Phenothiazine

(CAS No: 92-84-2)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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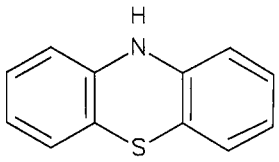
1 Introduction

The present document contains the assessment of the health hazard of phenothiazine by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by KJ van den Berg, Ph.D. and H. Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, The Netherlands).

The evaluation of the toxicity of phenothiazine has been based on the review by the American Conference of Governmental and Industrial Hygienists (ACG96). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in October 1997, literature was searched in the on-line databases Medline, Toxline, and CA, covering the period 1965-1967 to October 1997, and using the following key words: phenothiazine, thiodiphenylamine, and 92-84-2. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO98, NLM01). The final literature search was carried out in Toxline and Medline in December 2002.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identity

name	:	phenothiazine
synonyms	:	thiodiphenylamine; dibenzothiazine
molecular formula	:	$C_{12}H_9NS$
structural formula	:	
CAS number	:	92-84-2

3 Physical and chemical properties

molecular weight	:	199.28
boiling point	:	371°C
melting point	:	185.1°C (sublimes at 130°C and 0.133 kPa)
flash point	:	not available
vapour pressure	:	at 25°C: 1.2 x 10^{-4} Pa
solubility in water	:	insoluble (at 25°C: 0.2 mg/100 mL)
log $P_{octanol/water}$	:	4.15 (experimenatl); 3.82 (estimated)
conversion factors	:	not applicable

Data from ACG96, NLM01, http://esc.syrres.com.

Phenothiazine is a greyish-green to greenish-yellow powder, granules, flakes, or solid. It has a slight odour (NLM01).

4 Uses

Phenothiazine is used in the manufacture of dyes, in the synthesis of antipsychotic drugs, as a polymerisation inhibitor, and as an antioxidant with chemicals. It is used as a pesticide for the control of insects and is employed in veterinary medicine as an anthelmintic (Ric94, NLM01).

In the Netherlands, phenothiazine is not permitted for use as a pesticide and in veterinary medicines.

5 Biotransformation and kinetics

Phenothiazine is reported to be readily absorbed from the alimentary tract, with the free drug and reddish oxidation products appearing in the urine (ACG96)

Phenothiazine undergoes metabolic transformation by oxidation and conjugation (see Figure 1, Annex I). Oxidation takes place on the ring atoms opposing the heterocyclic nitrogen centre to form leucophenothiazine (3-hydroxy-phenothiazine) and leucothionol (3,7-dihydroxyphenothiazine). The hydroxyl groups may be further oxidised to yield phenothiazone (pheniothiaz-3-one) and thionol (7-hydroxyphenothiaz-3-one). Oxidation at the nitrogen atom does not apparently take place under *in vivo* conditions. The sulphur atom can be oxidised into phenothiazine sulphoxide (phenothiazine-5-oxide). In various

experimental animals, administration of the sulphoxide leads to the urinary excretion of phenothiazine and phenothiazone, indicating both reduction and oxygen migration around the ring (via phenazothionium and 3-carbonium ions) (Mit94). The oxidation reactions may involve cytochrome P448 (CYPIA), since the molecular conformation of phenothiazine is consistent with the specificity for interaction with cytochrome P448 (CYPIA) (Par88).

The conjugation reactions include direct conjugation of phenothiazine with glucuronic acid at the *N*-position, glucuronidation of thionol to the thionol glucuronide, and condensation of leucophenothiazone with sulphuric acid to leucophenothiazine sulphate. In addition, 2 unusual conjugates have been found: a phenothiazine-fat complex with the intestinal fluid and a series of polypeptide conjugates via the carboxy-terminal to the N atom of phenothiazine or leucophenothiazine (Mit94).

Phenothiazine and its metabolites are excreted via the urine and faeces, but the rate of excretion is found to be relatively low. In humans, 25% of the dose was excreted in urine after 1 day following an oral dose of 6 mg/kg bw (Mit94). A comparative study on urinary metabolites in rats, mice, hamsters, and gerbils indicated that the majority of the compound was excreted in conjugated form. In rats, mice, and gerbils, the major metabolite was leucophenothiazone sulphate, while in hamsters, this was phenothiazine-*N*-glucuronide. In all these species examined, the rate of urinary excretion in 24 hours was rather low, ranging from 18.2% of the administered dose for rats, via 29.9% for gerbils to 44% for hamsters and the mice (Mit80). In guinea pigs, about 7% of an administered oral dose was excreted as free phenothiazine within 24 hours in faeces and 3.7% in urine. Most of the dose (30%) was excreted in urine in the form of conjugates. In total, 86% of the dose (57% in urine and 29% in faeces) was excreted after 7 days, indicating a comparatively long retention time in body tissues (Mit79).

In 1- to 21-day-old neonatal guinea pigs, the excretion of metabolites in urine was comparable or even higher than in adult animals, depending on when phenothiazine was administered during the neonatal period (Mit81).

6 Effects and mechanism of action

Human data

(Photo)sensitisation

Patch testing in 43 animal-fodder plant workers revealed 11 cases sensitised to phenothiazine. The substance had not been used for the preceding 2 years (Cos90, Ric94).

In medical professions, occupational dermatosis in the form of contact dermatitis after exposure to phenothiazine has been reported (Rus94). It is, however, not clear whether this concerns some members of the pharmacological group of phenothiazines or the compound in question.

The phenomenon of photosensitisation has been frequently described in humans. The reaction consists mainly of an itchy rash and inflammatory dermatitis, resembling sunburn, developing after direct exposure of the skin to sunlight for several hours (Mit94). Workers exposed to phenothiazine during pesticide application, complained of intense pruritis with irritation and reddening of the skin. These symptoms were attributed to direct percutaneous absorption through the skin, with some possible contribution by ingestion or pulmonary absorption after inhalation of the spray. Based on 2 individuals each becoming photosensitive to ultraviolet light when given 3 doses of 0.25 g, the sensitising dose was suggested to be less than 0.75 g (ACG96).

In an unpublished communication of the Pennsylvania Department of Health to the ACGIH TLV Committee (dated 1968), it was reported that workers exposed to 15 to 48 mg/m^3 of phenothiazine dust developed coloured hair and fingernails and skin irritation (ACG96).

Both topical irritation and a systemic mechanism may play a role in the development of photosensitisation. Topical application of freshly prepared phenothiazine to the forearm of volunteers did not result in irritation, whereas a dermatitic reaction occurred after the product was allowed to oxidise, suggesting that the oxidation products are the causative agents. It is generally appreciated that both the substance and direct sunlight must be present for the reaction to occur (Mit94).

Anaemia

In patients treated with phenothiazine, an overall incidence of 13-18% was reported with respect to the development of haemolytic anaemia as a side effect. A few cases of severe haemolytic anaemia are known, and a fatal case led to the withdrawal of the compound for human use (Mit94).

Incubation of phenothiazine, phenothiazone, and thionol with human erythrocytes *in vitro* has been found to lead to rapid formation of methaemoglobin, without appreciable haemolysis (Mit94).

Other acute reactions

Large oral doses of phenothiazine may cause hepatotoxicity, renal damage, abdominal cramps, and tachycardia (ACG96).

Animal data

Irritation

Instillation of 100 mg of phenothiazine (purity: 99.8% and 95%) into the eyes of (female) New Zealand white rabbits (n=6/group) ('unwashed' procedure) did not cause any sign of irritation in any of the animals at any of the evaluation intervals (24, 48, and 72 hours) (Har77a, Har77b).

In a skin irritation test with rabbits, no acute irritating effect was observed. However, after prolonged and repeated exposures, a mild irritation was reported (Row44). Application of 500 mg of phenothiazine (purity: 99.8% and 95%) to the clipped intact or abraded skin of rabbits (New Zealand white California cross; sex unknown; n=6/group) did not cause any sign of irritation in any of the animals at any of the evaluation intervals (24, 72 hours) (Har77c, Har77d). In an acute dermal toxicity study performed in the same laboratory (see below under 'Acute toxicity') application of amounts up to 9400 mg/kg bw did not induce any sign of irritation either (Har77e, Har77f). Slight to moderate erythema, slight redness, and some necrosis were observed when amounts of 250-1000 mg/kg bw (solid moistened with water) were applied to the clipped skin of guinea pigs (n=3/group) (duration not reported). At 1 week, there were desquamation, some scattered eschars, and a couple of small areas of soar tissue while at 2 weeks, slight desquamation, none to medium area of fairly heavy soar tissue, and a small narrow strip of secondary eschar surrounded by grade 1 erythema were observed (Fas60). In the latter experiment, it was not clear which effects were seen at

which doses. For both the rabbit and the guinea pig study, it was not reported whether or not occlusive conditions were used or how long animals were exposed.

(Photo)sensitisation

Animal species, especially white animals or animals with white spots, e.g., horses, dogs, and mice, have been reported to develop rapid desquamation, severe skin pigmentation, and the loss of body hair upon irradiation following treatment with phenothiazine. However, such effects were not produced by irradiation in the absence of ingested phenothiazine. In pigmented animals, only inflammation of the cornea and associated signs such as lachrymation and oedema of the eyelids may occur (Mit94). Administration of phenothiazine, leucophenothiazone sulphate conjugate, thionol, or phenothiazine sulphoxide into calf eyes, followed by sunlight exposure, resulted in keratitis. Results of additional studies indicate that a metabolite of phenothiazine, viz., phenothiazine sulphoxide, is the reactive species in causing photosensitisation (Mit94). In a skin sensitisation test performed according to an unknown protocol and only very briefly reported, phenothiazine was concluded to be a 'sensitiser of low activity in 2/5 and moderate in 2/5 guinea pigs' (Fas60).

Acute toxicity

No effects were seen during exposure, during a 2-week observation period, and at autopsy in male albino rats (n=10/group) when they were exposed for 1 hour by spraying a concentration of phenothiazine (purity: 95 and 99.8%) stated to be 220 mg/L (i.e., 220,000 mg/m^3) into an inhalation chamber (Har77e, Har77f). The committee notices that this aerosol concentration is unrealistically high and technically not feasible.

No mortality or signs of toxicity were observed in rabbits (New Zealand white California cross; sex not reported; n=1/group) when amounts of 3900, 6000, or 9400 mg/kg bw of phenothiazine (purity: 95 and 99.8%) were applied to the intact or abraded skin for 24 hours (Har77g, Har77h).

Single oral doses of phenothiazine (purity: ca. 100%) of 200 to 3200 mg/kg bw (given as 10% suspension in 2% sodium cellulose sulphate in water) induced moderate to clear weakness (not indicated at which amounts) but no mortality in rats (n=5/group; sex, strain, and age not presented) (Fas60). No adverse effects were observed in ca. 120-day-old rats (Sprague-Dawley; n=1/sex/dose) at single oral doses of phenothiazine (purity: 99.8%; given in a dioctyl sodium

sulphosuccinate-methocal solution) of 951 to 2518 or 1600 to 10,098 mg/kg bw (observation time: 7 and 14 days, respectively) (Har77i). In a similar study, all 40- to 50-day-old rats (Sprague-Dawley; n=1/sex/dose) died within approximately 1 to 3 days at doses of phenothiazine (purity: 95%; vehiculum: winterised cottonseed oil) of 1992 to 12,623 mg/kg bw. All 2 rats survived a dose of 500 mg/kg bw while one male and one female died when given a dose of 793 and 1257 mg/kg bw, respectively. Clinical signs reported were diarrhoea, weakness, lethargy, and unconsciousness. From administration of doses of 600 to 1508 mg/kg bw (n=5/sex/group), an LD_{50} of 1330 mg/kg bw (95% CI: 1223-1534 mg/kg bw) was calculated (Har77j). In another study, all rats (strain, sex, age not reported) survived single oral doses of purified phenothiazine (purity not reported; given in a 5-10% gum arabic solution) of 600, 1000, and 2000 (n=1/dose) and 3000 (n=5) mg/kg bw. Doses of 4000 and 5000 mg/kg bw caused mortality in 4/5 and 5/5 animals, respectively (Row44). An oral LD_{50} of 5000 mg/kg bw has reported for rats (ACG96). In mice (n=5/group; sex, strain, and age not presented), single oral doses of phenothiazine (purity: ca. 100%) of 200 to 3200 mg/kg bw (given as 10% suspension in 2% sodium cellulose sulphate in water) induced slight to moderate weakness (not indicated at which amounts). At 3200 mg/kg bw, mortality was found (number not indicated (Fas60). An oral LD_{50} of 5000 mg/kg bw has been reported for mice (Ric94).

Following intravenous injection, an LD_{50} of 178 mg/kg bw has been found in mice (Ric94). Injected intraperitoneally, doses of 800 and 3200 mg/kg bw (purity: ca. 100%; vehiculum: 2% sodium cellulose sulphate in water) were lethal to mice and rats, respectively (Fas60).

Repeated-dose toxicity

Dogs (beagle; n=4/sex/group) were fed diets containing doses of ‘pharmaceutical grade’ phenothiazine (purity: not reported) of 0, 50, 200, 500, and 2000 ppm (i.e., 0, 1.5, 6.1, 16.9, and 69.3 and 0, 1.6, 6.8, 17.7, 67.1 mg/kg bw/day in males and females, respectively), for 13 weeks. During the study, observations (daily), body weight and food consumption recordings (weekly), and haematology, biochemistry, and urine analysis studies (initially and at week 4 and 13) were done regularly. After sacrifice, organ weights (thyroid, heart, liver, spleen, kidneys, adrenals, testes) of each animal were determined. Almost all tissues of the control and high-dose animals, spleen, bone marrow, and rib conjunction of the animals of the 500-ppm group, and the liver and kidneys of the animals of the other groups were histologically examined. No effects on survival, appearance, appetite and food consumption, body weight, and urinalysis parameters were

found in any of the treated groups, when compared with controls. Spleen/body weight ratios in female dogs of the highest dose group were significantly* increased. Effects on haematology and blood chemistry parameters observed included significant* decreases in haematocrit, haemoglobin, and total erythrocyte count values in the males of the highest dose group at week 4 and 13 and decreased fasting glucose values at week 4 in males and females of the highest dose group when compared with those of controls. Upon gross and microscopic examination, all animals of the 2000-ppm group showed dark coloured spleens, marked splenic congestion with areas of increased extramedullary haematopoiesis, haemosiderin deposition in spleen, liver, kidney, and bone marrow, and an increased cellularity of the bone marrow with a marked increase in erythroid elements. In the 500-ppm group, there were haemosiderin deposition (to a lesser degree when compared with the 2000-ppm group) in liver and kidney of 3/4 male and 1/4 female dogs and slightly increased extramedullary haematopoiesis and haemosiderin pigment deposition in the spleen with a slight increase in erythroid elements in the bone marrow in 1/4 males (Haz74a). Similar effects were found in dogs (n=4/sex) fed daily doses of 2000 ppm of technical-grade phenothiazine, for 13 weeks, although generally more pronounced or at a higher incidence (Haz74b). Based on the histological effects found in the animals of the 500-ppm group - haemosiderin deposition in liver and kidney (in 3/4 males and 1/4 females), haematopoiesis and haemosiderin pigment deposition in the spleen with a slight increase in erythroid elements in the bone marrow (in 1/4 males) -, the committee concludes 200 ppm (i.e., 6.5 mg/kg bw) to be the NOAEL in this 13-week oral (feed) dog study.

An unpublished study in which rats and rabbits were given 4 to 20 oral doses of 100 to 5000 mg/kg bw (Row44) was available to the committee. Nineteen doses of phenothiazine (purity not reported) of 100 mg/kg bw did not induce adverse effects in rats or rabbits (strain, sex, and age of both species not reported). Higher doses caused liver and spleen damage, bone marrow hyperplasia, and mortality (at 1000 mg/kg bw and higher). Although the results of this study support those of the dog study, the committee considers the design of the study especially concerning the number of animals exposed (rabbits: 1-3/group; rats: 1 or 2/group) too limited for a detailed presentation and discussion, and subsequent conclusions.

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* Statistical analysis was performed by the committee and consisted of analysis of variance followed by unplanned comparisons using the T-method.

Anaemia

The occurrence of anaemia, varying between slight and transient to fatal, has been reported in many species, including mice, rats, rabbits, dogs, pigs, cattle, and horses. In contrast, no significant blood changes have been reported in guinea pigs or golden hamsters (Mit94).

The clinical picture of anaemia is accompanied by decreased haemoglobin content, decreased red blood cell count, and an increase in the percentage of circulating reticulocytes and anisocytes, and poikilocytosis (Mit94).

In vitro studies have failed to reveal any haemolytic action of phenothiazine and its metabolites, indicating that the anaemia is not due to a direct action of the compound and its metabolites on erythrocytes. Other *in vitro* studies have suggested that phenothiazine may facilitate haemolysis by other lytic agents. Also on the white blood cells, effects have been observed in the form of neutrophilia, low polymorphonuclear cell counts, and general disposition to agranulocytosis (Mit94).

In vitro in cerebral arteries from dogs, phenothiazine (10^{-7} to $3x10^{-4}$ M) caused a dose-dependent inhibition of the contraction induced by 5-hydroxytryptamine (Doi92).

Neuromuscular effects

In animal species, e.g., pigs, horses, and cattle, undergoing phenothiazine treatment, neuromuscular problems have been encountered in the form of loss of equipoise and power of coordination in movement with difficulty in walking, staggering gait, muscle weakness, and general paralysis of the hind quarters. In cattle, these effects occurred with a dose of 250 g while a dose of 50 g showed no effects. A direct effect on peripheral nerves cannot be excluded since phenothiazine has been shown to depress neuromuscular threshold potential in the crab (*Carcinus maenus*) at a concentration of about 0.5 µM (Mit94).

Mutagenicity and genotoxicity

Phenothiazine at concentrations up to 10 mg/plate did not induce gene mutations in *S. typhimurium* strains T1535, TA1537, TA98, and TA100, tested with and without adding a metabolic activation system obtained from induced rat and hamster livers, using a pre-incubation method (Mor86). Using the plate incorporation method (concentration range: 5-500 µg/plate) and the liquid suspension method (concentration range: 1-20 µg/mL), negative results were

obtained as well in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, both in the absence and presence of a rat liver S9 mix (Lov80a, Lov80b). In a photogenotoxicity test system with the excision-repair-deficient *S. typhimurium* strain 2637, phenothiazine was negative when tested using a pre-incubation method in which bacteria were exposed to concentrations 10-200 µg/mL for 30 minutes in the absence of metabolic activation in the dark or followed by a 5-minute near UV-radiation (320-400 nm) (Jos79).

Phenothiazine was found positive when tested in the L5178Y $TK^{+/-}$ mouse lymphoma mutagenesis assay in the absence of a induced rat liver S9 mix, producing mutant frequencies ranging from 2.2 to 3.2 times the mean frequency of the solvent controls in 4/7 cultures (no significant increase was found in the other cultures). Negative results were obtained in the presence of a metabolic activation system. Cells were exposed for 4 hours to concentrations of 20-113 µg/mL in the absence or of 15-92 µg/mL in the presence of the S9 mix; higher concentrations were cytotoxic (Rog87).

Phenothiazine enhanced morphological transformation of Syrian hamster embryo cells by simian adenovirus (SA7) at concentrations of 22 µg/mL and higher (concentration range tested: 6-100 µg/mL) (reported in table) (Hei83).

Carcinogenicity

Phenothiazine was listed among compounds that did not cause a significant increase in tumours in mice after oral (gavage) exposure to the maximal tolerated oral dose for approximately 18 months. However, phenothiazine was the only compound in the table for which no data concerning daily dose and vehicle were presented (Inn69).

When an oral (diet) dose of 0.2% phenothiazine was given to female rats (Wistar; n=16) for 20 weeks (total dose: ca. 3000 mg), no bladder transitional cell carcinomas, papillomas, or hyperplasia were seen at the termination of the study at the end of 40 weeks. When similarly treated concomitantly with 0.188% *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) (total dose: ca. 2900 mg), a significantly higher incidence of transitional cell carcinoma of the bladder (27/49 vs. 8/47) and lower incidences of papillomas (3/49 vs. 6/47) and hyperplasia (17/49 vs. 28/47*)* were observed than with FANFT alone. Phenothiazine and phenothiazine-FANFT treatment were found to almost double the hepatic microsomal nitroreductase activity when compared with treatment with FANFT alone (Wan84).

Reproduction toxicity

Phenothiazine was reported to induce increased resorption rates in rats given a total dietary amount of 250 mg during pregnancy (Tel62). However, since no experimental details including statistical analysis were presented, the committee cannot evaluate these data.

In a teratogenicity study with phenothiazine (purity: not known), groups of pregnant rats (Charles River; n=18-21/ group) were exposed to oral (gavage) doses of 0, 15, 50, and 150 mg/kg bw, through days 6-15 of gestation. In control and treated dams, no mortality or unusual behavioural reactions were observed. In the high-dose animals, the body weights on gestation day 15 and the calculated body weight gains during gestation days 6-15 were significantly less than those of controls. No compound-related changes in the numbers of corpora lutea, implantation sites, resorption sites, and fetuses, fetal body weight, and fetal external, skeletal, and internal development were found in any of the treated groups when compared with controls (Mor77a). In a similar study in mice (Charles River CD-1; n=20-25 mice/ group), oral doses of 0, 30, 100, and 300 mg/kg bw, through days 6-15 of gestation, did not induce mortality or effects on body weight, body weight gain, and behaviour in any of the groups of dams. Increases in the number of resorption sites and in the number of dams with one or more resorption sites were observed but they were not dose-related and not considered to be significant effects. No developmental abnormalities were observed, based on evaluation of fetal body weight, external developmental anomalies, and skeletal and internal development (Mor77b).

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for phenothiazine in the Netherlands is 5 mg/m^3, 8-hour TWA, with a skin notation.

Existing occupational exposure limits in some European countries and the USA are summarised in Annex II.

8 Assessment of health hazard

Following an oral dose, phenothiazine is absorbed from the alimentary tract. Dermal uptake is possible, in view of the observed sensitising effects of the skin.

The metabolism of phenothiazine is well characterised and occurs mainly at the ring atoms opposing the nitrogen atom to form oxidation and conjugation

products. Excretion of phenothiazine and metabolites via urine and faeces is at a relatively low rate in humans and experimental animals.

In occupationally exposed workers, dermal effects such as sensitisation, contact dermatitis, skin irritation, coloured hair and fingernails, and photosensitisation have been described. Various dermatological effects have been observed at an exposure level of 15-48 mg/m^3. Other effects of large oral doses reported in humans include haemolytic anaemia, hepatotoxicity, renal damage, abdominal cramps, and tachycardia.

Single doses of phenothiazine were not irritating to the eyes and skin of rabbits and slightly irritating to the skin of guinea pigs. Prolonged and repeated exposure was mildly irritating to the skin of rabbits. A poorly reported study indicated a sensitising potential. In white animals and animals with white spots, photosensitisation was described.

The committee did not find data from valid experimental animal studies on the effects of phenothiazine following single or repeated exposure by inhalation. From acute dermal and oral mortality data, the committee concludes that phenothiazine is of low toxicity.

In a 13-week oral (feed) study, daily dosing of ca. 17 mg/kg bw caused histological changes in liver, kidney, spleen, and bone marrow (haematopoiesis, haemosiderin deposition) of male and female dogs while no effects were seen at ca. 6.5 mg/kg bw.

Phenothiazine was not mutagenic in *S. typhimurium*. It induced mutations in mouse lymhoma cells in the absence but not in the presence of a metabolic activating system.

Phenothiazine enhanced morphological transformation of Syrian hamster embryo cells by simian adenovirus (SA7).

No carcinogenic effects were reported from a dietary study for about 18 months with mice at the maximal tolerated dose (dose not specified). In rats fed phenothiazine for 20 weeks and sacrificed 40 weeks later, it did not cause an increase in the incidence of bladder tumours but following co-administration with *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT), a significantly greater incidence of bladder carcinomas was found than with FANFT alone.

No developmental effects were observed in teratogenicity studies in rats and mice following oral administration during gestation days 6-15 of doses up to 150 and 300 mg/kg bw, respectively, the highest doses tested. No maternal toxicity was observed in mice while dosing of 150 mg/kg bw caused a decrease in body weight (gain) in maternal rats.

The committee uses the NOAEL of 6.5 mg/kg bw/day in dogs as a starting point for the assessment of a health-based recommended occupational exposure limit (HBROEL). Since workers are exposed for 5 days a week this NOAEL from a continuous feeding study (i.e., 7 days/week) is adjusted by multiplying with a factor of 7/5, resulting in a no-adverse-effect level (NAEL) of 9.1 mg/kg bw/day. For the extrapolation to a HBROEL, a factor of 1.4 for the allometric scaling from dog to man and an overall factor of 27 for inter- and intraspecies variation and the duration of exposure are applied, resulting in an NAEL for humans of 0.24 mg/kg bw/day. Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100%, and applying the preferred-value approach, a health-based occupational exposure limit of 2 mg/m^3 is recommended for phenothiazine.

The committee recommends a health-based occupational exposure limit for phenothiazine of 2 mg/m^3 as inhalable dust, as an 8-hour time-weighted average (TWA).

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Annex I

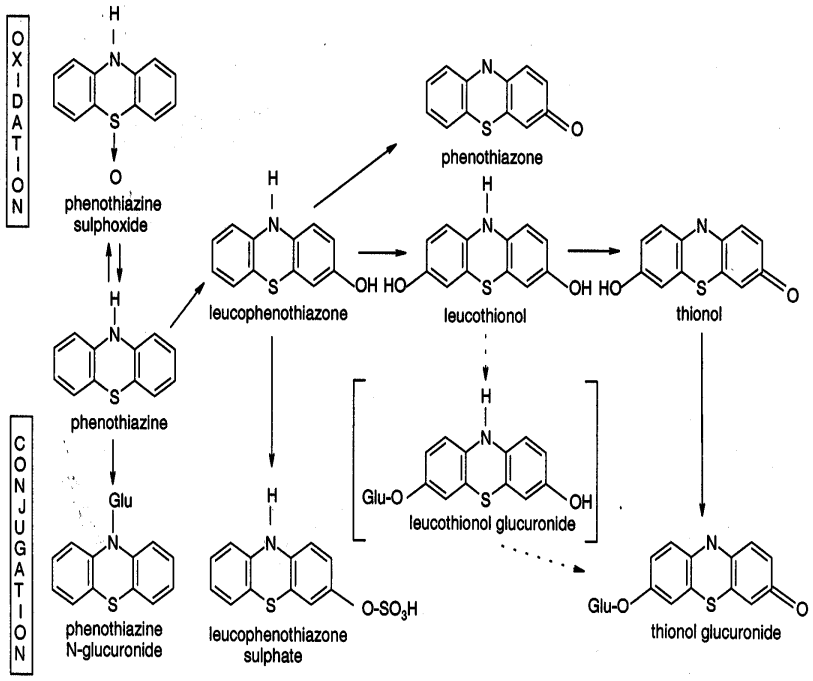

Figure 1 Metabolism scheme of phenothiazine (Mit94).

Annex II

Occupational exposure limits for phenothiazine in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	-	5	8 h	administrative	S	SZW03
Germany						
- AGS	-	-				TRG00
- DFG MAK-Kommission	-	-				DFG02
Great-Britain						
- HSE	-	-				HSE02
Sweden	-	-				Swe00
Denmark	-	5	8 h		S	Arb02
USA						
- ACGIH	-	5	8 h	TLV	S	ACG03b
- OSHA	-	-				ACG03a
- NIOSH	-	5	10 h	REL	S	ACG03a
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation; this means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.