

FOX VALLEY TRAFFIC PAINT BLUE

TOXICOLOGICAL REPORT

MOST IMPORTANT SYMPTOMS AND EFFECTS, BOTH ACUTE AND DELAYED

INHALED

Inhalation of aerosols (mists, fumes), generated by the material during the course of normal handling, may be harmful.

Inhalation of vapours may cause drowsiness and dizziness. This may be accompanied by narcosis, reduced alertness, loss of reflexes, lack of coordination and vertigo.

Limited evidence or practical experience suggests that the material may produce irritation of the respiratory system, in a significant number of individuals, following inhalation. In contrast to most organs, the lung is able to respond to a chemical insult by first removing or neutralising the irritant and then repairing the damage. The repair process, which initially evolved to protect mammalian lungs from foreign matter and antigens, may however, produce further lung damage resulting in the impairment of gas exchange, the primary function of the lungs. Respiratory tract irritation often results in an inflammatory response involving the recruitment and activation of many cell types, mainly derived from the vascular system.

Acute effects from inhalation of high concentrations of vapour are pulmonary irritation, including coughing, with nausea; central nervous system depression - characterised by headache and dizziness, increased reaction time, fatigue and loss of co-ordination

Material is highly volatile and may quickly form a concentrated atmosphere in confined or unventilated areas. The vapour may displace and replace air in breathing zone, acting as a simple asphyxiant. This may happen with little warning of overexposure.

WARNING: Intentional misuse by concentrating/inhaling contents may be lethal.

INGESTION

Accidental ingestion of the material may be harmful; animal experiments indicate that ingestion of less than 150 gram may be fatal or may produce serious damage to the health of the individual.

Not normally a hazard due to physical form of product.

Considered an unlikely route of entry in commercial/industrial environments

SKIN CONTACT

Skin contact with the material may be harmful; systemic effects may result following absorption.

The material produces moderate skin irritation; evidence exists, or practical experience predicts, that the material either

- ▶ produces moderate inflammation of the skin in a substantial number of individuals following direct contact, and/or
- ▶ produces significant, but moderate, inflammation when applied to the healthy intact skin of animals (for up to four hours), such inflammation being present twenty-four hours or more after the end of the exposure period.

Skin irritation may also be present after prolonged or repeated exposure; this may result in a form of contact dermatitis (nonallergic). The dermatitis is often characterised by skin redness (erythema) and swelling (oedema) which may progress to blistering (vesiculation), scaling and thickening of the epidermis. At the microscopic level there may be intercellular oedema of the spongy layer of the skin (spongiosis) and intracellular oedema of the epidermis.

Repeated exposure may cause skin cracking, flaking or drying following normal handling and use.

Spray mist may produce discomfort

Open cuts, abraded or irritated skin should not be exposed to this material

Entry into the blood-stream through, for example, cuts, abrasions, puncture wounds or lesions, may produce systemic injury with harmful effects. Examine the skin prior to the use of the material and ensure that any external damage is suitably protected.

EYE

Evidence exists, or practical experience predicts, that the material may cause eye irritation in a substantial number of individuals and/or may produce significant ocular lesions which are present twenty-four hours or more after instillation into the eye(s) of experimental animals.

Repeated or prolonged eye contact may cause inflammation characterised by temporary redness (similar to windburn) of the conjunctiva (conjunctivitis); temporary impairment of vision and/or other transient eye damage/ulceration may occur.

Direct contact with the eye may not cause irritation because of the extreme volatility of the gas; however concentrated atmospheres may produce irritation after brief exposures..

CHRONIC

On the basis, primarily, of animal experiments, concern has been expressed that the material may produce carcinogenic or mutagenic effects; in respect of the available information, however, there presently exists inadequate data for making a satisfactory assessment.

Harmful: danger of serious damage to health by prolonged exposure through inhalation.

Serious damage (clear functional disturbance or morphological change which may have toxicological significance) is likely to be caused by repeated or prolonged exposure. As a rule the material produces, or contains a substance which produces severe lesions. Such damage may become apparent following direct application in subchronic (90 day) toxicity studies or following sub-acute (28 day) or chronic (two-year) toxicity tests.

Exposure to the material may cause concerns for human fertility, generally on the basis that results in animal studies provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which are not a secondary non-specific consequence of other toxic effects.

Exposure to the material may cause concerns for humans owing to possible developmental toxic effects, generally on the basis that results in appropriate animal studies provide strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of other toxic effects.

Limited evidence suggests that repeated or long-term occupational exposure may produce cumulative health effects involving organs or biochemical systems.

Principal route of occupational exposure to the gas is by inhalation.

Repeated or prolonged exposure to mixed hydrocarbons may produce narcosis with dizziness, weakness, irritability, concentration and/or memory loss, tremor in the fingers and tongue, vertigo, olfactory disorders, constriction of visual field, paraesthesias of the extremities, weight loss and anaemia and degenerative changes in the liver and kidney. Chronic exposure by petroleum workers, to the lighter hydrocarbons, has been associated with visual disturbances, damage to the central nervous system, peripheral neuropathies (including numbness and paraesthesias), psychological and neurophysiological deficits, bone marrow

toxicities (including hypoplasia possibly due to benzene) and hepatic and renal involvement. Chronic dermal exposure to petroleum hydrocarbons may result in defatting which produces localised dermatoses. Surface cracking and erosion may also increase susceptibility to infection by microorganisms. One epidemiological study of petroleum refinery workers has reported elevations in standard mortality ratios for skin cancer along with a dose-response relationship indicating an association between routine workplace exposure to petroleum or one of its constituents and skin cancer, particularly melanoma. Other studies have been unable to confirm this finding.

Hydrocarbon solvents are liquid hydrocarbon fractions derived from petroleum processing streams, containing only carbon and hydrogen atoms, with carbon numbers ranging from approximately C5-C20 and boiling between approximately 35-370 deg C. Many of the hydrocarbon solvents have complex and variable compositions with constituents of 4 types, alkanes (normal paraffins, isoparaffins, and cycloparaffins) and aromatics (primarily alkylated one- and two-ring species). Despite the compositional complexity, most hydrocarbon solvent constituents have similar toxicological properties, and the overall toxicological hazards can be characterized in generic terms. Hydrocarbon solvents can cause chemical pneumonitis if aspirated into the lung, and those that are volatile can cause acute CNS effects and/or ocular and respiratory irritation at exposure levels exceeding occupational recommendations. Otherwise, there are few toxicologically important effects. The exceptions, n-hexane and naphthalene, have unique toxicological properties

Animal studies:

No deaths or treatment related signs of toxicity were observed in rats exposed to light alkylate naphtha (paraffinic hydrocarbons) at concentrations of 668, 2220 and 6646 ppm for 6 hrs/day, 5 days/wk for 13 weeks. Increased liver weights and kidney toxicity (male rats) was observed in high dose animals. Exposure to pregnant rats at concentrations of 137, 3425 and 6850 ppm did not adversely affect reproduction or cause maternal or foetal toxicity. Lifetime skin painting studies in mice with similar naphthas have shown weak or no carcinogenic activity following prolonged and repeated exposure. Similar naphthas/distillates, when tested at nonirritating dose levels, did not show any significant carcinogenic activity indicating that this tumorigenic response is likely related to chronic irritation and not to dose. The mutagenic potential of naphthas has been reported to be largely negative in a variety of mutagenicity tests. The exact relationship between these results and human health is not known. Some components of this product have been shown to produce a species specific, sex hormonal dependent kidney lesion in male rats from repeated oral or inhalation exposure. Subsequent research has shown that the kidney damage develops via the formation of a alpha-2u-globulin, a mechanism unique to the male rat. Humans do not form alpha-2u-globulin, therefore, the kidney effects resulting from this mechanism are not relevant in human.

Prolonged or repeated contact with xylenes may cause defatting dermatitis with drying and cracking. Chronic inhalation of xylenes has been associated with central nervous system effects, loss of appetite, nausea, ringing in the ears, irritability, thirst anaemia, mucosal bleeding, enlarged liver and hyperplasia. Exposure may produce kidney and liver damage. In chronic occupational exposure, xylene (usually mixed with other solvents) has produced irreversible damage to the central nervous system and ototoxicity (damages hearing and increases sensitivity to noise), probably due to neurotoxic mechanisms.

Industrial workers exposed to xylene with a maximum level of ethyl benzene of 0.06 mg/l (14 ppm) reported headaches and irritability and tired quickly.

Functional nervous system disturbances were found in some workers employed for over 7 years whilst other workers had enlarged livers.

Xylene has been classed as a developmental toxin in some jurisdictions.

Small excess risks of spontaneous abortion and congenital malformation were reported amongst women exposed to xylene in the first trimester of pregnancy. In all cases, however, the women were also been exposed to other substances. Evaluation of workers chronically exposed to xylene has demonstrated lack of genotoxicity. Exposure to xylene has been associated with increased risks of haemopoietic malignancies but, again, simultaneous exposure to other substances (including benzene) complicates the picture. A long-term gavage study to mixed xylenes (containing 17% ethyl benzene) found no evidence of carcinogenic activity in rats and mice of either sex.

Chronic toluene habituation occurs following intentional abuse (glue sniffing) or from occupational exposure. Ataxia, incoordination and tremors of the hands and feet (as a consequence of diffuse cerebral atrophy), headache, abnormal speech, transient memory loss, convulsions, coma, drowsiness, reduced colour perception, frank blindness, nystagmus (rapid, involuntary eye-movements), hearing loss leading to deafness and mild dementia have all been associated with chronic abuse. Peripheral nerve damage, encephalopathy, giant axonopathy electrolyte disturbances in the cerebrospinal fluid and abnormal computer tomographic (CT scans) are common amongst toluene addicts. Although toluene abuse has been linked with kidney disease, this does not commonly appear in cases of occupational toluene exposures. Cardiac and haematological toxicity are however associated with chronic toluene exposures. Cardiac arrhythmia, multifocal and premature ventricular contractions and supraventricular tachycardia are present in 20% of patients who abused toluene-containing paints. Previous suggestions that chronic toluene inhalation produced human peripheral neuropathy have been discounted. However central nervous system (CNS) depression is well documented where blood toluene exceeds 2.2 mg%. Toluene abusers can achieve transient circulating concentrations of 6.5 %. Amongst workers exposed for a median time of 29 years, to toluene, no subacute effects on neurasthenic complaints and psychometric test results could be established. The prenatal toxicity of very high toluene concentrations has been documented for several animal species and man. Malformations indicative of specific teratogenicity have not generally been found. Neonatal toxicity, described in the literature, takes the form of embryo death or delayed foetal growth and delayed skeletal system development. Permanent damage of children has been seen only when mothers have suffered from chronic intoxication as a result of "sniffing".

INDICATION OF ANY IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT NEEDED

Treat symptomatically.

For acute or short term repeated exposures to ethylene glycol:

- ▶ Early treatment of ingestion is important. Ensure emesis is satisfactory.
- ▶ Test and correct for metabolic acidosis and hypocalcaemia.
- ▶ Apply sustained diuresis when possible with hypertonic mannitol.
- ▶ Evaluate renal status and begin haemodialysis if indicated. [I.L.O]
- ▶ Rapid absorption is an indication that emesis or lavage is effective only in the first few hours. Cathartics and charcoal are generally not effective.
- ▶ Correct acidosis, fluid/electrolyte balance and respiratory depression in the usual manner. Systemic acidosis (below 7.2) can be treated with intravenous sodium bicarbonate solution.
- ▶ Ethanol therapy prolongs the half-life of ethylene glycol and reduces the formation of toxic metabolites.
- ▶ Pyridoxine and thiamine are cofactors for ethylene glycol metabolism and should be given (50 to 100 mg respectively) intramuscularly, four times per day for 2 days.
- ▶ Magnesium is also a cofactor and should be replenished. The status of 4-methylpyrazole, in the treatment regime, is still uncertain. For clearance of the material and its metabolites, haemodialysis is much superior to peritoneal dialysis.

[Ellenhorn and Barceloux: Medical Toxicology]

It has been suggested that there is a need for establishing a new biological exposure limit before a workshift that is clearly below 100 mmol ethoxy-acetic acids per mole creatinine in morning urine of people occupationally exposed to ethylene glycol ethers. This arises from the finding that an increase in urinary stones may be associated with such exposures.

Laitinen J., et al: Occupational & Environmental Medicine 1996; 53, 595-600

Following acute or short term repeated exposures to toluene:

- ▶ Toluene is absorbed across the alveolar barrier, the blood/air mixture being 11.2/15.6 (at 37 degrees C.) The concentration of toluene, in expired breath, is of the order of 18 ppm following sustained exposure to 100 ppm. The tissue/blood proportion is 1/3 except in adipose where the proportion is 8/10.

- ▶ Metabolism by microsomal mono-oxygenation, results in the production of hippuric acid. This may be detected in the urine in amounts between 0.5 and 2.5 g/24 hr which represents, on average 0.8 gm/gm of creatinine. The biological half-life of hippuric acid is in the order of 1-2 hours.
- ▶ Primary threat to life from ingestion and/or inhalation is respiratory failure.
- ▶ Patients should be quickly evaluated for signs of respiratory distress (eg cyanosis, tachypnoea, intercostal retraction, obtundation) and given oxygen. Patients with inadequate tidal volumes or poor arterial blood gases (pO2 <50 mm Hg or pCO2 > 50 mm Hg) should be intubated.
- ▶ Arrhythmias complicate some hydrocarbon ingestion and/or inhalation and electrocardiographic evidence of myocardial damage has been reported; intravenous lines and cardiac monitors should be established in obviously symptomatic patients. The lungs excrete inhaled solvents, so that hyperventilation improves clearance.
- ▶ A chest x-ray should be taken immediately after stabilisation of breathing and circulation to document aspiration and detect the presence of pneumothorax.
- ▶ Epinephrine (adrenaline) is not recommended for treatment of bronchospasm because of potential myocardial sensitisation to catecholamines. Inhaled cardioselective bronchodilators (e.g. Alupent, Salbutamol) are the preferred agents, with aminophylline a second choice.
- ▶ Lavage is indicated in patients who require decontamination; ensure use.

BIOLOGICAL EXPOSURE INDEX - BEI

These represent the determinants observed in specimens collected from a healthy worker exposed at the Exposure Standard (ES or TLV):

DETERMINANT	INDEX	SAMPLING TIME	COMMENTS
o-Cresol in urine	0.5 mg/L	End of shift	B
Hippuric acid in urine	1.6 g/g creatinine	End of shift	B, NS
Toluene in blood	0.05 mg/L	Prior to last shift of workweek	

NS: Non-specific determinant; also observed after exposure to other material

B: Background levels occur in specimens collected from subjects NOT exposed

For acute or short term repeated exposures to xylene:

- ▶ Gastro-intestinal absorption is significant with ingestions. For ingestions exceeding 1-2 ml (xylene)/kg, intubation and lavage with cuffed endotracheal tube is recommended. The use of charcoal and cathartics is equivocal.
- ▶ Pulmonary absorption is rapid with about 60-65% retained at rest.
- ▶ Primary threat to life from ingestion and/or inhalation, is respiratory failure.
- ▶ Patients should be quickly evaluated for signs of respiratory distress (e.g. cyanosis, tachypnoea, intercostal retraction, obtundation) and given oxygen. Patients with inadequate tidal volumes or poor arterial blood gases (pO2 < 50 mm Hg or pCO2 > 50 mm Hg) should be intubated.
- ▶ Arrhythmias complicate some hydrocarbon ingestion and/or inhalation and electrocardiographic evidence of myocardial injury has been reported; intravenous lines and cardiac monitors should be established in obviously symptomatic patients. The lungs excrete inhaled solvents, so that hyperventilation improves clearance.
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BIOLOGICAL EXPOSURE INDEX - BEI

These represent the determinants observed in specimens collected from a healthy worker exposed at the Exposure Standard (ES or TLV):

DETERMINANT	INDEX	SAMPLING TIME	COMMENTS
Methylhippu-ric acids in urine	1.5 gm/gm creatinine	End of shift	
	2 mg/min	Last 4 hrs of shift	

INFORMATION ON TOXICOLOGICAL EFFECTS

TOXICITY	IRRITATION
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FOX VALLEY TRAFFIC PAINT BLUE	

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For toluene:
Acute Toxicity
Humans exposed to intermediate to high levels of toluene for short periods of time experience adverse central nervous system effects ranging from headaches to intoxication, convulsions, narcosis, and death. Similar effects are observed in short-term animal studies.

Humans - Toluene ingestion or inhalation can result in severe central nervous system depression, and in large doses, can act as a narcotic. The ingestion of about 60 mL resulted in fatal nervous system depression within 30 minutes in one reported case.

Constriction and necrosis of myocardial fibers, markedly swollen liver, congestion and haemorrhage of the lungs and acute tubular necrosis were found on autopsy.

Central nervous system effects (headaches, dizziness, intoxication) and eye irritation occurred following inhalation exposure to 100 ppm toluene 6 hours/day for 4 days.

Exposure to 600 ppm for 8 hours resulted in the same and more serious symptoms including euphoria, dilated pupils, convulsions, and nausea. Exposure to 10,000-30,000 ppm has been reported to cause narcosis and death.

Toluene can also strip the skin of lipids causing dermatitis.

Animals - The initial effects are instability and incoordination, lachrymation and sniffles (respiratory exposure), followed by narcosis. Animals die of respiratory failure from severe nervous system depression. Cloudy swelling of the kidneys was reported in rats following inhalation exposure to 1600 ppm, 18-20 hours/day for 3 days.

Subchronic/Chronic Effects:

Repeat doses of toluene cause adverse central nervous system effects and can damage the upper respiratory system, the liver, and the kidney. Adverse effects occur as a result from both oral and the inhalation exposures. A reported lowest-observed-effect level in humans for adverse neurobehavioral effects is 88 ppm.

Humans - Chronic occupational exposure and incidences of toluene abuse have resulted in hepatomegaly and liver function changes. It has also resulted in nephrotoxicity and, in one case, was a cardiac sensitizer and fatal cardiotoxin.

Neural and cerebellar dystrophy were reported in several cases of habitual "glue sniffing." An epidemiological study in France on workers chronically exposed to toluene fumes reported leukopenia and neutropenia. Exposure levels were not given in the secondary reference; however, the average urinary excretion of hippuric acid, a metabolite of toluene, was given as 4 g/L compared to a normal level of 0.6 g/L.

Animals - The major target organs for the subchronic/chronic toxicity of toluene are the nervous system, liver, and kidney. Depressed immune response has been reported in male mice given doses of 105 mg/kg/day for 28 days. Toluene in corn oil administered to F344 male and female rats by gavage 5 days/week for 13 weeks, induced prostration, hypoactivity, ataxia, piloerection, lachrymation, excess salivation, and body tremors at doses 2500 mg/kg. Liver, kidney, and heart weights were also increased at this dose and histopathologic lesions were seen in the liver, kidneys, brain and urinary bladder. The no-observed-adverse effect level (NOAEL) for the study was 312 mg/kg (223 mg/kg/day) and the lowest-observed-adverse effect level (LOAEL) for the study was 625 mg/kg (446 mg/kg/day).

Developmental/Reproductive Toxicity

Exposures to high levels of toluene can result in adverse effects in the developing human foetus. Several studies have indicated that high levels of toluene can also adversely affect the developing offspring in laboratory animals.

Humans - Variable growth, microcephaly, CNS dysfunction, attentional deficits, minor craniofacial and limb abnormalities, and developmental delay were seen in three children exposed to toluene in utero as a result of maternal solvent abuse before and during pregnancy.

Animals - Sterebral alterations, extra ribs, and missing tails were reported following treatment of rats with 1500 mg/m³ toluene 24 hours/day during days 9-14 of gestation. Two of the dams died during the exposure. Another group of rats received 1000 mg/m³ 8 hours/day during days 1-21 of gestation. No maternal deaths or toxicity occurred, however, minor skeletal retardation was present in the exposed fetuses. C57BL/6 Mice were exposed to 500 or 1500 mg/m³ toluene continuously during days 6-13 of pregnancy. All dams died at the high dose during the first 24 hours of exposure, however none died at 500 mg/m³. Decreased foetal weight was reported, but there were no differences in the incidences of skeletal malformations or anomalies between the treated and control offspring.

Absorption - Studies in humans and animals have demonstrated that toluene is readily absorbed via the lungs and the gastrointestinal tract. Absorption through the skin is estimated at about 1% of that absorbed by the lungs when exposed to toluene vapor.

Dermal absorption is expected to be higher upon exposure to the liquid; however, exposure is limited by the rapid evaporation of toluene.

Distribution - In studies with mice exposed to radiolabeled toluene by inhalation, high levels of radioactivity were present in body fat, bone marrow, spinal nerves, spinal cord, and brain white matter. Lower levels of radioactivity were present in blood, kidney, and liver. Accumulation of toluene has generally been found in adipose tissue, other tissues with high fat content, and in highly vascularised tissues.

Metabolism - The metabolites of inhaled or ingested toluene include benzyl alcohol resulting from the hydroxylation of the methyl group. Further oxidation results in the formation of benzaldehyde and benzoic acid. The latter is conjugated with glycine to yield hippuric acid or reacted with glucuronic acid to form benzoyl glucuronide. o-cresol and p-cresol formed by ring hydroxylation are considered minor metabolites.

Excretion - Toluene is primarily (60-70%) excreted through the urine as hippuric acid. The excretion of benzoyl glucuronide accounts for 10-20%, and excretion of unchanged toluene through the lungs also accounts for 10-20%. Excretion of hippuric acid is usually complete within 24 hours after exposure.

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For Low Boiling Point Naphthas (LBPNS): Acute toxicity: LBPNS generally have low acute toxicity by the oral (median lethal dose [LD50] in rats > 2000 mg/kg-bw), inhalation (LD50 in rats > 5000 mg/m³) and dermal (LD50 in rabbits > 2000 mg/kg-bw) routes of exposure. Most LBPNS are mild to moderate eye and skin irritants in rabbits, with the exception of heavy catalytic cracked and heavy catalytic reformed naphthas, which have higher primary skin irritation indices.

Sensitisation: LBPNS do not appear to be skin sensitizers, but a poor response in the positive control was also noted in these studies. Repeat dose toxicity: The lowest-observed-adverse-effect concentration (LOAEC) and lowest-observed-adverse-effect level (LOAEL) values identified following short-term (2-89 days) and subchronic (greater than 90 days) exposure to the LBPNS substances. These values were determined for a variety of endpoints after considering the toxicity data for all LBPNS in the group.

Most of the studies were carried out by the inhalation route of exposure. Renal effects, including increased kidney weight, renal lesions (renal tubule dilation, necrosis) and hyaline droplet formation, observed in male rats exposed orally or by inhalation to most LBPNS, were considered species- and sex-specific. These effects were determined to be due to a mechanism of action not relevant to humans -specifically, the interaction between hydrocarbon metabolites and alpha-2-microglobulin, an enzyme not produced in substantial amounts in female rats, mice and other species, including humans. The resulting nephrotoxicity and subsequent carcinogenesis in male rats were therefore not considered in deriving LOAEC/LOAEL values. Only a limited number of studies of short-term and subchronic duration were identified for site-restricted LBPNS. The lowest LOAEC identified in these studies, via the inhalation route, is 5475 mg/m³, based on a concentration-related increase in liver weight in both male and female rats following a 13-week exposure to light catalytic cracked naphtha. Shorter exposures of rats to this test substance resulted in nasal irritation at 9041 mg/m³. No systemic toxicity was reported following dermal exposure to light catalytic cracked naphtha, but skin irritation and accompanying histopathological changes were increased, in a dose-dependent manner, at doses as low as 30 mg/kg-bw per day when applied 5 days per week for 90 days in rats. No non-cancer chronic toxicity studies (= 1 year) were identified for site-restricted LBPNS and very few non-cancer chronic toxicity studies were identified for other LBPNS. An LOAEC of 200 mg/m³ was noted in a chronic inhalation study that exposed mice and rats to unleaded gasoline (containing 2% benzene). This inhalation LOAEC was based on ocular discharge and ocular irritation in rats. At the higher concentration of 6170 mg/m³, increased kidney weight was observed in male and female rats (increased kidney weight was also observed in males only at 870 mg/m³). Furthermore, decreased body weight in male and female mice was also observed at 6170 mg/m³. A LOAEL of 714 mg/kg-bw was identified for dermal exposure based on local skin effects (inflammatory and degenerative skin changes) in mice following application of naphtha for 105 weeks. No systemic toxicity was reported. Genotoxicity: Although few genotoxicity studies were identified for the site-restricted LBPNS, the genotoxicity of several other LBPNS substances has been evaluated using a variety of in vivo and in vitro assays. While in vivo genotoxicity assays were negative overall, the in vitro tests exhibited mixed results. For in vivo genotoxicity tests, LBPNS exhibited negative results for chromosomal aberrations and micronuclei induction, but exhibited positive results in one sister chromatid exchange assay although this result was not considered definitive for clastogenic activity as no genetic material was unbalanced.

or lost. Mixtures that were tested, which included a number of light naphthas, displayed mixed results (i.e., both positive and negative for the same assay) for chromosomal aberrations and negative results for the dominant lethal mutation assay. Unleaded gasoline (containing 2% benzene) was tested for its ability to induce unscheduled deoxyribonucleic acid (DNA) synthesis (UDS) and replicative DNA synthesis (RDS) in rodent hepatocytes and kidney cells. UDS and RDS were induced in mouse hepatocytes via oral exposure and RDS was induced in rat kidney cells via oral and inhalation exposure. Unleaded gasoline (benzene content not stated) exhibited negative results for chromosomal aberrations and the dominant lethal mutation assay and mixed results for atypical cell foci in rodent renal and hepatic cells. For in vitro genotoxicity studies, LBPNS were negative for six out of seven Ames tests, and were also negative for UDS and for forward mutations LBPNS exhibited mixed or equivocal results for the mouse lymphoma and sister chromatid exchange assays, as well as for cell transformation and positive results for one bacterial DNA repair assay. Mixtures that were tested, which included a number of light naphthas, displayed negative results for the Ames and mouse lymphoma assays Gasoline exhibited negative results for the Ames test battery, the sister chromatid exchange assay and for one mutagenicity assay . Mixed results were observed for UDS and the mouse lymphoma assay. While the majority of in vivo genotoxicity results for LBPNS substances are negative, the potential for genotoxicity of LBPNS as a group cannot be discounted based on the mixed in vitro genotoxicity results. Carcinogenicity: Although a number of epidemiological studies have reported increases in the incidence of a variety of cancers, the majority of these studies are considered to contain incomplete or inadequate information. Limited data, however, are available for skin cancer and leukemia incidence, as well as mortality among petroleum refinery workers. It was concluded that there is limited evidence supporting the view that working in petroleum refineries entails a carcinogenic risk (Group 2A carcinogen). IARC (1989a) also classified gasoline as a Group 2B carcinogen; it considered the evidence for carcinogenicity in humans from gasoline to be inadequate and noted that published epidemiological studies had several limitations, including a lack of exposure data and the fact that it was not possible to separate the effects of combustion products from those of gasoline itself. Similar conclusions were drawn from other reviews of epidemiological studies for gasoline (US EPA 1987a, 1987b). Thus, the evidence gathered from these epidemiological studies is considered to be inadequate to conclude on the effects of human exposure to LBPNS substances. No inhalation studies assessing the carcinogenicity of the site-restricted LBPNS were identified. Only unleaded gasoline has been examined for its carcinogenic potential, in several inhalation studies. In one study, rats and mice were exposed to 0, 200, 870 or 6170 mg/m³ of a 2% benzene formulation of the test substance, via inhalation, for approximately 2 years. A statistically significant increase in hepatocellular adenomas and carcinomas, as well as a non-statistical increase in renal tumours, were observed at the highest dose in female mice. A dose-dependent increase in the incidence of primary renal neoplasms was also detected in male rats, but this was not considered to be relevant to humans, as discussed previously. Carcinogenicity was also assessed for unleaded gasoline, via inhalation, as part of initiation/promotion studies. In these studies, unleaded gasoline did not appear to initiate tumour formation, but did show renal cell and hepatic tumour promotion ability, when rats and mice were exposed, via inhalation, for durations ranging from 13 weeks to approximately 1 year using an initiation/promotion protocol However, further examination of data relevant to the composition of unleaded gasoline demonstrated that this is a highly-regulated substance; it is expected to contain a lower percentage of benzene and has a discrete component profile when compared to other substances in the LBPNS group. Both the European Commission and the International Agency for Research on Cancer (IARC) have classified LBPNS substances as carcinogenic. All of these substances were classified by the European Commission (2008) as Category 2 (R45: may cause cancer) (benzene content = 0.1% by weight). IARC has classified gasoline, an LBPNS, as a Group 2B carcinogen (possibly carcinogenic to humans) and "occupational exposures in petroleum refining" as Group 2A carcinogens (probably carcinogenic to humans). Several studies were conducted on experimental animals to investigate the dermal carcinogenicity of LBPNS. The majority of these studies were conducted through exposure of mice to doses ranging from 694-1351 mg/kg-bw, for durations ranging from 1 year to the animals lifetime or until a tumour persisted for 2 weeks. Given the route of exposure, the studies specifically examined the formation of skin tumours. Results for carcinogenicity via dermal exposure are mixed. Both malignant and benign skin tumours were induced with heavy catalytic cracked naphtha, light catalytic cracked naphtha, light straight-run naphtha and naphtha Significant increases in squamous cell carcinomas were also observed when mice were dermally treated with Stoddard solvent, but the latter was administered as a mixture (90% test substance), and the details of the study were not available. In contrast, insignificant increases in tumour formation or no tumours were observed when light alkylate naphtha, heavy catalytic reformed naphtha, sweetened naphtha, light catalytically cracked naphtha or unleaded gasoline was dermally applied to mice. Negative results for skin tumours were also observed in male mice dermally exposed to sweetened naphtha using an initiation/promotion protocol. Reproductive/ Developmental toxicity: No reproductive or developmental toxicity was observed for the majority of LBPNS substances evaluated. Most of these studies were carried out by inhalation exposure in rodents. NOAEC values for reproductive toxicity following inhalation exposure ranged from 1701 mg/m³ (CAS RN 8052-41-3) to 27 687 mg/m³ (CAS RN 64741-63-5) for the LBPNS group evaluated, and from 7690 mg/m³ to 27 059 mg/m³ for the site-restricted light catalytic cracked and full-range catalytic reformed naphthas. However, a decreased number of pups per litter and higher frequency of post-implantation loss were observed following inhalation exposure of female rats to hydrotreated heavy naphtha (CAS RN 64742-48-9) at a concentration of 4679 mg/m³, 6 hours per day, from gestational days 7-20. For dermal exposures, NOAEL values of 714 mg/kg-bw (CAS RN 8030-30-6) and 1000 mg/kg-bw per day (CAS RN 68513-02-0) were noted . For oral exposures, no adverse effects on reproductive parameters were reported when rats were given site-restricted light catalytic cracked naphtha at 2000 mg/kg on gestational day 13 . For most LBPNS, no treatment-related developmental effects were observed by the different routes of exposure However, developmental toxicity was observed for a few naphthas. Decreased foetal body weight and an increased incidence of ossification variations were observed when rat dams were exposed to light aromatized solvent naphtha, by gavage, at 1250 mg/kg-bw per day. In addition, pregnant rats exposed by inhalation to hydrotreated heavy naphtha at 4679 mg/m³ delivered pups with higher birth weights. Cognitive and memory impairments were also observed in the offspring. Low Boiling Point Naphthas [Site-Restricted] Studies indicate that normal, branched and cyclic paraffins are absorbed from the mammalian gastrointestinal tract and that the absorption of n-paraffins is inversely proportional to the carbon chain length, with little absorption above C30. With respect to the carbon chain lengths likely to be present in mineral oil, n-paraffins may be absorbed to a greater extent than iso- or cyclo-paraffins.

The major classes of hydrocarbons have been shown to be well absorbed by the gastrointestinal tract in various species. In many cases, the hydrophobic hydrocarbons are ingested in association with dietary lipids. The dependence of hydrocarbon absorption on concomitant triglyceride digestion and absorption, is known as the "hydrocarbon continuum hypothesis", and asserts that a series of solubilising phases in the intestinal lumen, created by dietary triglycerides and their digestion products, afford hydrocarbons a route to the lipid phase of the intestinal absorptive cell (enterocyte) membrane. While some hydrocarbons may traverse the mucosal epithelium unmetabolised and appear as solutes in lipoprotein particles in intestinal lymph, there is evidence that most hydrocarbons partially separate from nutrient lipids and undergo metabolic transformation in the enterocyte. The enterocyte may play a major role in determining the proportion of an absorbed hydrocarbon that, by escaping initial biotransformation, becomes available for deposition in its unchanged form in peripheral tissues such as adipose tissue, or in the liver.

For petroleum: This product contains benzene, which can cause acute myeloid leukaemia, and n-hexane, which can be metabolized to compounds which are toxic to the nervous system. This product contains toluene, and animal studies suggest high concentrations of toluene lead to hearing loss. This product contains ethyl benzene and naphthalene, from which animal testing shows evidence of tumour formation.

Cancer-causing potential: Animal testing shows inhaling petroleum causes tumours of the liver and kidney; these are however not considered to be relevant in humans.

Mutation-causing potential: Most studies involving gasoline have returned negative results regarding the potential to cause mutations, including all recent studies in living human subjects (such as in petrol service station attendants).

Reproductive toxicity: Animal studies show that high concentrations of toluene (>0.1%) can cause developmental effects such as lower birth weight and developmental toxicity to the nervous system of the foetus. Other studies show no adverse effects on the foetus.

Human effects: Prolonged or repeated contact may cause defatting of the skin which can lead to skin inflammation and may make the skin more susceptible to irritation and penetration by other materials.

Animal testing shows that exposure to gasoline over a lifetime can cause kidney cancer, but the relevance in humans is questionable.

Reproductive effector in rats

The substance is classified by IARC as Group 3:

NOT classifiable as to its carcinogenicity to humans.

Evidence of carcinogenicity may be inadequate or limited in animal testing.

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NOTE: Changes in kidney, liver, spleen and lungs are observed in animals exposed to high concentrations of this substance by all routes. ** ASCC (NZ) SDS

For ethylene glycol monoalkyl ethers and their acetates (EGMAEs):

Typical members of this category are ethylene glycol propylene ether (EGPE), ethylene glycol butyl ether (EGBE) and ethylene glycol hexyl ether (EGHE) and their acetates.

EGMAEs are substrates for alcohol dehydrogenase isozyme ADH-3, which catalyzes the conversion of their terminal alcohols to aldehydes (which are transient metabolites). Further, rapid conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant urinary metabolites of mono substituted glycol ethers.

Acute Toxicity: Oral LD50 values in rats for all category members range from 739 (EGHE) to 3089 mg/kg bw (EGPE), with values increasing with decreasing molecular weight. Four to six hour acute inhalation toxicity studies were conducted for these chemicals in rats at the highest vapour concentrations practically achievable. Values range from LC0 > 85 ppm (508 mg/m³) for EGHE, LC50 > 400ppm (2620 mg/m³) for EGBEA to LC50 > 2132 ppm (9061 mg/m³) for EGPE. No lethality was observed for any of these materials under these conditions. Dermal LD50 values in rabbits range from 435 mg/kg bw (EGBE) to 1500 mg/kg bw (EGBEA). Overall these category members can be considered to be of low to moderate acute toxicity. All category members cause reversible irritation to skin and eyes, with EGBEA less irritating and EGHE more irritating than the other category members. EGPE and EGBE are not sensitisers in experimental animals or humans. Signs of acute toxicity in rats, mice and rabbits are consistent with haemolysis (with the exception of EGHE) and non-specific CNS depression typical of organic solvents in general. Alkoxyacetic acid metabolites, propoxyacetic acid (PAA) and butoxyacetic acid (BAA), are responsible for the red blood cell hemolysis. Signs of toxicity in humans deliberately ingesting cleaning fluids containing 9-22% EGBE are similar to those of rats, with the exception of haemolysis. Although decreased blood haemoglobin and/or haemoglobinuria were observed in some of the human cases, it is not clear if this was due to haemolysis or haemodilution as a result of administration of large volumes of fluid. Red blood cells of humans are many-fold more resistant to toxicity from EGPE and EGBE *in vitro* than those of rats.

Repeat dose toxicity: The fact that the NOAEL for repeated dose toxicity of EGBE is less than that of EGPE is consistent with red blood cells being more sensitive to EGBE than EGPE. Blood from mice, rats, hamsters, rabbits and baboons were sensitive to the effects of BAA *in vitro* and displayed similar responses, which included erythrocyte swelling (increased haematocrit and mean corpuscular hemoglobin), followed by hemolysis. Blood from humans, pigs, dogs, cats, and guinea pigs was less sensitive to haemolysis by BAA *in vitro*.

Mutagenicity: In the absence and presence of metabolic activation, EGBE tested negative for mutagenicity in Ames tests conducted in *S. typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 and EGHE tested negative in strains TA98, TA100, TA1535, TA1537 and TA1538. *In vitro* cytogenicity and sister chromatid exchange assays with EGBE and EGHE in Chinese Hamster Ovary Cells with and without metabolic activation and *in vivo* micronucleus tests with EGBE in rats and mice were negative, indicating that these glycol ethers are not genotoxic.

Carcinogenicity: In a 2-year inhalation chronic toxicity and carcinogenicity study with EGBE in rats and mice a significant increase in the incidence of liver haemangiosarcomas was seen in male mice and forestomach tumours in female mice. It was decided that based on the mode of action data available, there was no significant hazard for human carcinogenicity

Reproductive and developmental toxicity. The results of reproductive and developmental toxicity studies indicate that the glycol ethers in this category are not selectively toxic to the reproductive system or developing fetus, developmental toxicity is secondary to maternal toxicity. The repeated dose toxicity studies in which reproductive organs were examined indicate that the members of this category are not associated with toxicity to reproductive organs (including the testes).

Results of the developmental toxicity studies conducted via inhalation exposures during gestation periods on EGPE (rabbits -125, 250, 500 ppm or 531, 1062, or 2125 mg/m³ and rats - 100, 200, 300, 400 ppm or 425, 850, 1275, or 1700 mg/m³), EGBE (rat and rabbit - 25, 50, 100, 200 ppm or 121, 241, 483, or 966 mg/m³), and EGHE (rat and rabbit - 20.8, 41.4, 79.2 ppm or 124, 248, or 474 mg/m³) indicate that the members of the category are not teratogenic.

The NOAELs for developmental toxicity are greater than 500 ppm or 2125 mg/m³ (rabbit-EGPE), 100 ppm or 425 mg/m³ (rat-EGPE), 50 ppm or 241 mg/m³ (rat EGBE) and 100 ppm or 483 mg/m³ (rabbit EGBE) and greater than 79.2 ppm or 474 mg/m³ (rat and rabbit-EGHE).

Exposure of pregnant rats to ethylene glycol monobutyl ether (2-butoxyethanol) at 100 ppm or rabbits at 200 ppm during organogenesis resulted in maternal toxicity and embryotoxicity including a decreased number of viable implantations per litter. Slight foetotoxicity in the form of poorly ossified or unossified skeletal elements was also apparent in rats. Teratogenic effects were not observed in other species.

At least one researcher has stated that the reproductive effects were less than that of other monoalkyl ethers of ethylene glycol.

Chronic exposure may cause anaemia, macrocytosis, abnormally large red cells and abnormal red cell fragility.

Exposure of male and female rats and mice for 14 weeks to 2 years produced a regenerative haemolytic anaemia and subsequent effects on the haemopoietic system in rats and mice. In addition, 2-butoxyethanol exposures caused increases in the incidence of neoplasms and nonneoplastic lesions (1). The occurrence of the anaemia was concentration-dependent and more pronounced in rats and females. In this study it was proposed that 2-butoxyethanol at concentrations of 500 ppm and greater produced an acute disseminated thrombosis and bone infarction in male and female rats as a result of severe acute haemolysis and reduced deformability of erythrocytes or through anoxic damage to endothelial cells that compromise blood flow. In two-year studies, 2-butoxyethanol continued to affect circulating erythroid mass, inducing a responsive anaemia. Rats showed a marginal increase in the incidence of benign or malignant pheochromocytomas (combined) of the adrenal gland. In mice, 2-butoxyethanol exposure resulted in a concentration dependent increase in the incidence of squamous cell papilloma or carcinoma of the forestomach. It was hypothesised that exposure-induced irritation produced inflammatory and hyperplastic effects in the forestomach and that the neoplasia were associated with a continuation of the injury/ degeneration process. Exposure also produced a concentration - dependent increase in the incidence of haemangiosarcoma of the liver of male mice and hepatocellular carcinoma.

1: NTP Toxicology Program Technical report Series 484, March 2000.

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For acetone:

The acute toxicity of acetone is low. Acetone is not a skin irritant or sensitiser but is a defatting agent to the skin. Acetone is an eye irritant. The subchronic toxicity of acetone has been examined in mice and rats that were administered acetone in the drinking water and again in rats treated by oral gavage. Acetone-induced increases in relative kidney weight changes were observed in male and female rats used in the oral 13-week study. Acetone treatment caused increases in the relative liver weight in male and female rats that were not associated with histopathologic effects and the effects may have been associated with microsomal enzyme induction. Haematologic effects consistent with macrocytic anaemia were also noted in male rats along with hyperpigmentation in the spleen. The most notable findings in the mice were increased liver and decreased spleen weights. Overall, the no-observed-effect-levels in the drinking water study were 1% for male rats (900 mg/kg/d) and male mice (2258 mg/kg/d), 2% for female mice (5945 mg/kg/d), and 5% for female rats (3100 mg/kg/d). For developmental effects, a statistically significant reduction in foetal weight, and a slight, but statistically significant increase in the percent incidence of later resorptions were seen in mice at 15,665 mg/m³ and in rats at 26,100 mg/m³. The no-observable-effect level for developmental toxicity was determined to be 5220 mg/m³ for both rats and mice.

Teratogenic effects were not observed in rats and mice tested at 26,110 and 15,665 mg/m³, respectively. Lifetime dermal carcinogenicity studies in mice treated with up to 0.2 mL of acetone did not reveal any increase in organ tumor incidence relative to untreated control animals.

The scientific literature contains many different studies that have measured either the neurobehavioural performance or neurophysiological response of humans exposed to acetone. Effect levels ranging from about 600 to greater than 2375 mg/m³ have been reported. Neurobehavioral studies with acetone-exposed employees have recently shown that 8-hr exposures in excess of 2375 mg/m³ were not associated with any dose-related changes in response time, vigilance, or digit span scores. Clinical case studies, controlled human volunteer studies, animal research, and occupational field evaluations all indicate that the NOAEL for this effect is 2375 mg/m³ or greater.

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Liver changes, uterine tract, effects on fertility, foetotoxicity, specific developmental abnormalities (musculoskeletal system) recorded.

Ethylbenzene is readily absorbed following inhalation, oral, and dermal exposures, distributed throughout the body, and excreted primarily through urine. There are two different metabolic pathways for ethylbenzene with the primary pathway being the alpha-oxidation of ethylbenzene to 1-phenylethanol, mostly as the R-enantiomer. The pattern of urinary metabolite excretion varies with different mammalian species. In humans, ethylbenzene is excreted in the urine as mandelic acid and phenylglyoxylic acids; whereas rats and rabbits excrete hippuric acid and phenaceturic acid as the main metabolites. Ethylbenzene can induce liver enzymes and hence its own metabolism as well as the metabolism of other substances.

Ethylbenzene has a low order of acute toxicity by the oral, dermal or inhalation routes of exposure. Studies in rabbits indicate that ethylbenzene is irritating to the skin and eyes. There are numerous repeat dose studies available in a variety of species, these include: rats, mice, rabbits, guinea pig and rhesus monkeys. Hearing loss has been reported in rats (but not guinea pigs) exposed to relatively high exposures (*400 ppm and greater*) of ethylbenzene

In chronic toxicity/carcinogenicity studies, both rats and mice were exposed via inhalation to 0, 75, 250 or 750 ppm for 104 weeks. In rats, the kidney was the target organ of toxicity, with renal tubular hyperplasia noted in both males and females at the 750 ppm level only. In mice, the liver and lung were the principal target organs of toxicity. In male mice at 750 ppm, lung toxicity was described as alveolar epithelial metaplasia, and liver toxicity was described as hepatocellular syncytial alteration, hypertrophy and mild necrosis; this was accompanied by increased follicular cell hyperplasia in the thyroid. As a result the NOAEL in male mice was determined to be 250 ppm. In female mice, the 750 ppm dose group had an increased incidence of eosinophilic foci in the liver (44% vs 10% in the controls) and an increased incidence in follicular cell hyperplasia in the thyroid gland.

In studies conducted by the U.S. National Toxicology Program, inhalation of ethylbenzene at 750 ppm resulted in increased lung tumors in male mice, liver tumors in female mice, and increased kidney tumors in male and female rats. No increase in tumors was reported at 75 or 250 ppm. Ethylbenzene is considered to be an animal carcinogen, however, the relevance of these findings to humans is currently unknown. Although no reproductive toxicity studies have been conducted on ethylbenzene, repeated-dose studies indicate that the reproductive organs are not a target for ethylbenzene toxicity

Ethylbenzene was negative in bacterial gene mutation tests and in a yeast assay on mitotic recombination.

NOTE: Substance has been shown to be mutagenic in at least one assay, or belongs to a family of chemicals producing damage or change to cellular DNA.

WARNING: This substance has been classified by the IARC as Group 2B: Possibly Carcinogenic to Humans.

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No significant acute toxicological data identified in literature search.

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The material may cause skin irritation after prolonged or repeated exposure and may produce a contact dermatitis (nonallergic). This form of dermatitis is often characterised by skin redness (erythema) and swelling the epidermis. Histologically there may be intercellular oedema of the spongy layer (spongiosis) and intracellular oedema of the epidermis.

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The material may produce severe irritation to the eye causing pronounced inflammation. Repeated or prolonged exposure to irritants may produce conjunctivitis.

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The material may cause skin irritation after prolonged or repeated exposure and may produce a contact dermatitis (nonallergic). This form of dermatitis is often characterised by skin redness (erythema) and swelling epidermis. Histologically there may be intercellular oedema of the spongy layer (spongiosis) and intracellular oedema of the epidermis.