Strychnine

(CAS No: 57-24-9)

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

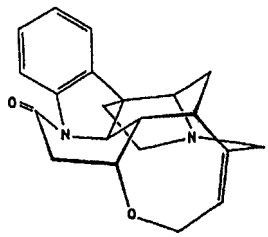
The present document contains the assessment of the health hazard of strychnine by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by C de Heer, Ph.D. and H Stouten, M.Sc. (TNO Nutrition and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

The evaluation of the toxicity of strychnine has been based on the review by the American Conference of Governmental Industrial Hygienists (ACGIH) (ACG91). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 1997, literature was searched in the on-line databases Medline, Cancerlit, and Toxline starting from 1966, 1963, and 1965, respectively, and using the following key words: strychnine and 57-42-9.

In March 2000, the President of the Health Council released a draft of the document for public review. The committee received comments by the following individuals and organisations: P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany) and L Whitford (Health and Safety Executive, London, England). These comments were taken into account when deciding on the final version of the document.

An additional search in Toxline and Medline in October 2003 did not result in information changing the committee's conclusions.

2 Identity

name	:	strychnine
synonyms	:	strychnidin-10-one, strychinos
molecular formula	:	$C_{21}H_{22}N_2O_2$
structural formula:	:	
CAS number	:	57-24-9

3 Physical and chemical properties

molecular weight	:	334.40
boiling point	:	at 101.3 kPa: decomposes (at 0.67 kPa: 270°C)
melting point	:	287°C
flash point	:	not available
vapour pressure	:	at 20°C: 0 kPa
solubility in water	:	insoluble (at 20°C: 15 mg/100 mL)
log $P_{octanol/water}$	:	1.93 (experimental); 1.85 (estimated)
conversion factors	:	not applicable

Data from ACG91, NLM03.

Strychnine is a non-combustible, colourless, odourless, bitter-tasting crystalline solid. It is an alkaloid that is isolated from the dried seeds of *Strychnos nux-vomica* and other *Strychnos* (*Loganiaceae*) species (Muh86).

The pH of a saturated strychnine solution is 9.5 (Muh86).

4 Uses

Strychnine salts (nitrate, sulphate, phosphate) have been used as rodenticides, in poisoned grain and other baits for larger wild animals, and to destroy birds. Further, its use in medicine, as an adjunct in the treatment of non-ketotic hyperglycaemia, impotence, and sleep apnoea, and in veterinary medicine has been reported (ACG91, Ray91, Yam92). Nowadays, in the USA, it is used only for laboratory, research, and restricted (i.e., only for below-ground, bait applications to control pocket gophers) pesticide purposes (EPA96, Ros00). Strychnine is reported to have been found as an adulterant in street drugs such as amphetamines, heroin, and cocaine and as trace ingredient in certain homeopathic remedies (Flo99, Woo02).

According to the database of the Dutch Pesticide Authorisation Board (CTB)*, strychnine is at present not permitted in the Netherlands for use as an active ingredient in pesticides. The 'Geneesmiddelen Repertorium', an overview of information on pharmaceutical specialties registered by the Dutch Medicines Evaluation Board, did not list strychnine-containing products**.

* At: http://www.ctb-wageningen.nl.
** At: http://www.geneesmiddelenrepertorium.org.

5 Biotransformation and kinetics

While the serum of healthy subjects does not contain strychnine in detectable amounts, significant, endogenous amounts were found in patients with epilepsy, Parkinson's disease, and manic-depressive psychosis (Kum02).

Absorption

Strychnine is rapidly absorbed from the gastrointestinal tract, mucous membranes, and parental sites of injection. Ingested strychnine is absorbed primarily from the intestine (ACG91, NLM03). Dermal absorption may occur as well as was indicated by a case of non-fatal poisoning of a woman wiping up a strychnine spill with a cloth soaked in a diluted sodium hypochlorite solution (which converted the strychnine salt into the free base that is more efficiently absorbed through the skin) (Gre01).

Distribution

Once absorbed, strychnine rapidly leaves the blood stream. There is very little protein binding. In poisonings, the blood will usually contain more than 2 mg/L, the liver more than 4 mg/kg (McB73). At autopsy following fatal poisoning of humans and dogs, the highest concentrations were found in the blood, liver, bile, kidney, and stomach, with much lower levels detected in muscle and brain (Bla84, Niy73, Ray91). In cases of fatal ingestion, strychnine was detected in blood (at levels ranging from 0.4-61 mg/L), brain (0.5-66 mg/kg), spinal cord (0.1-1.9 mg/L), kidney (0.1-106 mg/kg), liver (0.3-515 mg/kg), bile (9-11 mg/L), spleen (11.8 mg/kg), skeletal muscle (trace-2.3 mg/kg), urine (0.5-33 mg/L), and stomach content (1-3000 mg) (Cin99, Mar00, Oli79, Ros00). Generally, although strychnine acts principally on the spinal cord, it is not concentrated there. Strychnine was detected in blood, urine, and gastric contents following non-fatal ingestion (Ray91).

Analysis of strychnine levels in stomach contents and liver tissue from 44 dogs that died after manifesting typical signs of strychnine poisoning showed that these levels were not related to each other (Hat68).

Metabolism

Strychnine metabolism occurs largely by the hepatic microsomal enzyme system, where up to 80% of the dose is oxidised. Biotransformation rates in liver microsomal preparations of rats were 64-144 µg/g liver/hour, whereas in guinea pig liver slices, rates of 387-649 µg/g liver/hour have been reported (Ray91). In rats given strychnine in the drinking water at doses of 0.15 mg/mL for 5 days, profound induction of cytochrome P450 isoenzymes CYP2B1 and CYP2B2 was found. The maximal increase was attained after 3 days of administration. In addition, strychnine induced some glutathione *S*-transferase and UDP-glucuronosyltransferase activities (Fuj94).

Urinary metabolites identified *in vivo* in rats after subcutaneous injection of doses of strychnine of 0.5 mg/kg bw were strychnine *N*-oxide (M-1), 21α,22α–dihydroxy-22-hydrostrychnine (M-11), 21α,22β-dihydroxy-22-hydrostrychnine (M-12), 2-hydroxystrychnine (M-2), strychnine 21,22-epoxide (M-3), and 16-hydroxystrychnine (M-7) (see Annex I). The major metabolite of strychnine *in vivo* in rats was M-3 (Ogu89).

The *in vitro* metabolism of strychnine was studied in 9000g supernatant fractions of rat and rabbit livers. The metabolism was markedly inhibited by cytochrome P450 inhibitors, but only slightly by a microsomal FAD-containing monooxygenase inhibitor, methimazole. Five metabolites formed *in vitro* with rabbit liver were identified as 2-hydroxystrychnine (M-2), strychnine *N*-oxide (M-1), 21α,22α -dihydroxy-22-hydrostrychnine (M-11), strychnine 21,22-epoxide (M-3), and 11,12-dehydrostrychnine (M-13). Although M-2 was the major of the characterised metabolites (15%), whereas all other metabolites accounted for less than 1%, this may be of limited relevance because almost 85% of metabolites were not identified (Mis85).

Primary metabolism of strychnine was also examined *in vitro* in liver microsomes of mice, rats, guinea pigs, rabbits, and dogs. Six out of 8 metabolites were identified, i.e., strychnine *N*-oxide (M-1), 2-hydroxystrychnine (M-2), strychnine 21,22-epoxide (M-3), 22-hydroxystrychnine (M-5), 16-hydroxystrychnine (M-7), and 18-oxostrychnine (M-8) (Tan90, Tan91a). Significant differences in metabolic profiles were observed among the above species, although the indicated metabolites were detected in all species (with the exception of M-3 in rabbits). M-7 was the main metabolite in mice and rats, M-2 in guinea pigs and rabbits, and M-1 in dogs. M-3 and M-8 were minor metabolites (Tan90). This latter finding contrasts with the *in vivo* data obtained in rats, where M3 was identified as a major metabolite (Ogu89). The metabolic activity in guinea pig liver microsomes was much higher than those of other

species. Except for dogs, there seemed to be a fairly good inverse correlation between the observed metabolic activity and the acute toxicity data on strychnine reported elsewhere (Tan90).

The *N*-oxide metabolite (M-1) can readily be reduced to the parent compound and M-7 by human intestinal flora under anaerobic conditions (ElM93).

Animals treated with phenobarbital or other microsomal enzyme inducers metabolised strychnine faster than untreated animals. Phenobarbital treatment resulted in increased formation of especially M-2 and M-1 strychnine metabolites, but also of other oxidative metabolites. Similar increases, albeit to a lesser extent, were observed after 3-methylcholanthrene treatment (Tan91b).

The metabolites did not appear to contribute to the toxicity of strychnine but to detoxification (Ogu89, Tan90).

Female rats showed more pronounced responses to strychnine than males. This sex difference was due to a difference in the rate of metabolism of strychnine in the liver, as male rats oxidised strychnine about 2.5 times faster than female rats; castration abolished the observed difference in metabolism and toxicity. In mice, no clear sex differences were noted in metabolism of strychnine (Kat74).

A metabolism scheme is presented in Figure 1 (Annex I).

Excretion

The urinary and faecal excretions of radioactivity in rats subcutaneously dosed with [^{3}H]-strychnine at 0.5 mg/kg bw, were approximately 30% and 65% of the dose in 7 days, respectively. Almost 80% of the radioactivity was excreted within 24 hours. Approximately 6% and 3% were excreted unchanged in urine and faeces, respectively (Ogu89).

In humans, a variable amount (1-20%) was excreted unchanged in the urine, depending on the amount ingested (Hei92, Muh86, Sga73, Smi90, Yam92). Seventy percent of the excretion of the unchanged parent compound occurs in the first 6 hours. Trace concentrations persist in urine for up to 5 days after ingestion (ACG91, Ray91). Strychnine is very stable and may be found in cadavers exhumed many years after death (Muh86).

At 1 hour after fatal ingestion, no strychnine was detected in urine. Serial serum strychnine levels detected at 0.5, 8, 22, 35, and 43 hours decreased from 3.8 to less than 0.1 mg/L, and this was best described by a (non-linear) single compartment model with saturating (Michaelis-Menten) elimination. Assuming 100% absorption, the following parameters were calculated: absorption rate

constant (k_a=2.68/h), absorption half-life ($T_{½\,a}$=15.5 min), maximum elimination rate (V_{max}=3.71 mg/kg/h), Michaelis constant (k_m=1.46 mg/L), and volume of distribution (V_d=13 L/kg). When absorption is less complete, then V_d would be proportionally less (Hei92). Two other reports described a first-order kinetics of elimination from the blood in humans after oral ingestion of strychnine (Edm86, Pal97). In the first study, 19 serial serum samples were obtained from 4 to 53 hours post-ingestion. The elimination after oral ingestion (peak strychnine level 1.6 mg/L at 4-hour post-ingestion) was found to be consistent with first-order kinetics, with an elimination half-life of 10 h (Edm86). In the second study, 18 serial serum samples were obtained from 20 minutes to 51 hours post-ingestion. The highest serum strychnine concentration was 2.1 mg/L and occurred 3 hours after ingestion. Disappearance from the blood was best described by first-order kinetics, with an elimination half-life of 15.9 hours (Pal97).

Together, the results indicate that strychnine is readily metabolised and rapidly excreted into the urine and faeces (Ogu89).

6 Effects and mechanism of action

Human data

Strychnine produces excitation at all levels of the nervous system by selectively and competitively blocking the post-synaptic action of the inhibitory neurotransmitter glycine. This leads to increased neuronal activity such that any sensory stimuli may produce exaggerated reflex arcs, leading to muscular spasms, convulsions, or respiratory muscle paralysis (Hei92, Yam92). Early symptoms of poisoning occurring within 15-30 min include tremors, slight twitching, and stiffness of face and legs. Painful convulsions subsequently develop. All sensation is heightened. Convulsive seizures become more frequent and death eventually occurs from exhaustion or anoxia during a tetanic seizure. Few patients survive more than 5 episodes of convulsions with respiratory arrest causing death. Lactic acidosis, renal failure, hyperthermia, and rhabdomyolysis occur as secondary effects arising from the severe spasms. In addition, exposure to strychnine may lead to photophobia, muscular rigidity, stiffness in joints, hysteria, myalgia, lassitude, and headache. Finally, the occurrence of abnormal eye movements (horizontal and vertical nystagmus) has been reported (ACG91, Bla82, Edm86, Gon90, Hei92, Nis95, Osw77, Per85, Ric94, Smi90, Spa90, Tei70, Yam92).

In human beings, 15-30 mg of strychnine usually proves lethal, but deaths have been reported from as little as 5-10 mg, and survival after a dose of 3750 mg (ACG91, Niy73, Ray91, Ric94). Children may be more susceptible to strychnine than adults (ACG91, Ray91). The latter observation contrasts with animal data (Hun89). There is a wide individual variability in the manifestations of poisoning, as both people surviving doses as large as 3.75 g and people dying within 15 minutes after ingestion of 3.4 g (with no signs of the classic spasms or convulsions) have been reported (ACG91).

In accidental, suicidal, or homicidal poisonings with strychnine, toxic doses usually produce some muscular tightness and fasciculations. Movements may be abrupt and vomiting may occur. With a fatal dose, only 10-20 minutes elapse from the time of ingestion to the onset of symptoms, and death occurs in about 40 minutes (DiP81). Within 15-30 minutes after ingestion, generalised convulsions occur that may be clonic initially but quickly become tonic. Patients given doses of 5 to 7 mg reported a tightness of their muscles, especially those of the neck and jaws; individual muscles, especially those of the little fingers, may twitch (Ray91).

Pathological findings are entirely non-specific. They usually consist of petechial haemorrhages and congestion of the organs, indicating combined action of severe convulsions and anoxia (Per85, Ray91).

At autopsy, necrosis was observed throughout the brain probably as a result of hypoxic damage (Hei92). Histologically, a human autopsy liver containing 108 mg/kg strychnine showed an intense formation by lipofuscin pigment throughout the liver parenchyma together with small-droplet hyaline change. It was suggested that high levels of strychnine in the liver may result in death without evidence of physical struggle, whereas low levels result in a delayed death probably accompanied by the physical responses commonly attributed to strychnine poisoning (Oli79).

Full recovery from strychnine poisoning was observed after 7-10 days (Nis95). In contrast, after recovery from strychnine ingestion, other patients suffered from 70% loss of visual acuity together with a left hemiparesia. This is considered secondary to severe acidaemia and prolonged hypoxia (Gon90).

Animal data

Irritation of tissues and sensitisation was stated not to be associated with strychnine (Ray91), but no data were available. Oral LD_{50} values reported in rats ranged from 2.35 to 16 mg/kg bw (ACG91, Ric94). In mice and dogs, oral LD_{50} values were 2 and 0.5-1.1 mg/kg bw, respectively (Ric94, Sga73).

Intraperitoneal LD_{50} values were 0.9-2.8 mg/kg bw in rats and 1.4-1.8 mg/kg bw in mice (ACG91, Lam68). There was no difference in intraperitoneal toxicity between the sulphate, benzoate, salicylate, and *o*-nitrobenzoate expressed in terms of their alkaloid content (Ray91). Subcutaneous LD_{50} values of 1.2-4.0, 0.47, and 0.46 mg/kg bw have been reported for rats, mice, and dogs, respectively. Strychnine was more toxic to female than to male rats after oral, subcutaneous, or intraperitoneal administration, a difference that has been attributed to a higher rate of metabolism in males. Intravenous LD_{50} values were as low as 0.57-0.96 and 0.39 mg/kg bw in rats and guinea pigs, respectively (ACG91, NLM03, Ray91, Ric94, Sei82).

The circadian toxicity of strychnine (sulphate) was evaluated at 6-hour intervals in male Ha/ICR mice, previously conditioned on a 12-hour light (from 08.00 to 20.00 h) and 12-hour darkness schedule in a controlled environment. The highest acute lethality was observed in animals exposed during the light phase (at 18.00 h), whereas the lowest toxicity was observed in animals exposed during the dark phase (dose resulting in 50% acute lethality 1.57±0.12 and 1.84±0.20 mg/kg bw, respectively) (Pie77).

In vitro [^{3}H]-strychnine binding was decreased by 38 and 34% in the medulla and spinal cord, respectively, of 24-month-old rats compared to 2-month-old rats. Comparison of these age groups after intraperitoneal injection of strychnine of 1.75 mg/kg bw showed that senescent animals had a higher incidence of seizures and mortality (with faster onset times) compared to young animals (seizures 6/8 vs. 0/8, mortality 5/8 vs. 0/8). These differences may be attributed to age-related changes in glycinergic neurotransmission (Hun89). The findings contrast with data on strychnine poisoning in humans.

The ED_{50}* for convulsions is remarkably close to the LD_{50}. In male COBS-CDI mice, the intraperitoneal LD_{50} was 1.34 mg/kg, whereas the intraperitoneal ED_{50} for both clonic and tonic convulsions was 1.24 mg/kg bw (Mac77). Following single subcutaneous administration of strychnine doses of 0.75, 1.25, and 1.50 mg/kg bw to adult CBA mice, convulsions developed in 8/20, 19/20, and 21/21 animals, respectively, with an average latency time ranging from 6.1 to 10.3 minutes. Death occurred in 4/20, 17/20, and 19/21 mice, respectively. No sex difference was observed (Man87). Strychnine, intraperitoneally administered at 0.5-4 mg/kg bw, dose-dependently produced tonic seizures in male ‘albino mice’. The strychnine seizures in mice were potentiated by enhancement of noradrenergic neurotransmission (Ama94).

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* ED_{50}: dose at which a described effect is found in 50% of the exposed animals or at which the effect is changed by up to 50% compared to the control value.

The convulsing action of strychnine (0.25-4 mg/kg bw, intraperitoneal) was studied in 3- to 25-day-old rats. Generalised tonic-clonic seizures occurred in all age groups. The convulsing effects increased from day 3 to 18, and decreased again from day 25, as indicated by the incidence and latencies of seizures. Lethal effects did not occur before day 12 (Kub95).

In rabbits, strychnine produces a continuous discharge of synchronous waves at 30 c/sec at the level of the spinal cord, the cerebellum, and the midbrain; only desynchronisation can be noticed in cortical leads (Lon83). Rabbits, anaesthetised with urethane and administered doses of strychnine of 400 µg/kg bw (route not specified), developed tonic-clonic convulsions. Afterwards, one-third of the animals displayed irreversible paralysis of the hind limbs due to transverse lesions. Microscopically, only limited degenerative changes were observed at 100 days after exposure (Jäg66).

Injection of strychnine into the brain of cats caused convulsing effects in a laminar-specific manner. No effects of strychnine were noted in rats attempting to solve a stressful task in either terms of probability or rapidity. Intravenous administration to rats inhibited bethanechol-stimulated secretion in the stomach and was associated with convulsions. Inhibition did not occur in *d*-tubocurarine-paralysed animals (Ric94). In cats, the strychnine-sensitive synapses appeared to be limited only to a subset of cortical neurons driven by somatic inputs (Tre88).

In anaesthetised and paralysed dogs, administration of strychnine in cumulative doses of up to 0.1 to 0.2 mg/kg bw caused significant pressor, as well as positive inotropic and chronotropic effects on the heart, which were abolished by adrenergic blocking agents. The cardiovascular responses possibly were elicited by a central mechanism in contrast to the peripheral inhibitory action of strychnine on the sympathetic system (Sof76).

Autopsy findings were usually entirely non-specific, reflecting only the presence of violent convulsions and anoxia. Congestion and small haemorrhages may be found in the brain and sometimes in the viscera (Ray91). Convulsive doses of strychnine (2.5 mg/kg bw strychnine sulphate, subcutaneously) caused a marked depletion of the neurosecretory material from the hypothalamic nuclei as well as from the neurohypophysis (Vij72).

The biochemical mechanism of strychine poisoning is dependent upon inhibition of outward sodium ion flux in spinal nerves, manifest as increased cerebrospinal excitability, tetanic contractions of the diaphragm and striated muscles, sympathetic discharge (accounting for the tachycardia and hypertension), and death in respiratory arrest (ACG91).

Individual subcutaneous injection of dogs and guinea pigs with strychnine at 0.25 to 0.35 mg/kg bw every 3 to 7 days occasionally produced no increase of

reflexes but generally produced increased reflexes or tonic-clonic variable convulsions (ACG91).

Based on maximally tolerated single doses, determined in a pilot experiment, of 8 and 2.5 mg/kg bw/day for males and females, respectively, male and female Sprague-Dawley/SIV rats (n=12/sex/group) were orally (gavage) exposed to strychnine (given as a 2% solution of strychnine hydrochloride in distilled water) at doses of 0, 5, and 10 or 0 and 2,5 mg/kg bw, respectively, for 28 days. Apart from haematological, blood chemistry, urinalysis, ophthalmological, macroscopic, and microscopic investigations, animals were submitted to a rotating rod test and an electrocardiography before and during treatment. Ten to 20 minutes after each administration, the animals showed increased muscle tone and slight tremors gradually subsiding during the following hour. Mortality occurred in 1/12 and 5/12 male rats of the low- and high-dose group, respectively, and in 1/12 females. Animals died within 1/2 to 6 hours following administration showing tonic muscle contractions and respiratory paralysis and, at autopsy, pulmonary oedema and cyanosis. Comparison with control animals did not show treatment-related changes in body weight gains and food and water consumption or in any of the investigations performed (Sei82).

The committee did not find further data on repeated-dose toxicity, including carcinogenicity or reproduction toxicity, of strychnine.

Mutagenicity and genotoxicity

Strychnine was stated to be negative in the gene mutation assay using *S. typhimurium* strains TA98, TA100, TA1537, and TA1538 (no reference or details presented (Wür91). It induced a dose-dependent increase in the frequency of Trp^+ genetic duplications in *S. typhimurium* strain TS1121 (*aroC321 hisG46*), with very high frequencies at high doses. Doses that were recombinagenic did not cause increases in the frequency of base-pair substitution or frameshift mutations in the *hisG46*, *hisD3052*, or *hisC3076* alleles in the same strain (Hof87). Strychnine was stated to have induced mitotic recombination and/or gene conversion in *S. cerevisiae* (unpublished results; no details presented) (Wür86).

Strychnine did not induce sex-linked recessive lethal mutations or clastogenic effects in *D. melanogaster* germ cells (unpublished results; no details presented) (Wür86). In somatic *Drosophila* cells, it was negative in the white-ivory reversion assay when tested at one single dose of 1.14 mM (Wür91) while

positive results were obtained in he wing-spot assay in DNA repair-proficient larvae (Wür86).

These results suggest that strychnine may be specifically recombinagenic, but not mutagenic.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for strychnine in the Netherlands is 0.15 mg/m^3, 8-hour TWA.

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

8 Assessment of health hazard

Strychnine is rapidly absorbed from the gastrointestinal tract and mucous membranes. It concentrates primarily in the liver, where it is detoxified by oxidation by hepatic microsomal enzymes. Elimination from the blood is probably best described by first-order kinetics with an elimination half-life of 10-16 hours. It is rapidly excreted in urine and faeces (80% as metabolites, 1-20% as parent compound).

There are no human data from which an inhalation exposure concentration-effect relation can be estimated for strychnine. There are no data on irritation and sensitisation.

Strychnine is an acute convulsant poison acting at the level of the spinal cord in man and animals, but there is no evidence for cumulative toxicity. Doses as low as 5 mg have been fatal for man. The committee did not find data on acute toxicity after inhalation or dermal exposure. Acute lethal toxicity data from other routes indicate that strychnine is a very toxic compound. Oral LD_{50} values were 2.35-16, 2, and 0.5-1.1 mg/kg bw in rats, mice, and dogs, respectively. Values found in rats, mice, dogs, or guinea pigs following intraperitoneal, subcutaneous, or intravenous administration were 0.9-2.8, ca. 0.5-4.0, and ca. 0.4-1 mg/kg bw, respectively. Strychnine was more toxic to female than to male rats after oral, subcutaneous, or intraperitoneal administration, a difference that has been attributed to a higher rate of metabolism in males.

Administration via the drinking water of strychnine doses of 2.5 mg/kg bw/day to female and of 5 and 10 mg/kg bw to male Sprague-Dawley rats caused transient increased muscle tone and slight tremors 10-20 minutes after each administration. Mortality occurred in 1/12 female and in 1/12 low-dose and 5/12 high-dose male rats, animals showing tonic muscle contractions, respiratory

paralysis, pulmonary oedema, and cyanosis. In the surviving animals, no changes were seen at haematological, blood chemistry, urinalysis, ophthalmological, electrocariographic, macroscopic, and microscopic investigations and in a rotating rod test.

Strychnine induced genetic duplications in *S. typhimurium*, in *D. melanogaster*, and in yeast. It was negative in the *D. melanogaster* white-ivory reversion test. It was negative in mutagenicity assays in *S. typhimurium*. These results suggest that strychnine may be specifically recombinagenic, but not mutagenic.

There are no further data available on repeated-dose toxicity of strychnine, including carcinogenicity and reproduction toxicity.

The committee considers the database on strychnine too poor to justify recommendation of a health-based occupational exposure limit.

In view of the occurrence of deaths in humans at doses as low as 5 mg and the present MAC-value of 0.15 mg/m^3, 8-hour TWA, (equivalent to a dose of 1.5 mg per day for workers, assuming a respiratory volume of 10 m^3 per working day), the committee concludes that the present MAC-value may be too high.

References

ACG91 American Conference of Governmental Industrial Hygienists (ACGIH). Documentation of the threshold limit values and biological exposure indices. 6th ed. Cincinnati OH, USA; ACGIH®, Inc, 1991: 1433-5.

ACG03a American Conference of Governmental Industrial Hygienists (ACGIH). Guide to occupational exposure values - 2003. Cincinnati OH, USA: ACGIH®, Inc, 2003: 111.

ACG03b American Conference of Governmental Industrial Hygienists (ACGIH). 2003 TLVs® and BEIs® based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. Cincinnati OH, USA: ACGIH®, Inc, 2003: 48.

Ama94 Amabeoku G, Chandomba R. Strychnine-induced seizures in mice: the role of noradrenaline. Prog Neuropsychopharmacol Biol Psychiatry 1994; 18: 753-63.

Arb02 Arbejdstilsynet. Grænseværdier for stoffer og materialer. Copenhagen, Denmark: Arbejdstilsynet, 2002: 29 (At-vejledning C.0.1).

Bla82 Blain PG, Nightingale S, Stoddart JC. Strychnine poisoning: abnormal eye movements. J Toxicol Clin Toxicol 1982; 19: 215-7.

Bla84 Blakley BR. Epidemiologic and diagnostic considerations of strychnine poisoning in the dog. J Am Vet Med Assoc 1984; 1: 46-7.

Cin99 Cingolani M, Froldi R, Mencarelli, et al. Analytical detection and quantitation of strychnine in chemically fixed organ tissues. J Anal Toxicol 1999; 23: 219-21.

DFG03 Deutsche Forschungsgemeinschaft (DFG): Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. List of MAK and BAT values 2003. Maximum concentrations and biological tolerance values at the workplace. Weinheim, FRG: Wiley-VCH Verlag GmbH & Co. KGaA, 2003; rep no 39.

DiP81 DiPalma JR. Human toxicity from rat poisons. Am Fam Physician 1981; 24: 186-9.

EC03 European Commission: Directorate General of Employment and Social Affairs. Occupational exposure limits (OELs); http://europe.eu.int/comm/employment_social/h&s/areas/oels_en.htm.

Edm86 Edmunds M, Sheenan TMT, Van't Hoff W. Strychnine poisoning: clinical and toxicological observations on a non-fatal case. Clin Toxicol 1986; 24: 245-5.

ElM93 El-Mekkawy S, Meselhy MR, Kawata Y, et al. Metabolism of strychnine N-oxide and brucine N-oxide by human intestinal bacteria. Planta Med 1993; 59: 347-50.

EPA96 US Environmental Protection Agency (EPA). R.E.D. Facts. Strychnine. Washington DC, USA: US Environmental Protection Agency, Office of Pesticide Programs, Special Review and Reregistration Division, 1996; http://www.epa.gov/oppsrrd1/REDs/facsheets/3133fact.pdf.

Flo99 Flood RG. Strychnine poisoning. Pediatr Emerg Care 1999; 15: 286-7.

Fuj94 Fujisaki H, Mise M, Ishii Y, et al. Strychnine and brucine as the potent inducers of drug metabolizing enzymes in rat liver: different profiles from phenobarbital on the induction of cytochrome P450 and UDP-glucuronosyltransferase. J Pharmacol Exp Ther 1994; 268: 1024-31.

Gon90 Gonzalez M, Guillaume JE, Laloux P, et al. Strychnine poisoning, hypoxic damage, severe acidosis: a case report. Acta Clin Belg Suppl 1990; 13: 94-5.

Gre01 Greene R, Meatherall R. Dermal exposure to strychnine. J Anal Toxicol 2001; 25: 344-7.

Hat68 Hatch RC, Funnell HS. Strychnine levels in tissues and stomach contents of poisoned dogs: an eleven year survey. Can Vet J 1968; 9: 161-4.

Hei92 Heiser JM, Daya MR, Magnussen AR, et al. Massive strychnine intoxication: serial blood levels in a fatal case. Clin Toxicol 1992; 30: 269-83.

Hof87 Hoffmann GR, Sprague KM, Wrobel JA, et al. A recombinagenic effect of strychnine in Salmonella typhimurium. Environ Mol Mutagen 1987; 10: 27-33.

HSE02 Health and Safety Executive (HSE). EH40/2002. Occupational Exposure Limits 2002. Sudbury (Suffolk), UK: HSE Books, 2002:

Hun89 Hunter C, Chung E, Van Woert MH. Age-dependent changes in brain glycine concentration and strychnine-induced seizures in the rat. Brain Res 1989; 482: 247-51.

Jäg66 Jäger J. Traumatisch bedingte Rückenmarkveränderungen bei Kaninchen nach Strychnin. Gegenbaurs Morphol Jahrb 1966; 109: 243-4.

Kat74 Kato R. Sex-related differences in drug metabolism. Drug Metab Rev 1974; 3: 1-32.

Kub95 Kubová H, Mareš P. Different postnatal development of convulsions and lethality induced by strychnine in rats. Pharmacol Toxicol 1995; 77: 219-24.

Kum02 Kurup RK, Kurup PA. Endogenous strychnine: description of hypo- and hyperstrychninergic state in relation to neuropsychiatric diseases. Int J Neurosci 2002; 112: 1229-41.

Lam68 Lamanna C, Hart ER. Relationship of lethal toxic dose to body weight of the mouse. Toxicol Appl Pharmacol 1968; 13: 307-15.

Lon83 Longo VG, Massotti M, Sagratella S. Convulsant drugs and changes in the electrical activity of the brain: an investigation of the effects of opioids on chemoconvulsions. Prog Clin Biol Res 1983; 124: 121-7.

Mac77 Mackerer CR, Kochman RL, Shen TF, et al. The binding of strychnine and strychnine analogs to synaptic membranes of rat brainstem and spinal cord. J Pharmacol Exp Ther 1977; 201: 326-31.

Man87 Manev H, Peričić D, Anić-Stojiljković S. Sex differences in the sensitivity of CBA mice to convulsions induced by GABA antagonists are age-dependent. Psychopharmacology 1987; 91: 226-9.

Mar00 Marques EP, Gil F, Proença P, et al. Analytical method for the determination of strychnine in tissues by gas chromatography/mass spectrometry: two case reports. Forensic Sci Int 2000: 110: 145-52.

McB73 McBay AJ. Toxicological findings in fatal poisonings. Clin Chem 1973; 19: 361-5.

Mis85 Mishima M, Tanimoto Y, Oguri K, et al. Metabolism of strychnine in vitro. Drug Metab Dispos 1985; 13: 716-21.

Muh86 Muhtadi FJ, Hifnawy MS. Strychnine. Analytical Profiles of Drug Substances 1986; 15: 563-646.

NIO97 National Institute of Occupational Safety and Health (NIOSH). Registry of Toxic Effects of Chemical Substances (RTECS) [CD-ROM, issue April 1997. SilverPlatter International, 1997 (last update strychnine file: April 1997).

Nis95 Nishiyama T, Nagase M. Strychnine poisoning: natural course of a nonfatal case. Am J Emerg Med 1995; 13: 172-3.

Niy73 Niyogi SK. Drug levels in cases of poisoning. Forensic Sci 1973; 2: 67-98.

NLM03 US National Library of Medicine (NLM), ed. Strychnine. In: Hazardous Substances Data Bank (HSDB) (last revision date strychnine file: January 2003; last review date: September 1999); http://toxnet.nlm.nih.gov.

Ogu89 Oguri K, Tanimoto Y, Mishima M, et al. Metabolic fate of strychnine in rats. Xenobiotica 1989; 19: 171-8.

Oli79 Oliver JS, Smith H, Watson AA. Poisoning by strychnine. Med Sci Law 1979; 19: 134-7.

Osw77 Osweiler GD. Strychnine poisoning. Curr Vet Ther 1977; 6: 115-7.

Pal97 Palatnick, Meatherall R, Sitar D, et al. Toxicokinetics of acute strychnine poisoning. Clin Toxicol 1997; 35: 617-20.

Per85 Perper JA. Fatal strychnine poisoning - a case report and review of the literature. J Forensic Sci 1985; 30: 1248-55.

Pie77 Piepho RW, Friedman AH. Chronopharmacology of strychnine and allylglycine in the mouse. Clin Exp Pharmacol Physiol 1977; 4: 263-6.

Ray91 Ray DE. Pesticides derived from plants and other organisms. In: Classes of pesticides. Hayes WJ Jr, Laws ER Jr, eds, Academic Press Inc, New York, 1991: 585-636 (Handbook of pesticide toxicology; Vol 2).

Ric94 Richardson ML, Gangolli S, eds. S118 Strychnine. In: The dictionary of substances and their effects. Cambridge, UK: Royal Society of Chemistry, 1994: 172-4 (Vol 7).

Ros00 Rosano TG, Hubbard JD, Meola JM, et al. Fatal strychnine poisoning: application of gas chromatography and tandem mass spectrometry. J Anal Toxicol 2000; 24: 642-7.

Sei82 Seidl I, Zbinden G. Subchronic oral toxicity of strychnine in rats. Arch Toxicol 1982; 51: 267-72.

Sga73 Sgaragli GP, Mannaioni PF. Pharmacokinetic observations on a case of massive strychnine poisoning. Clin Toxicol 1973; 6: 533-40.

Smi90 Smith BA. Strychnine poisoning. J Emerg Med 1990; 8: 321-5.

Sof76 Sofola OA, Odusote KA. Sympathetic cardiovascular effects of experimental strychnine poisoning in dogs. J Pharmacol Exp Ther 1976; 196: 29-34.

Spa90 Spapen H, Reynaert H, Debeuckelaere S, et al. A case of concomitant ethanol and strychnine intoxication. Acta Clin Belg 1990; 45: 343-6.

Swe00 Swedish National Board of Occupational Safety and Health. Occupational exposure limit values and measures against air contaminants. Solna, Sweden: National Board of Occupational Safety and Health, 2000; Ordinance AFS 2000:3.

SZW03 Ministerie van Sociale Zaken en Werkgelegenheid (SZW). Nationale MAC-lijst 2003. The Hague, the Netherlands: Sdu, Servicecentrum Uitgevers, 2003: 40.

Tan90 Tanimoto Y, Ohkuma T, Oguri K, et al. Species difference in metabolism of strychnine with liver microsomes of mice, rats, guinea pigs, rabbits, and dogs. J Pharmacobiodyn 1990; 13: 136-41.

Tan91a Tanimoto Y, Ohkuma T, Oguri K, et al. A novel metabolite of strychnine, 22-hydroxystrychnine. Xenobiotica 1991; 21: 395-402.

Tan91b Tanimoto Y, Kaneko H, Ohkuma T, et al. Site-selective oxidation of strychnine by phenobarbital inducible cytochrome P-450. J Pharmacobiodyn 1991; 14: 161-9.

Tei70 Teitelbaum DT, Ott JE. Acute strychnine intoxication. Clin Toxicol 1970; 3: 267-73.

Tre88 Tremblay N, Warren R, Dykes RW. The effects of strychnine on neurons in cat somatosensory cortex and its interaction with the inhibitory amino acids, glycine, taurine and β-alanine. Neuroscience 1988; 26: 745-62.

TRG00 TRGS 900. Grenzwerte in der Luft am Arbeitsplatz; Technische Regeln für Gefahrstoffe. BArbBl 2000; 2.

Yam92 Yamarick W, Walson P, DiTraglia J. Strychnine poisoning in an adolescent. Clin Toxicol 1992; 30: 141-8.

Vij72 Vijayan E, Mukherjee A. Strychnine induced changes in the neurosecretory material of rat neurohypophysis. Endocrinol Exp 1972; 6: 45-9.

Woo02 Wood DM, Webster E, Martinez D, et al. Case report: survival after deliberate strychnine self-poisoning, with toxicokinetic data. Crit Care 2002; 6: 456-9.

Wür86 Würgler FE, Vogel EW. In vivo mutagenicity testing using somatic cells of Drosophila melanogaster. In: de Serres FJ, ed. Chemical mutagens, principles and methods for their detection, 1986: 1-72 (Chemical mutagens; Vol 10).

Wür91 Würgler FE, Kägi A. Genotoxicity testing with the somatic white-ivory system in the eye of Drosophila melanogaster. Mutat Res 1991; 263: 33-9.

Annex I

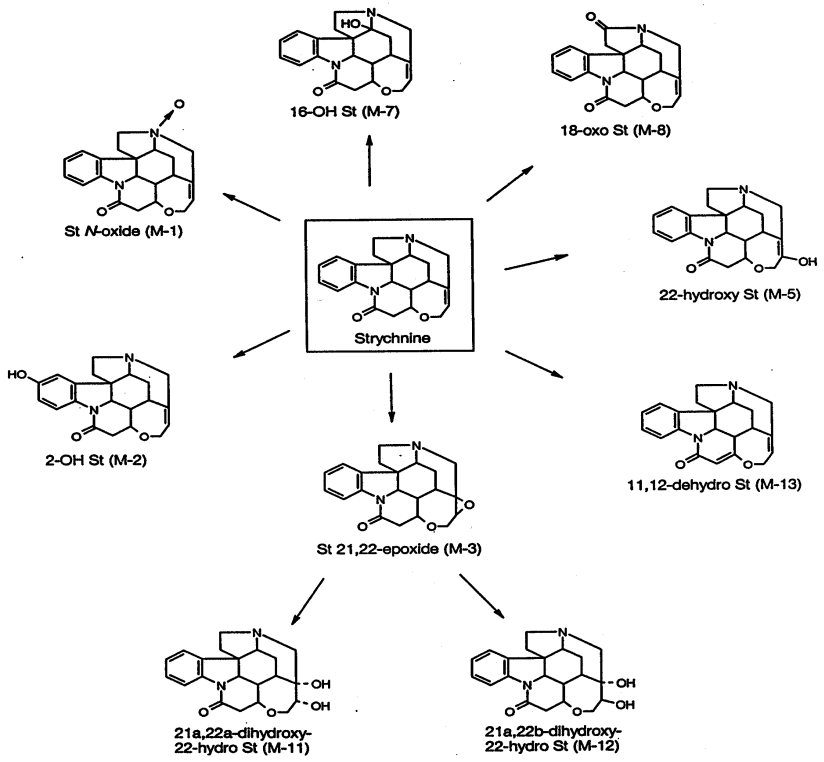

Figure 1 Metabolism scheme for strychnine in rats (Mis85, Ogu89, Tan90, Tan91a).

Annex II

Occupational exposure limits for strychnine 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	-	0.15	8 h	administrative		SZW03
Germany						
- AGS	-	0.15[c]	8 h			TRG00
- DFG MAK-Kommission	-	-[d]	8 h			DFG03
Great-Britain						
- HSE	-	0.15	8 h	OES		HSE02
		0.45	15 min			
Sweden	-	-				Swe00
Denmark	-	0.15	ceiling			Arb02
USA						
- ACGIH	-	0.15	8 h	TLV		ACG03b
- OSHA	-	0.15	8 h	PEL		ACG03a
- NIOSH	-	0.15	10 h	REL		ACG03b
European Union						
- SCOEL	-	-				EC03

[a] S = skin notation; which mean 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

[c] The inhalable fraction of the aerosol.

[d] Listed among compounds for which studies of the effects in man or experimental animals have yielded insufficient information for the establishment of MAK values.