6PPD-QUINONE
TOXICOLOGICAL REPORT

MOST IMPORTANT SYMPTOMS AND EFFECTS, BOTH ACUTE AND DELAYED

INHALED

The material is not thought to produce either adverse health effects or irritation of the respiratory tract following inhalation (as classified by EC Directives using animal models). Nevertheless, adverse systemic effects have been produced following exposure of animals by at least one other route and good hygiene practice requires that exposure be kept to a minimum and that suitable control measures be used in an occupational setting.
Persons with impaired respiratory function, airway diseases and conditions such as emphysema or chronic bronchitis, may incur further disability if excessive concentrations of particulate are inhaled.
If prior damage to the circulatory or nervous systems has occurred or if kidney damage has been sustained, proper screenings should be conducted on individuals who may be exposed to further risk if handling and use of the material result in excessive exposures.

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.

SKIN CONTACT

Skin contact is not thought to produce harmful health effects (as classified under EC Directives using animal models). Systemic harm, however, has been identified following exposure of animals by at least one other route and the material may still produce health damage following entry through wounds, lesions or abrasions. Good hygiene practice requires that exposure be kept to a minimum and that suitable gloves be used in an occupational setting.
Many phenylenediamine derivatives are suspected of producing occupational dermatoses with clinical course of the condition closely related to exposure; the dermatoses generally disappear when exposure ceases and reappears if exposure reoccurs.
Oxidation of the phenylenediamines reduces dermal absorption. All three isomers are absorbed following ingestion. m- and p-phenylenediamine are metabolised rapidly and excreted predominantly in acetylated form in the urine. There is no selective accumulation of p-phenylenediamine in target organs; corresponding studies have not been carried out with o- or m-phenylenediamine. In contrast to m-phenylenediamine, for which binding to DNA in the kidney and liver has been described, p-phenylenediamine was found to bind to protein in the liver but not to DNA. Oedema, possibly caused by increased vascular permeability, is the dominant symptom of intoxication with p-phenylenediamine, while oedema occurs rarely, if ever, following intoxication with o- or m-phenylenediamine.
o-, m- and p-Phenylenediamine cause gene mutation in bacteria following metabolic activation. Additionally, o-phenylenediamine has been observed to damage bacterial DNA in the repair test. All three isomers had predominantly no effect on gene mutation in fungi, even with metabolic activation, while positive results were recorded with o-, m- and p-phenylenediamine in mammalian cells. Studies of the damaging effect of o-phenylenediamine on DNA and chromosomes in mammalian cells produced predominantly positive results, even without metabolic activation. The damaging effects of m- and p-phenylenediamine on DNA and chromosomes, however, vary according to the test system, and both positive and negative findings have been obtained. The three phenylenediamine isomers have been observed to form strongly mutagenic oxidation products which influence test results.
There are a few studies on the carcinogenic effect of m- and p-phenylenediamine using various methods of administration in which only subcutaneous injection produced localised tumours. o-Phenylenediamine, on the other hand, produced liver tumours in the rat and mouse only after oral administration. No short-term carcinogenicity studies have been carried out with o-phenylenediamine. m- and p-phenylenediamine led to cell transformations ***in vitro***; ***in vivo*** studies of tumour promotion in the liver were negative.
o-, m- and p-Phenylenediamine do not impair fertility in spite of the fact that o-phenylenediamine was observed to have embryotoxic and sperm-damaging effects in unvalidated studies. p-Phenylenediamine is not teratogenic. Embryotoxic and slight teratogenic effects were observed with m-phenylenediamine at clearly maternotoxic doses, possibly as a result of a deficiency of nutrient supply to the fetus. No studies have been carried out on the teratogenic effect of o-phenylenediamine.
o-, m- and p-phenylenediamine all form methaemoglobin. The highest level of methaemoglobin formation was observed with m-phenylenediamine.
There are only isolated reports of human sensitization by o- and m-phenylenediamine.
p-Phenylenediamine, on the other hand, is a very common allergen in man because of allergy to the para-group. Cases of photosensitisation induced by p-phenylenediamine have also been recorded.
Current higher molecular weight N,N'-dialkyl or N-alkyl-N'-aryl derivatives are not primary skin irritants. A notable exception is N-(1-methylethyl)-N'-phenyl-p-PDA, which causes dermatitis. However, since some individuals are more sensitive than others, antiozonants should always be handled with care.
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

Although the material is not thought to be an irritant (as classified by EC Directives), direct contact with the eye may cause transient discomfort characterised by tearing or conjunctival redness (as with windburn). Slight abrasive damage may also result. The material may produce foreign body irritation in certain individuals.

CHRONIC

Practical experience shows that skin contact with the material is capable either of inducing a sensitisation reaction in a substantial number of individuals, and/or of producing a positive response in experimental animals.
Substances that can cause occupational asthma (also known as asthmagens and respiratory sensitisers) can induce a state of specific airway hyper-responsiveness via an immunological, irritant or other mechanism. Once the airways have become hyper-responsive, further exposure to the substance, sometimes even to tiny quantities, may cause respiratory symptoms. These symptoms can range in severity from a runny nose to asthma. Not all workers who are exposed to a sensitiser will become hyper-responsive and it is impossible to identify in advance who are likely to become hyper-responsive.
Substances than can cuase occupational asthma should be distinguished from substances which may trigger the symptoms of asthma in people with pre-existing air-way hyper-responsiveness. The latter substances are not classified as asthmagens or respiratory sensitisers
Wherever it is reasonably practicable, exposure to substances that can cuase occupational asthma should be prevented. Where this is not possible the primary aim is to apply adequate standards of control to prevent workers from becoming hyper-responsive.

Activities giving rise to short-term peak concentrations should receive particular attention when risk management is being considered. Health surveillance is appropriate for all employees exposed or liable to be exposed to a substance which may cause occupational asthma and there should be appropriate consultation with an occupational health professional over the degree of risk and level of surveillance.
There is sufficient evidence to establish a causal relationship between human exposure to the material and impaired fertility
There is sufficient evidence to establish a causal relationship between human exposure to the material and subsequent developmental toxic effects in the off-spring.

There is sufficient evidence to provide a strong presumption that human exposure to the material may result in impaired fertility on the basis of: - clear evidence in animal studies 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 is not a secondary non-specific consequence of other toxic effects.
There is sufficient evidence to provide a strong presumption that human exposure to the material may result in developmental toxicity, generally on the basis of: - clear results in appropriate animal studies where effects have been observed in the absence of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not secondary non-specific consequences of the 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.

Long term exposure to high dust concentrations may cause changes in lung function (i.e. pneumoconiosis) caused by particles less than 0.5 micron penetrating and remaining in the lung. A prime symptom is breathlessness. Lung shadows show on X-ray.
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INDICATION OF ANY IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT NEEDED

As in all cases of suspected poisoning, follow the ABCDEs of emergency medicine (airway, breathing, circulation, disability, exposure), then the ABCDEs of toxicology (antidotes, basics, change absorption, change distribution, change elimination).
For poisons (where specific treatment regime is absent):

BASIC TREATMENT

- Establish a patent airway with suction where necessary.
- Watch for signs of respiratory insufficiency and assist ventilation as necessary.
- Administer oxygen by non-rebreather mask at 10 to 15 L/min.
- Monitor and treat, where necessary, for pulmonary oedema.
- Monitor and treat, where necessary, for shock.
- Anticipate seizures.
- **DO NOT** use emetics. Where ingestion is suspected rinse mouth and give up to 200 ml water (5 ml/kg recommended) for dilution where patient is able to swallow, has a strong gag reflex and does not drool.

ADVANCED TREATMENT

- Consider orotracheal or nasotracheal intubation for airway control in unconscious patient or where respiratory arrest has occurred.
- Positive-pressure ventilation using a bag-valve mask might be of use.
- Monitor and treat, where necessary, for arrhythmias.
- Start an IV D5W TKO. If signs of hypovolaemia are present use lactated Ringers solution. Fluid overload might create complications.
- Drug therapy should be considered for pulmonary oedema.
- Hypotension with signs of hypovolaemia requires the cautious administration of fluids. Fluid overload might create complications.
- Treat seizures with diazepam.
- Proparacaine hydrochloride should be used to assist eye irrigation.

BRONSTEIN, A.C. and CURRANCE, P.L.
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INFORMATION ON TOXICOLOGICAL EFFECTS

TOXICITY	IRRITATION
6PPD-QUINONE	
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The following information refers to contact allergens as a group and may not be specific to this product.
Contact allergies quickly manifest themselves as contact eczema, more rarely as urticaria or Quincke's oedema. The pathogenesis of contact eczema involves a cell-mediated (T lymphocytes) immune reaction of the delayed type. Other allergic skin reactions, e.g. contact urticaria, involve antibody-mediated immune reactions. The significance of the contact allergen is not simply determined by its sensitisation potential: the distribution of the substance and the opportunities for contact with it are equally important. A weakly sensitising substance which is widely distributed can be a more important allergen than one with stronger sensitising potential with which few individuals come into contact. From a clinical point of view, substances are noteworthy if they produce an allergic test reaction in more than 1% of the persons tested.
p-Phenylenediamines are oxidised by the liver microsomal enzymes (S9). Pure p-phenylenediamine is non-mutagenic in but becomes mutagenic after it is oxidized. Azo dyes containing phenylenediamine are mutagenic in certain assay most likely due to the formation of oxidized p-phenylenediamine. Modification of the moieties that can be metabolized to p-phenylenediamine by sulfonation, carboxylation or copper complexation eliminated the mutagenic responses.