



COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

STRYCHNI SEMEN

SUMMARY REPORT

1. *Strychni semen* (synonym *Nux vomica*) is the dried ripe seed of *Strychnos nux vomica*. The crude drug contains the following relevant active substances: indole alkaloids (2 to 5%), of which the main alkaloids (approximately in a 1:1 ratio) are strychnine and brucine both with similar action, furthermore among others 12-hydroxystrychnine and 15-hydroxystrychnine. The alcoholic extract contains 16% alkaloids and the tincture contains 0.25% alkaloids.
2. In veterinary medicine the substance is used in mono-preparations and in combination products as bitter, digestive and nerve tonic. Preparation equivalents are stated to be: 0.1 g powder equals 0.016 g extract equals 1 g tincture and should contain 2.5 mg total alkaloids. A product containing *Strychni semen* is marketed in one Member State. It contains 3% *Strychni semen* in combination with propionic acid and is licensed for use in cattle, sheep and goats to stimulate ruminal motoric activity after digestive disorders such as observed after weaning. The therapeutic doses are 100 g product (i.e. 3 g *Strychni semen*) per day for adult cattle, 12.5 g product per day for sheep and goats, 15 g product per day for weanling calves, and 5 g product per day for weanling sheep. This product is only intended for oral administration over a period of usually two to seven days.

Both *Strychni semen* as well as its component strychnine have been widely used in human medicine for several indications: orally for digestive disorders, as a bitter, digestive tonic, nerve tonic and as emetic. In man, therapeutic oral doses of strychnine as a stimulant are 1 to 6 mg/person as a single dose or 3 to 18 mg/person per day when given in fractions. For treatment of non-ketotic hyperglycinaemia daily oral doses of 0.16 to 2 mg/kg have been employed.

3. *Strychni semen* properties are attributed to strychnine.

Strychnine is a competitive antagonist of glycine, the neurotransmitter of inhibitory spinal interneurons and of gamma-amino-butyric acid inhibitory neurons in higher parts of the central nervous system. At high concentrations *in vitro* it also interferes with other neurotransmitters.

The tone of the whole skeletal musculature is increased due to obstruction of post-synaptic inhibition of spinal motor-reflexes. At acutely lethal doses tonic convulsions result, triggered by external stimuli. The sensory acuity is increased. Action on respiratory, vaso-motor and cardiac centres of the medulla oblongata results in increased respiratory frequency and amplitude, increased arterial pressure due to vaso-constriction, and reduced cardiac output. Strychnine action on higher parts of the brain causes anxiety. Consciousness is not affected. A memory enhancing effect has been observed in mice. At the neuro-muscular level strychnine has a pseudo-curarising effect.

4. Strychnine is quickly and comprehensively absorbed by mucous membranes and from injection sites, with fast onset of clinical signs.

Distribution is rapid. Within 5 minutes of intravenous injection of strychnine to cats (1 mg/kg bw) 50% of the administered amount has left the blood compartment. Within 40 minutes only traces of strychnine are recovered from blood. In dogs within 4 minutes after intravenous injection of 50 mg strychnine 7-fold higher concentrations of strychnine are detected in the liver than in blood.

An epidemiological study on dogs which died of strychnine poisoning reports highest average concentrations in stomach contents (229 mg/kg), then liver (18.1 mg/kg), kidney (14.6 mg/kg) and blood (0.17 mg/kg). No data on tissue distribution of non-lethal doses are available.

Strychnine undergoes rapid and extensive oxidative metabolism by hepatic cytochrome P-450 IIB.

After a subcutaneous dose of 0.5 mg/kg of benzene-ring labelled tritiated strychnine, 6 metabolites were identified in rats *in vivo*: strychnine N-oxide, 21a,22a- and 21a,22β-dihydroxy-22-hydrostrychnine, 2-hydroxystrychnine (urine, faeces), strychnine-21,22-epoxide (main *in vivo* metabolite) and 16-hydroxystrychnine (the latter two in urine). They constitute 58% of the faecal and urinary radioactivity, respectively. Eight percent of the urinary radioactivity are conjugations of the above mentioned metabolites. Six percent and 3% of the administered dose are found as unchanged strychnine in urine and faeces, respectively. Thirty four percent of the urinary and 42% of the faecal radioactivity are unidentified water-soluble metabolites.

In vitro studies on metabolism of strychnine by liver microsomes show some species differences. Main metabolites are 16-hydroxystrychnine in rats and mice, 2-hydroxystrychnine in guinea pigs and rabbits, and strychnine N-oxide in dogs. 18-Oxo-strychnine was noted for rabbits only. Three structurally unidentified metabolites were noted for most species studied (2 of them not identified for rat, 1 not identified for mouse and guinea pig). The quantities of metabolites formed differed between species. The metabolic capacity is highest for guinea pig, then rat and dog, and least in mouse and rabbit.

In rats more than 80% of the subcutaneously administered tritiated strychnine is excreted within the first 24 hours, about 28% in urine and about 60% in faeces. Within 7 days total excretion of radioactivity adds up to 95%, 30% in urine and 65% in faeces.

As a general rule it is said that, for all mammalian species, approximately twice the lethal dose can be excreted within 24 hours.

Strychnine is reported to be excreted via saliva (no supporting data submitted). Excretion via milk is thought possible but has not been investigated.

6. The toxicity of strychnine results from its pharmacodynamic action. The symptoms are similar in all species. First signs of intoxication are anxiety, restlessness, nausea and vomiting (when possible). Twitching of the facial musculature, convulsive retraction of the corners of the mouth, increased sensitivity to touch and noise and general muscular rigidity follow. External stimuli provoke generalised symmetric cramps of the whole skeletal musculature, which inhibit respiration. Opisthotonus, extended extremities and cyanotic mucous membranes are noted. With increasing asphyxia and central hypoxia the muscles relax. The apparent recuperation is followed by new convulsive attacks resulting in death due to anoxia. Death may occur within 20 to 30 minutes after ingestion of a large dose but may appear as late as 48 hours after intake of strychnine.

In literature an oral dose of 0.5 to 1.0 mg/kg bw is generally held as lethal for most mammalian species, though conflicting higher values have been reported. The parenteral toxicity is stated as being higher by a factor 2 to 10. Large interindividual variations are documented for all species.

The acute toxicity of strychnine varies with route of administration (higher for parenteral application), species, strain, sex (observed in rats and mice) and age (rats).

The toxicity of the metabolites 2-hydroxystrychnine, 16-hydroxystrychnine and strychnine N-oxide was reported to be lower than that of the parent compound.

7. No signs of cumulative toxicity are observed after repeated application of non-lethal doses to individual cats (0.1 to 0.25 mg/kg bw intramuscular), dogs (0.08 to 0.25 mg/kg subcutaneous), and guinea pigs (0.5 to 2.0 mg/kg bw subcutaneous) at varying time intervals over periods of 1 to 12 days.

An oral 28 day study was conducted in Sprague-Dawley rats (60 days old, 12 animals per group, male and female controls). Strychnine sulphate was administered *via* gavage at a dose of 2.5 mg/kg bw to females while males received 5 mg/kg bw and 10 mg/kg bw. One rat each at the 2.5 and 5 mg/kg bw dose levels and 5 rats at the 10 mg/kg bw dose level died of acute intoxication within 6 hours after several doses. Increased muscle tone and slight tremors were observed 10 to 20 minutes after each treatment, subsiding during the next hour. At autopsy of the animals, which had died due to the treatment only, findings consistent with strychnine poisoning were noted. In the other animals no abnormal histological changes were observed. No difference between control and treated animals was seen for all observed parameters.

No other repeated dose toxicity studies were performed.

8. Mutagenicity studies were not provided in accordance with the requirements of Volume VI of the Rules Governing Medicinal Products in the European Community.

Strychnine had a strong dose-related recombinagenic effect in *Salmonella typhimurium* strain TS1121 but did not elicit base pair or frame-shift mutations in this strain when tested without metabolic activation. In a review it was reported that in *Drosophila* strychnine was also found to be positive in a test for recombinagenicity in somatic cells but negative for sex-linked recessive lethal mutations and clastogenic effects in germ cell.

9. No information on reproductive toxicity, carcinogenicity and other effects of strychnine has been submitted. Strychnine is reported to have no structural analogies to known carcinogens.
10. No data on tolerance in target animals have been submitted. The lethal oral dose for cattle and horses is reported as 0.5 mg/kg bw.
11. In humans the minimal lethal dose is given as 0.5 to 1.0 mg/kg bw, though death of adults has been seen after a dose of 16 mg while, with appropriate treatment, 2 g have been survived.

After oral intake of 700 mg strychnine nitrate by a man of 60 kg bw, about 90% of the dose was absorbed within 1 hour; 79 mg were found in the stomach. Blood levels were below 0.5 mg/l throughout the observation period. Urinary excretion of unchanged strychnine began 2 hours after ingestion. Within the first 24 hours 4 mg were recovered (less than 1% of the ingested dose). Following oral and intramuscular administration of 4 mg/person and oral intake of 13 to 15 mg/person in two healthy male volunteers, urinary excretion of unchanged strychnine in the first 24 hours was 5 to 8% of the administered amount for the high oral doses and 12 to 20% for the low dose irrespective of the route of administration. In a child treated orally with strychnine nitrate for non-ketotic hyperglycinaemia for 3.5 years, 24 hour urinary excretion of unchanged strychnine amounted to 1 to 12% of the administered dose.

In cases of fatal accidental poisoning, strychnine concentrations of 5 to 11 mg/kg in blood, of 8 mg/kg in urine and of 1.3 mg/kg in kidneys have been noted.

The available data support the assumption that pharmacokinetics and metabolism in man is similar to that in other mammalian species.

12. No information on residues of *Strychni semen* and their depletion following treatment of food producing animals was provided.
13. Recent studies on metabolism of strychnine including a radiotracer study in rats have been published. Similarity of lethal oral doses of strychnine in most mammals, similarity of *in vitro* metabolism with hepatic microsomes of several species and the consistency of observations in humans with the available animal data allow the assumption that absorption, distribution, metabolism and excretion of strychnine in the target species and humans will be comparable to the findings in rats and within 24 hours approximately 80% of the administered amount will be excreted in faeces and urine, largely as metabolites.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for Veterinary Medicinal Products for inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90, and in particular that:

- *Strychni semen* is used only in a small number of individual animals, for infrequent or non-regular treatments,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- the available information indicates that strychnine, the active and toxicological relevant substance of *Strychni semen*, is rapidly excreted,
- strychnine has already been recommended to be included in Annex II for oral use in bovine species at doses up to 0.1 mg/kg bw;

the Committee considers that there is no need to establish an MRL for *Strychni semen* and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
<i>Strychni semen</i>	Bovine, ovine, caprine	For oral use only at doses up to the equivalent of 0.1 mg strychnine/kg bw