal headache. Stronger concentrations may result in narcotic coma (Lob 1985). Exposure routes include inhalation of toluene vapours, ingestion of contaminated food or drink and absorption through skin contact. Results from several studies of workers acutely or chronically exposed to toluene in workplace air, studies of volunteers under controlled acute exposure conditions and studies of chronic solvent abusers have indicated the adverse effects on the nervous system from inhalation exposure (Dorsey *et al.* 2000).

Toluene is known to cause headaches, sleepiness and can impair the ability of one to think clearly. Symptoms such as tiredness, confusion, weakness, drunken-type actions, memory loss, nausea and loss of appetite are prevalent after low to moderate, continuous exposure to toluene in the workplace. When exposure to toluene is stopped, symptoms usually disappear since more than 75% of the toluene will be removed from the body after 12 hours. Following inhalation of toluene, irritation is experienced in the respiratory tract. In animal studies, toluene exposure leads to irritation of the upper airways and degeneration of the nasal epithelium (Dorsey *et al.* 2000). No evidence was found to indicate that toluene has an affect on bone marrow (Lob 1985).

Long-term daily exposure in the workplace can also lead to hearing and colour vision impairment. Eye irritation develops in humans who are exposed for 6-8 hours to toluene concentrations of >100 ppm (Dorsey *et al.* 2000). Colour confusion in occupationally exposed workers was observed with chronic exposure of < 100 ppm toluene (Zavalic *et al.* 1998). A direct relation was identified between exposure to toluene and colour blindness (Zavalic *et al* 1998, Campagna *et al.* 2001). Toyonaga and co-workers (1989), tested the eyes of three toluene dependant patients and found that chronic inhalation of toluene can lead to damage of the visual pathway, including the distal portion of the retina and the retinal pigment epithelium. Dysfunction of the central nervous system is a critical human

health concern following acute, intermediate or chronic inhalation exposure to toluene (Dorsey *et al.* 2000). Accurate exposure data are not available for solvent abusers, but the concentrations inhaled by chronic abusers have been estimated to range from 4000 to 12000 ppm (Gospe *et al.* 1994). Symptoms characteristic to solvent abusers include light-headedness, dizziness and sleepiness which may lead to unconsciousness and even death.

Chronic exposure of workers to average concentrations as low as 30 - 130 ppm damages hearing and colour vision with the probability of damage to the neurological components of these systems (Zavalic *et al.* 1998, Campagna *et al.* 2001). Experimental studies in volunteers show that acute exposure to toluene concentrations below 50 ppm results in few observable effects (Dorsey *et al.* 2000). The threshold limit value for exposure to toluene is set at 50 ppm (for a 8 hour workday). Long-term daily exposure to toluene in the workplace might result in hearing and colour vision loss.

2.6 Colour vision impairment:

The pathogenesis of occupational colour vision loss due to exposure to solvents and other industrial chemicals is not clear yet. It has been proposed that colour vision impairment results from a direct action of neurotoxins on receptors (possibly the membrane metabolism of the cone) and/or an interference with neurotransmitters within the retina. Another possibility is a direct effect on the optic nerve (Gobba and Cavalleri 2003).

Sensitive tests such as the Farnsworth-Munsell 100 Hue or the Lanthony D-15 desaturated panel can be used to assess colour vision impairment (Gobba and Cavalleri 2003). The following chemicals have been linked to colour vision impairment as a result of occupational exposure to chemicals; styrene, perchloroethylene, toluene, carbon disulfide, n-hexane, solvent mixtures, mercury. Results from several studies have indicated that toluene does affect the central nervous system and the effect of toluene on colour vision is well documented in literature. This is not surprising since the eye is a potential target organ for many hazardous chemicals and manifests the entire spectrum of toxic responses (Heywood 1986). A reduced capacity for colour discrimination has been reported after short-term exposure to toluene. To understand how toluene affects colour perception it is necessary to have a thorough understanding of visual physiology.

2.7 Vision

2.7.1 Protective physiological barriers of the eye:

The eye is protected by two physiological barriers which are the blood-retina and the blood-aqueous barriers. These barriers comprise layers of cells that are connected by tight junctions which restrict intercellular diffusion of proteins, ions, and lipid-insoluble electrolytes (Heyman 1986). The main purpose of these two barriers is to restrict the rate of exchange of certain solutes between blood plasma and the ocular fluids. The only way a molecule can penetrate the barrier is for it to escape the polar environment of plasma water and plasma protein and enter the non-polar environment of the lipid membrane of the endothelial cells.

Polar solutes which are sufficiently lipid-soluble, are able to escape into the membrane. Common metabolic substances which are lipid-insoluble, can not penetrate the barrier by lipid mediated transport. Penetration of these substances is only possible if carrier substances are found in the barrier with an affinity for the specific molecular configuration to aid with the escape from water.

Hypertonic solutions increase the permeability of the barriers by promoting cell shrinkage and deforming the tight junctions (Heywood 1986). The chamber in front of the lens contains the aqueous humor and the chamber behind the lens contains the vitreous. These two chambers form the extracellular compartments of the eye. The aqueous humor is of great importance to the toxicologist. The electrolyte composition of the aqueous humor is similar to that of extracellular fluid (high sodium and chloride concentration and low potassium concentration).

2.7.2 Ocular toxicity:

Local toxicity: Direct exposure of the eye to chemicals, accidentally or deliberately, increases the risks of oral toxicity. This type of exposure can either be accidentally or deliberately. The degree of damage induced after exposure to chemicals is determined by the following: 1) intimacy and duration of contact, 2) physical properties which determine the penetrability, and 3) the chemical reactivity with the tissues of the eye (Heywood 1986). The cornea would be the first structure of the eye to be affected by contact with

chemicals. Chemicals can also be absorbed from the conjunctival sac and the nasopharynx and may even result in systemic toxicity (Heywood 1986).

Systemic toxicity: Several ocular side effects have been reported following systemic administration of chemicals. The eye structures that can be affected include the eyelids and peri-orbital tissues, cornea, conjunctiva, pupil, iris, lens, retina and optic nerve. It has been shown that a lot of compounds bind to the melanin from the retinal pigment epithelial layer. The uptake of the compound increases with time and once it is bound to the melanin, it is retained for long periods. Substances known to bind to melanin include polycyclic aromatic compounds, antibiotics such as ethabutol, rifampicin and tetracyclines, glycosides, quinolines and many other.

2.7.3 Anatomy and physiology of the eye:

The globe of the eye consists of three layers enclosing the refractive media. The sclera and cornea form the outermost, protective tunic. The middle layer is vascular and consists of the choroid, ciliary body and the iris. The innermost layer is the retina (Davson 1980). The retina is the light-sensitive part of the eye and plays a very important role in vision since it contains the photoreceptor cells (Cohen 1987). The dioptric apparatus is made up of the cornea, the lens which is supported by the zonule which is itself attached to the ciliary body. Aqueous humour (a clear fluid) and the vitreous body (jelly) fill the spaces within the eye. The iris adjust the amount of light entering the eye whilst the ciliary body contains muscle fibers which can increase the refractive power of the lens by contracting (accommodation). The formation of an image is possible when light waves from an external object go through the dioptric apparatus and falls on the retina (Davson 1980).

The innermost layer of the retina is called the pigment epithelium layer. This layer has a mechanical, nutritional, phagocytic and supportive role and contains high levels of melanin which act as electron acceptor. It is in this layer that retinal is reconverted to vitamin A and the vitamin A is stored for subsequent transfer to the photoreceptors (Cohen 1987, Martini 1998).

2.7.4 Visual physiology:

The retina consists largely of nerve cells and fibers relaying the responses of the visual stimuli to the optic nerve. The layer of rods and cones forms an integral part of the retina. These are photoreceptors because they detect light. Light is radiated in waves that have a characteristic frequency and wavelength. The human eye is sensitive to wavelengths of 700 – 400nm (Martini 1998).

The rods provide the central nervous system with information on the presence or absence of light, irrespective of wavelength while the cones provide information about the wavelength, giving the perception of colour. The rods and cones are divided into an outer and inner segment. The outer segment contains thousands of discs as well as the visual pigments. The cones differ from the rods with regard to the visual pigment and the shape of the discs. In the case of the cone, the discs are infoldings of the cell membrane while the rod has thousands of independent discs (Martini 1998).

It is the visual pigments that absorb the photons that lead to photoreception. Rods and cones contain the pigment called retinal which is bound to a protein. In case of the rods, the protein is opsin, but the cones contain different forms of the protein, opsin. The type of opsin present in a cone determines the wavelength that can be absorbed by the retinal pigment. There are three types of cones; blue, green and red cones. Photoreception occurs when light strikes the cone and the pigment, retinal switches from the 11-*cis* to the 11-*trans* form and activates the protein. A chain of reactions start and the result is hyperpolarization of the cone membrane and a decrease in neurotransmitter release to the bipolar cells. Evidence suggest that aspartate or glutamate may serve as a neurotransmitter for cones in the vertebrate retina (Saari 1987). Colour discrimination is possible through the integration of information arriving from all three types of cones. The perception of yellow results from a combination of inputs from green cones (highly stimulated), red cones (stimulated) and blue cones (unaffected).

Difficulty with colour discrimination or colour blindness occurs when one or more classes of cones are nonfunctional. The cones may be present but unable to manufacture the necessary visual pigments. Inherited colour blindness that involves one or two cone

pigments is not unusual. Total colour blindness is extremely rare; 1/ 300 000 fails to manufacture any cone pigments (Martini 1998).

2.7.5 The visual pathway: The visual impulses are relayed from the retina through the optic tract to the lateral geniculate nucleus and then to the cerebral cortex. Sensory fibers carrying messages from the medial or nasal half of the retina cross over in the optic chiasma. This crossing over means the lateral geniculate nucleus on the left side, receives fibers from the temporal half of the left retina and the nasal half of the right. This is important for binocular vision. The brain stem also plays an important role in visual processing. The brain stem receives visual information from the lateral geniculates or via the collaterals from the optic tracts (Martini 1998). Deleu and Hanssens (2000) found evidence of cerebellar dysfunction and visual deterioration in a patient who chronically used toluene for seven years.

2.8 Minimal Risk Levels (MRLs):

Minimal risk levels (MRLs) have been derived for inhalation and oral routes of entry at each duration of exposure (acute, intermediate and chronic). These levels are derived using a modified version of the risk assessment methodology of the Environmental Protection Agency (EPA) to determine reference doses for lifetime exposure (RfDs). The intention of these MRLs are not to support regulatory action but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans (Dorsey *et al.* 2000). Minimal risk levels for the inhalation of toluene have been identified for acute-duration (14 days or less) and for chronic-duration (365 days). The MRL for acute duration inhalation exposure to toluene is 1ppm (3.8mg/m^3). These values are based on a study by Andersen *et al.* (1983). A MRL of 0.08 ppm (0.3 mg/ m^3) was derived for chronic-duration (365 days or more) inhalation exposure to toluene. Minimal risk levels are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty approach. Below these levels, no adverse health effects are expected even in people most sensitive to such chemical-induced effects (Dorsey *et al.* 2000).

The chronic inhalation MRL is based on a LOAEL (lowest-observed-adverse-effect level) of 35 ppm toluene for colour vision impairment in a group of toluene-exposed workers

studied by Zavalic *et al.* (1998). Exposure to a level above the MRL does not imply that adverse health effects will occur (Dorsey *et al.* 2000).

2.9 Environmental factors

Major urban air pollutants include carbon monoxide, sulfur dioxide, nitrogen oxides and volatile organic compounds. During 1985, emissions of VOC's in the USA reached more than 20 metric tons (Zakrzewski 1997). Natural emissions of VOC's are estimated at 30 – 60million metric tons annually. Anthropogenic emission results from incomplete combustion of fossil fuels and from evaporation of liquid fuels and solvents during storage, refining and handling. These substances once released into the air are carried aloft with the wind. Temperature, humidity and wind direction further play a role in the distribution of these airborne substances. Temperature inversions can intensify the effects of air pollutants in particular areas (Miller and Armstrong 1982). In short, a temperature or thermal inversion is when a layer of dense, cool air is trapped under a layer of less dense, warm air. The result is that pollutants slowly accumulate to dangerous and even lethal levels if the inversion persists (Miller and Armstrong 1982).

CHAPTER 3

EXPERIMENTAL DESIGN AND METHODOLOGY

It is difficult to quantify the exposure to a specific organic substance when workers are exposed to a mixture of substances. Determining the dose-response relation of a mixture and assessing the risks further complicates the matter (Ariëns *et al.* 1976). The total population of crane operators (N = 30) and control group (N = 30) completed questionnaires on several aspects pertaining to the state of their visual abilities.

Questionnaires: The questionnaires were designed to include questions on habits, smoking, alcohol intake, medication and eye diseases or problems they experience regarding vision. All individuals from the control and experimental group had to complete questionnaires to eliminate individuals with a predisposition for eye problems or other factors eg. alcohol intake in order to get an accurate picture of colour vision impairment. Colour vision and contrast sensitivity tests were performed on all 30 operators and on the control group. In the experimental group, the eye tests were performed on a Monday, before the start of the work-shift as well as on a Friday afternoon, after the shift. Of these 30 operators, ten individuals (experimental group B) were randomly chosen to wear the OVM badges and urine samples were also collected from them. Again, the distinction was made between before and after a work-shift in collecting the urine samples. The significance of this is to determine what the effect of a 64 hour period of no exposure to the chemicals will have on the vision tests and metabolites of toluene (half-life of toluene being 12 hours).

The control group also consisted of 30 people with no or very little exposure to toluene. The control group was also subjected to the vision tests, and air samples and urine samples were collected from 10 (control group B) randomly chosen from the control group.

The effective percent exposure levels were calculated for the experimental group using the Recommended Exposure Limit Standards or Occupational Exposure Limit – Recommended Limit (OEL-RL). The following equation was used to investigate the combined effects of all the potentially toxic or hazardous components in the air breathed by the crane operators at the plant:

$$\%\,REL = 100\left[\sum_{i=1}^{n}\frac{TWA_i}{REL_i}\right] = 100\left[\frac{TWA_1}{REL_1}+\frac{TWA_2}{REL_2}+\ldots+\frac{TWA_n}{REL_n}\right]$$

% REL = the Effective Percent Exposure Level from the perspective of the Recommended Exposure Limit Standards, for the mixture being evaluated, expressed as a percentage

TWA_i = the time weighted average concentration of the ith component in the mixture and REL_i = the listed recommended exposure level (OEL - RL) of the ith component.

The significance of the % REL value is as follows: 1) In case the % REL value is equal or smaller than 100%, it implies that the effective Recommended Exposure Level (REL) for the mixture has not been exceeded and 2) In case the % REL value is greater than 100%, the Effective REL for the mixture has been exceeded.

3.1 Determining the Exposure:

Air sampling: Personal exposure to toluene and hydrocarbons in the air were determined by attaching a OVM badge to the clothes of the experimental group as close to the breathing zone as possible. The badges used were OVM-1 monitors from Trace-air system and were worn for the entire 8 hour work shift. After the work shift the badges were collected, sealed and stored in a refrigerator at 4 °C. Analysis of the air samples were performed by SKC laboratories according to the NIOSH 1500/1501 analytical method. Ten subjects from the experimental group B participated in the air sampling tests. Air samples were also collected from 10 subjects from control group B.

Biological monitoring: The ACGIH (American Conference of Governmental Industrial Hygienists) recommend assessing the levels of ortho-cresol and hippuric acid in urine at the end of a work-shift. To determine the metabolites of toluene, ortho-cresol and hippuric acid, urine samples were collected from 10 subjects from the experimental group on four occasions; 1. Monday (before start of shift), 2. Monday (after shift), 3. Wednesday (after shift), and 4. Friday (after shift). Urine samples were collected from the control group on the Wednesday (after the shift). The samples were kept in a freezer at -20 °C until it was analyzed for concentrations of mmol Hippuric acid/ mmol creatinine and mmol ortho-cresol/ mmol creatinine. Analysis was done by the Department of Biochemistry, University of Pretoria.

3.2 Vision Tests:

Minimum standards are set for near visual acuity, distance visual acuity and colour perception for aircraft maintenance inspectors (Beard *et al.* 2003). Although the duties of a crane operator require good vision, there are no set standards for visual abilities.

Colour discrimination is very important for a crane operator in order to perform his duties. Ishihara Plates (Ishihara 1986) and Farnsworth Dichotomous Test (D-15) were used to test for impairment in colour vision. The subject was instructed to read the numbers from Ishihara's plates. Assessment of reading of the plates determined the normality or defectiveness of colour vision. The Farnsworth panel D-15 test is a shortened version of the Farnsworth-Munsell 100 Hue Test. The tests were conducted under daylight illumination and the subject had to arrange the coloured caps in sequential order of colours with reference to a reference cap. All subjects who failed the test the first time were retested to minimize experimental errors in the form of confusion or misunderstanding of the instructions. A pass-fail criterion was adopted for this test and test failure resulted when a subject made more than two simple errors or more than one major crossing.

Contrast sensitivity testing was included since a person with low contrast sensitivity may have trouble discriminating objects that are not outlined clearly or that do not stand out from their background. This include trouble seeing traffic lights or cars at night. For the crane operators it is essential to be able to work under dim light when contrast is very low.

The total population of crane operators and the control group, underwent these tests with the emphasis on the ten subjects of whom the hydrocarbon exposure were also tested. Vision tests for the experimental group were performed on Monday (before start of shift) and on Friday (after the shift) and on Wednesday for the control group.

3.2.1 Contrast sensitivity:

Contrast sensitivity tests were performed on the total population of crane operators by using the "CSV-1000 Contrast Sensitivity" apparatus. Previous studies have shown that the distal part of the retina as well as the retinal pigment epithelium might be impaired by chronic inhalation of toluene. The test therefore can give an indication of damage to the retina that can in turn lead to night blindness. The CSV apparatus has circular patches of gratings. The chart has 4 rows, each containing a different spatial frequency. Each row has eight contrast levels with the highest on the left and the lowest on the right. The contrast sensitivity of the subjects were determined by the lowest grating patch orientation that the subject identified correctly.

3.2.2 Colour vision deficiency:

It is widely known in the literature that colour blindness can result from exposure to toluene in particular. The mechanism of colour vision impairment is not clearly understood but it seems as if toluene interferes with the dopaminergic mechanisms of retinal cells or toxic demylelinization of optic nerve fibers may be involved (Muttray *et al.* 1999, Zavalic *et al.* 1998). Therefore it was essential to have the crane operators undergo tests for colour blindness. Colour vision deficiency were tested by using two methods; 1) Ishihara's Colour chart test and 2) Farnsworth – Panel D15.

3.3 Statistical calculations of data:

Statistical calculation of data was performed using "SPSS" software. Descriptive statistics were used to determine means and standard deviations. The normal t-test was used to indicate significant differences between the mean toluene levels found in urine of the control and that of the experimental group as well as toluene and hydrocarbons in the air of the control and experimental group. The correlation between the toluene levels in the air and toluene levels in the urine was calculated. Paired t-tests were used to determine the

correlation between the toluene levels the operators are exposed to at two different periods (Monday morning - 64 hours after exposure and Wednesday morning - 16 hours after exposure). Cross tabulation and Fisher's exact tests were used to determine the relation between smokers and non-smokers and levels of toluene.

CHAPTER 4

RESULTS

4.1 Personal monitoring

4.1.1 Air

The results obtained from analysis of the OVM badges revealed levels of toluene ranging from 0 to 0.477 ppm. The highest levels for toluene exposure were observed on Monday. The average levels of toluene for the three day period observed in the experimental group, ranged from 0.01 to 0.232 ppm. These levels are well below the Occupational Exposure Limit (OEL) threshold limit value (TLV) for toluene which is 50ppm (Occupational Health and Safety Act No. 85 of 1993).

Other hydrocarbons that were tested included benzene, n-heptane, n-hexane and xylene (see Table 4.1). The exposure levels to these hydrocarbons also never exceeded the threshold limit values for any of the subjects of the experimental group. The effective percent exposure level (%REL) for the mixture of hydrocarbons ranged from 0.4% - 5.4%. The highest exposure level of 5.4% was calculated for Wednesday for subject E4. On Monday, Wednesday and Friday the %REL values calculated for the individuals of the experimental group ranged from 0.6 % – 4.8%, 0.5% - 5.4% and 0.4% - 4% respectively. Exposure of the subjects from the experimental group, to the hydrocarbons were sometimes 2 - 3 times more than for that of the control group. However, no significant differences were observed for any of the hydrocarbons tested for the two groups using the t-test for independent samples.

The experimental group was exposed to low levels of hydrocarbons for the three days which explains why no significant differences were found between the control and experimental group. The exposure to hydrocarbons for some of the subjects of the experimental group were in some cases undetectable (see Table 4.1). The levels of toluene, benzene, hexane and heptane were the highest on Monday. On the three days, exposure to the different hydrocarbons revealed a significant correlation (using Spearman's correlation coefficients) between toluene and benzene with $P< 0.05$. Other correlations

were found for; benzene and hexane, hexane and heptane, toluene and hexane, toluene and xylene and toluene and heptane. When the exposure levels to benzene and toluene exceeded that of the derived MRLs for these substances, it was indicated with an asterisk (see Table 4.1). Calculation of partial correlation coefficients controlling for age and the years of service, revealed no associations for colour vision deficiency and contrast sensitivity tests.

Table 4.1: Average exposure to hydrocarbons in ppm for the ten subjects of experimental group B

	Hexane	Benzene	Heptane	Toluene	Xylene
E1	0.044	0.025*	0	0.232*	0
E2	0.0075	0.0185*	0.0025	0.0215	0.005
E3	0.005	0.019*	0	0.015	0
E4	0.038	0.065*	0.03	0.101*	0.015
E5	0.004	0.028*	0.0016	0.030	0
E6	0.046	0.039*	0.023	0.168*	0.009
E7	0.022	0.018*	0.031	0.036	0
E8	0.031	0.014*	0	0.010	0
E9	0.015	0.015*	0.002	0.01	0
E10	0.01	0.045*	0.003	0.049	0.011

* Level of hydrocarbon exceeds MRL MRL for Benzene: 0.004 ppm
MRL for Toluene: 0.08 ppm

4.1.2 Urine

Ortho-cresol and hippuric acid levels in urine were also analyzed to assess exposure of workers to toluene in the workplace. The levels of hippuric acid/ g creatinine ranged from 0 to 0.182 g hippuric acid/ g creatinine which is below the limit of 0.426 g hippuric acid/ g creatinine. The highest levels of hippuric acid/ g creatinine were observed on Wednesday after the shift but there were no significant differences between the exposure on the different times (Monday before and after the shift and on Friday, after the shift). No significant differences were observed for the experimental and the control group regarding the levels of hippuric acid/ g creatinine and ortho-cresol/ g creatinine. Paired samples

correlations were used to examine the exposure levels of the experimental group between the different work-shifts. It is important to keep in mind that the presence of substances such as hippuric acid and creatinine in urine is not definite proof of toluene exposure since they are also produced by metabolism from the normal diet (Maestri *et al.* 1997).

Alcohol consumption and smoking can also influence the levels of these metabolites found in the urine (Kawamoto *et al.* 1996). The levels of ortho-cresol/ g creatinine were in the range of 0 - 0.001 g ortho-cresol/ g creatinine. Again no significant differences were observed in the experimental group for the different work-shifts using paired samples test. Comparison of the control and experimental group, using independent samples test also revealed no significant differences for the metabolites found in the urine. The highest average levels of ortho-cresol/ g creatinine in urine were observed on Wednesday afternoon although no significant differences were observed between the different work-shifts.

4.2 Vision tests

Not one of the subjects of the experimental group had problems with Ishihara's colour plates on both the test days. Cross tabulation of the results from the Farnsworth panel-D colour vision test, showed that 20% more of the subjects from the experimental group experienced problems with colour discrimination (see Table 4.2). Thirty percent of the subjects of the experimental group experienced difficulty with the colour vision test on Friday, with only 3% experiencing problems on Monday (before shift). It is apparent that subjects performed better with the vision tests on Monday than on Friday.

Table 4.2: Cross tabulation for colour vision testing: Farnsworth Panel -D.

Result of test	Experimental (N = 30)	Control (N = 30)
Normal	73.3% (N = 22)	93.3% (N = 28)
Problem	26.7% (N = 8)	6.7% (N = 2)

The contrast sensitivity test revealed 33.3% of the subjects of the experimental group experienced problems regarding contrast sensitivity discrimination on Friday compared to

13.3 % on Monday (before shift). Using Fisher's exact test, no association was identified between the results obtained for this test on the different days.

In order to refine the results on exposure to the hydrocarbons, each individual of the experimental group (N = 10), was categorized according to the level of exposure to the different hydrocarbons. A point system was used where one point indicates the highest level of exposure to a specific substance and ten points indicate the lowest exposure. For each individual, a score was then calculated adding the points allocated for exposure to each hydrocarbon analysed. Addition of these points gives a better indication of the level of exposure. The final scores calculated ranged between 10 – 40 (see Table 4.3). An individual with the lowest score indicates that he/ she had on average the highest exposure to all the hydrocarbons. For example, E1 had the highest level of exposure to toluene, but a score of 29 indicates less exposure to the other hydrocarbons.

All of the subjects are exposed to some level of noise. From their medical records, it was evident that some of them do experience auditory problems which range from ear infection to some degree of hearing loss. Subject E4 had on average, the highest level of exposure when taking all hydrocarbons into consideration with a score of 10 (see Table 4.3) and did not experience any problems with the vision tests. Three subjects of the experimental group (E3, 6 and 7), had problems with contrast sensitivity discrimination on both days (Monday and Friday). Of these three, one (E6) experienced a problem with Farnsworth Panel-D test for colour discrimination on Monday. With a score of 13, E6 had the average highest exposure to hexane, second most to toluene and third most to benzene, with the highest single exposure to benzene and toluene on Monday.

Table 4.3: Score calculated from exposure of the experimental group B to hydrocarbons, vision tests results and other factors.

	Age	Years (service)	Toluene	Farns.	Contrast	Other	Score
E1	49	14	1			N	29
E2	60	10	8			N	30
E3	49	25	6		X	N, S, A, HB	34
E4	63	20	3			N, S, A	10
E5	40	20	7			N	37
E6	61	18	2	X	X	N, HB	13
E7	40	18	5		X	N, S, A	29
E8	50	15	9			N	43
E9	46	6	10			None	40
E10	34	8	4			None	20

HB: High blood pressure **N:** Noise **A:** Alcohol

S: Smoking

Toluene: 1 – 10 indicates the level of exposure (from highest to lowest)

Score: Exposure to all the hydrocarbons (10 highest exposure on average, 40 = lowest exposure on average)

CHAPTER 5

DISCUSSION

From the results it is clear that at the time of investigation, the level of exposure to the hydrocarbons including toluene were below the TWA OEL-RL according to South African regulations for hazardous substances. The levels of toluene exposure were also well below the TWA OEL-RL of 50 ppm. The combined effects of all the potentially hazardous chemicals present in the ambient air (by calculating the %REL values), revealed levels < 100%, indicating that the effective recommended exposure levels for the mixture of hydrocarbons has not been exceeded for the crane operators under investigation.

The low observed levels (toluene < 0.5 ppm) can not be taken as being representative of the overall exposure at this plant since air samples were only collected on three days over a 6 day period and this does not exclude the possibility that exposure might be higher at other periods. The presence of hydrocarbons such as benzene, n-heptane, n-hexane and xylene emphasize the fact that the crane operators are exposed to a combination of substances. Concurrent exposure to other solvents at similar industries, limits the conclusions that can be drawn from the results.

With these low levels of exposure to toluene (below OELs) and the other hydrocarbons one would expect no adverse health effects. However, some subjects of the experimental group did have problems with colour and contrast discrimination. Evident from the results is the fact that more problems regarding contrast sensitivity and colour discrimination were observed on the Friday than on the Monday but not statistically significantly so. This emphasizes that after a period of no exposure symptoms and health effects disappear. After approximately 60 hours, most of the toluene is removed from the body.

The findings of Toyonaga *et al.* (1989) suggests that exposure to toluene may lead to problems in contrast discrimination and night blindness. It should be stressed that chronic exposure to average concentrations as low as 30 - 130 ppm damages hearing and color vision presumably involving effects on the neurological components of these systems

(Zavalic *et al.* 1998). Campagna and co-workers (2001) have also found impairment of colour vision at toluene exposure levels below the actual ACGIH TLV-TWA of 50 ppm. They raised the question of whether or not the limit for toluene is sufficiently protective.

In the case of the crane operators, the exposure to toluene for the test period was much lower at < 0.5 ppm but vision and hearing problems do occur. Several studies have indicated that colour vision impairment results from chronic exposure to toluene rather than to acute exposure (Muttray *et al.* 1999 and Zavalic *et al.* 1998) The crane operators are exposed to hydrocarbons and other substances including toluene for between 10 to 25 years.

Since contrast sensitivity can be influenced by age, one would expect the older subjects to experience more problems regarding contrast sensitivity. Colour vision on the other hand is not age dependent. Only eight subjects of the total experimental group (N= 30), experienced problems with colour discrimination. All individuals of this group (N=8), have more than 18 years service experience at this plant. However, ten subjects who have more than 18 years service, experienced no problems with colour discrimination. There were no significant correlation between colour vision and years of service or colour vision and toluene levels.

Unfortunately, because of financial restraints, toluene exposure was only measured in experimental group B, which included only one subject who experienced colour vision problems. He had second most exposure to toluene and second most to all the other hydrocarbons and also experienced problems with the contrast sensitivity test on Monday and Friday. It is also important to note that another subject with 20 years of service and age 63, experienced no problems with colour discrimination or with contrast sensitivity. For the test period, he was exposed third most to toluene but had on average the highest exposure to the hydrocarbons in total. From the total experimental group with more than 15 years service, 11 individuals experienced no problems with colour discrimination while N = 7 for those who did have problems with colour discrimination. Of these seven individuals, only two use alcohol.

From the results it is also evident that no individual with less than 10 years of service, had problems with colour discrimination, and therefore it can not be ruled out that exposure to very low levels of toluene over a long period may result in colour vision impairment. Low level occupational exposure to an average of 97 ppm toluene for 12 - 14 years had an apparent effect on hearing (Abbate *et al.* 1993) and slightly reduced colour vision performance was observed in painters chronically exposed to a mixture of organic solvents (Ihrig *et al.* 2002).

The levels for toluene observed at this plant are very low but the workers are exposed to these substances for up to 25 years. Therefore it would be wise to investigate the derived minimal risk levels as identified by the Agency for Toxic Substances and Disease Registry (ATSDR) in the US. They classified chronic exposure to toluene from 365 days or more and has prepared a toxicological profile which characterizes the toxicologic and adverse health effects of toluene.

Although the levels of exposure was low during this investigation, MRLs enable health professionals to identify exposure levels at which adverse health effects are not expected to occur. From the results of this study it is clear that exposure to toluene exceeded the MRL only in three of the subjects. Levels for benzene exposure was higher in all ten subjects than the MRL for benzene. It is important to note that MRLs are intended to serve as a screening tool to help public health professionals decide where to investigate more closely and is not intended to define clean-up or action levels.

The influence of other chemicals on the toxicity of toluene can not be ignored. It has been indicated that co-exposure to ethanol caused a decrease in hippuric acid and inhibits the metabolism of toluene (Campo *et al.* 1998). Ingestion of alcohol prolongs the presence of toluene in blood in humans and this indicates that workers exposed to toluene who regularly drink alcohol may be at greater risk of developing toluene-related neurological problems than non drinkers.

The levels of metabolites of toluene (hippuric acid and ortho-cresol) were low in the experimental group and no correlation was found between the levels of toluene and its

metabolites. A number of factors can influence the urinary excretion of toluene metabolite eg. diet, alcohol consumption and smoking. Again, the low levels of toluene that the subjects were exposed to and the influence of the other hydrocarbons can not be ruled out since they interact with toluene and can influence toluene toxicity.

CHAPTER 6

CONCLUSIONS

The level of toluene exposure was very low, below the TWA OEL-RL for toluene. Levels of the other hydrocarbons were also below the TWA OEL-RLs. Some crane operators did experience problems regarding colour and contrast discrimination. Statistical analysis of the results from this study does not indicate that toluene is responsible for the vision impairments. The chemical interaction between toluene and other solvents will have an influence on the toxicity of toluene and results should be considered carefully.

The problems observed regarding colour vision and the hearing problems might indicate that the levels of hydrocarbons to which the operators were exposed to in the past, were much higher than the present levels. Although the levels of toluene were low, in some cases the exposure was higher than that of the derived MRLs for chronic exposure to toluene.

Evidence from literature suggests and support in most cases that chronic exposure to toluene does result in colour vision impairment. Results have shown that exposure to toluene even below the TWA OEL, can result in colour vision impairment. Should the TWA OEL not be reconsidered?

Recommendations:

1. Warn workers who are exposed to toluene that alcohol intake and concurrent exposure to other chemicals eg. medication can have effects on their health.
2. The crane operators at this plant are chronically exposed to toluene and other hydrocarbons. It is therefore recommended to investigate minimal risk levels for toluene and other hydrocarbons.
3. Use MRLs as a estimate of the daily human exposure to a hazardous substance that is likely to be without adverse health effects over a specified duration of exposure.

4. Investigate blood toluene levels since it is the most accurate biomarker of toluene exposure.
5. Perform frequent colour vision tests to detect any vision impairment which may result from chronic exposure to toluene. Colour vision impairment is the first indication of physiological damage as a result of exposure to toluene.

REFERENCES:

ABBATE, C., GIORGIANNI, C., MUNAO, F., *et al.* 1993. Neurotoxicity induced by exposure to toluene. An electrophysiology study. *Int. Arch. Occup. Environ. Health* 64: 389-392.

ALI, N., TARDIFF, R. 1999. Toxicokinetic modeling of the combined exposure to toluene and *n*-hexane in rats and humans. *J. Occup. Health.* 41:95-103.

AMENO, K., KIRIU, T., FUKE, C., *et al.* 1992. Regional brain distribution of toluene in rats and in a human autopsy. *Arch. Toxicol.* 66:152-156.

ANDERSEN, I., LUNDQVIST, G.R., MOLHAVE, L. 1983. Human response to controlled levels of toluene in six-hour exposures. *Scand. J. Work. Environ. Health.* 9:405-418.

ARIENS, E.J., SIMONIS, A.M., OFFERMEIER, J. 1976. Introduction to general toxicology. Academic Press, New York, San Francisco, London. 230 p.

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological profile for total petroleum hydrocarbons (TPH). Atlanta, GA: *U.S. Department of Health and Human Services, Public Health Service.*

BARHAD, B. Petrochemicals. (*In* Parmeggiani, L. ed. Encyclopedia of Occupational Health and Safety. Vol. (2). 1985. Third revised edition. International Labour Office, Geneva).

BEARD, B.L., HISLE, W.A., AHUMADA, A.J. Jr. 2003. Occupational Vision Standards: A Review. NASA Ames Research Center, Moffet Field, CA 94035 – 1000.

CAMPAGNA, D., STENGEL, B., MERGLER, D., LIMASSET, J.C., DIEBOLD, F., MICHARD, D., HUEL, G. 2001. Color vision and occupational toluene exposure. *Neurotoxicol. Teratol.* 23: 473-480.

CAMPO, P., LATYE, R., COSSEC, B., *et al.* 1998. Combined effects of simultaneous exposure to toluene and ethanol on auditory function in rats. *Neurotoxicol. Teratol.* 20 (3): 321-332.

COHEN, A.I. 1987. The Retina. (*In* Moses, R.A., Hart, W.M. eds. Adler's Physiology of the Eye. Clinical application. Eigth edition. The C.V. Mosby Company, St.Louis, Missouri, USA).

DAVSON, H. 1980. Physiology of the Eye. Fourth Edition. Churchill Livingstone. Edinburgh, London and New York.

DELEU, D., HANSSENS, Y. 2000. Cerebellar dysfunction in chronic toluene abuse: beneficial response to amantadine hydrochloride. *J. Toxicol. Clin. Toxicol.* 38(1): 37-41.

DORSEY, A., McCLURE, P.R., McDONALD, A.R., SINGH, M. 2000. Toxicological Profile for Toluene. U.S. Department of Health and Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry. P. 222.

FRANKS, N.P., LIEB, W.R. 1987. Anaesthetics on the mind. *Nature* 328:113-114.

GOBBA, F., CAVALLERI, A. 2003. Color Vision Impairment in workers exposed to Neurotoxic chemicals. *Neurotoxicology* 24: 693-702.

GOSPE, S.M. Jr., AL-BAYATI, M.A.S. 1994. Comparison of oral and inhalation exposures to toluene. J. *Am. Coll. Toxicol.* 11:54-545.

GOSSEL, T.A., BRICKER, J.D. 1994. Principles of Clinical Toxicology. Third edition. Raven Press. New York.

HART, H., SCHUETZ, R.D. 1978. Organic Chemistry. A Short Course. Fifth edition. Houghton Mifflin Company, Boston, USA.

HEYMAN, R. 1986. The Eye. (*In* Cohen, G.M. ed. Target Organ Toxicity. Vol. II. CRC Press, Inc. Boca Raton, Florida).

HJELM, E.W., NASLUND, P.H., WALLEN, M. 1988. Influence of cigarette smoking on the toxicokinetics of toluene in humans. *J. Toxicol. Environ. Health.* 25: 155-163.

IARC. 1999. IARC monographs on the evaluation of carcinogenic risks to humans: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. Vol. 71 (2). Lyon, France: WHO, International Agency for Research on Cancer.

IHRIG, A., NASTERLACK, M., DIETZ, M.C., HOFFMANN, J., TRIEBIG, G. 2003. Pilot study on prevalence of color vision dysfunction in long-term solvent-exposed painters. *Industrial Health* 41:39-42.

IREGREN, A., ANDERSSON, M., NYLEN, P. 2002. Color vision and Occupational Exposures: I. An Overview of Tests and Effects. *NeuroToxicology* 23 (6): 719-733.

ISHIHARA, S. 1986. Ishihara's Tests for Colour-Blindness. Kanehara and Co., Ltd. Tokyo, Japan.

KAMRIN, M.A. 1988. Toxicology: a primer on toxicology principles and applications. Lewis Publishers, Inc. Chelsea, Michigan, USA.

KAWAMOTO, T., KOGA, M., OYAMA, T., *et al.* 1996. Habitual and genetic factors that affect urinary background levels of biomarkers for organic solvent exposure. *Arch. Environ. Contam. Toxicol.* 30(1): 114-120.

LEBEL, C.P., SCHATZ, R.A. 1990. Altered synaptosomal phospholipid metabolism after toluene: Possible relationship with membrane fluidity, Na^+, K^+ –adenosine triphosphatase and phospholipid methylation. *J. Pharmacol. Exp. Ther.* 253(3) :1189-1197.

LOB, M. Toluene and derivatives. (*In* Parmeggiani, L. ed. Encyclopedia of Occupational Health and Safety. Vol. (2). 1985. Third revised edition. International Labour Office, Geneva).

LOF, A., HJELM, E.W., COLMSJO, A., *et al.* 1993. Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to $^2H_8$ –toluene. *Br. J. Ind. Med.* 50:55-59.

MAESTRI, L., GHITTORI, S., IMBRIANI, M. 1997. Determination of specific mercapturic acids as an index of exposure to environmental benzene, toluene and styrene. *Ind. Health.* 35: 489-501.

MILLER, G.P., ARMSTRONG, P. 1982. Living in the Environment. Wadsworth. Bellmont, California, USA.

MUTTRAY, A., WOLTERS, V., JUNG, D., *et al.* 1999. Effects of high doses of toluene on color vision. *Neurotoxicol. Teratol.* 21(1): 41-45.

NAKAJIMA, T., WANG, R-S. 1994. Induction of cytochrome P450 by toluene. *Int. J. Biochem.* 26 (12): 1333-1340.

NAKAJIMA, T., WANG, R-S., ELOVAARA, E., *et al.* 1997. Toluene metabolism by cDNA-expressed human hepatic cytochrome P-450. *Biochem. Pharmacol.* 53 (3):271-277.

PATERSON, S.C., SARVESVARAN, R. 1983. Plastic bag death: A toluene fatality. *Med. Sci. Law.* 23(1): 64-66.

PARMEGGIANI, L. 1985. Aromatic Hydrocarbons. (*In* Parmeggiani, L. ed. Encyclopedia of Occupational Health and Safety. Vol. (2). Third revised edition. International Labour Office, Geneva).

PURCELL, K.J., CASON, G.H., GARGAS, M.L., *et al.* 1990. In vivo metabolic interactions of benzene and toluene. *Toxicol. Lett.* 52:141-152.

ROSENBERG, N.L., SPITZ, M.C., FILLEY, C.M., *et al.* 1988. Central nervous system effects of chronic toluene abuse: clinical, brainstem evoked response and magnetic resonance imaging studies. *Neurotoxicol. Teratol.* 10: 489-495.

SAARI, J.C. 1987. Metabolism and photochemistry in the retina. (*In* Moses, R.A., Hart, W.M. eds. Adler's Physiology of the Eye. Clinical application. Eighth edition. The C.V. Mosby Company, St.Louis, Missouri, USA).

SEMPLE, S., DICK, F., OSBORNE, A., CHERRIE, J.W., SOUTAR, A., SEATON, A., HAITES, N. 2000. Impairment of colour vision in workers exposed to organic solvents. *Occup. Environ. Med.* 57: 582-587.

TAKEICHI, S., YAMADA, T., SHIKATA, I. 1986. Acute toluene poisoning during painting. *Forensic Sci. Int.* 32:109-115.

TARDIF, R., PLAA, G.L., BRODEUR, J. 1992. Influence of various mixtures of inhaled toluene and xylene on the biological monitoring of exposure to these solvents in rats. *Can. J. Physiol. Pharmacol.* 70:385-395.

TOYONAGA, N., ADACHI-USAMI, E., YAMAZAKI, H. 1989. Clinical and electrophysiological findings in three patients with toluene dependency. *Doc. Ophthalmol.* 73 (2): 201-207.

VRCA, A., KARACIC, V., BOZ ICEVIC, D., *et al.* 1996. Brainstem evoked potentials in individuals exposed to long-term low concentrations of toluene. *Am. J. Ind. Med.* 30:62-66.

ZAKRZEWSKI, S.F. 1997. Principles of Environmental Toxicology. Second edition. American Chemical Society, Washington DC.

ZAVALIC, M., MANDIC, Z., TURK, R., *et al.* 1998. Quantitative assessment of color vision impairment in workers exposed to toluene. *Am. J. Ind. Med.* 33(3): 297-304.