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Food and Chemical Toxicology 42 (2004) 1373–1382
Food and Chemical Toxicology
www.elsevier.com/locate/foodchemtox

Review

Poison hemlock (*Conium maculatum* L.)

J. Vetter *

Faculty of Veterinary Science, Department of Botany, Szent István University, 1400 Budapest, Pf. 2. Hungary

Received 18 January 2004; accepted 16 April 2004

Abstract

One of the most poisonous species amongst higher plants is *Conium maculatum*. It is a very common nitrophile weed species, belonging to the Apiaceae (formerly Umbelliferae) family. It contains some piperidine alkaloids (coniine, *N*-methyl-coniine, conhydrine, pseudoconhydrine, γ-coniceine), which are formed by the cyclisation of an eight-carbon chain derived from four acetate units. γ-Coniceine is the precursor of the other hemlock alkaloids. All vegetative organs, flowers and fruits contain alkaloids. The concentrations (both absolute and relative) of the different alkaloids depend on plant varieties, on ecological conditions and on the age of the plant. The characteristic biological effects of the plants are summarised on cattle, sheep, goat, swine, rabbit, elk, birds and insects and the symptoms of the human toxicosis (some cases of poisonings) are discussed according to the literature data. The general symptoms of hemlock poisoning are effects on nervous system (stimulation followed by paralysis of motor nerve endings and CNS stimulation and later depression), vomiting, trembling, problems in movement, slow and weak later rapid pulse, rapid respiration, salivation, urination, nausea, convulsions, coma and death.

Keywords: *Conium maculatum*; Hemlock; Piperidine alkaloids; Poisoning; Animals; Human

Contents

* Tel./fax: +36-1-478-4238.
E-mail address: jvetter@univet.hu (J. Vetter).

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doi:10.1016/j.fct.2004.04.009

1. Introduction

The plant species *Conium maculatum* (hemlock, poisonous hemlock) is one of the most toxic members of the plant kingdom. There are numerous reports of deaths for a wide range of animal species including humans. *Conium maculatum* has a worldwide distribution; it is a very common plant species, a member of the family Apiaceae (formerly Umbelliferae), the carrot family. This review summarises the botanical, chemical and toxicological aspects of this plant.

2. History of the plant

The juice or the extract of *Conium maculatum* was allegedly administered to criminals, and was the lethal poison, which the Greek philosopher Socrates was condemned to drink (399 BC). The symptoms of poisoning were described by Plato (a pupil of Socrates). The old Roman name of the plant was *Cicuta*, but this name was later applied (by Gesner, 1541) to another umbelliferous plant, *Cicuta virosa* (water hemlock). The consequent confusion was solved by the nomenclature of Linnaeus, who restored the classical Greek name describing the plant as *Conium maculatum*. The generic name was derived from the Greek word Konas, meaning to whirl about, because the consumption of the plant causes ataxia, tremor and convulsions. The specific name (*maculatum*) is a Latin word, meaning spotted and refers to the very characteristic brownish–reddish spots of stem.

The plant was used in ancient Anglo-Saxon medicine; and the English name—hemlock—is derived from the Anglo-Saxon words hemlic or hymelic. Through the centuries, spelling and pronunciation have taken many forms, ranging from hymlice to hymlic, hemeluc, hemlake, hemlocke, and finally hemlock. William Shakespeare, in "Life of Henry the Fifth", first used the modern spelling hemlock (Simpson and Weiner, 1989). *Conium maculatum* was employed externally to treat herpes, erysipelas (a form of superficial cellulites) and breast tumours. More recently, unripe *Conium* seeds were, dried and stored to be used as an antispasmodic, a sedative or an analgesic. The dried leaf and juice of the plant were listed in pharmacopoeias of London and Edinburgh from 1864 to 1898 and the last official medicinal recognition appeared in the British Pharmaceutical Codex of 1934 in Great Britain (Bowman and Snaghvi, 1963).

The medicinal importance of hemlock is very limited because of the closeness between therapeutic and poisonous levels (Holm, 1997). Both Greek and Arabian physicians were in the practice of using it for the cure of indolent tumours, swellings and pains of the joins. The bitter juice of the plant was mixed with betony (*Stachys officinalis*) and fennel (*Foeniculum vulgare*) seeds for the bite of a mad dog. Later in history, this juice was administered as a last resort, as an antidote for strychnine and other strongly poisonous compounds (Le Stragne, 1977). Religious sects of the 15th and 16th centuries used the roasted roots for relieving the pains of gout. In the 1760s, it began to be used as a cure for cancerous ulcers. The US imported annually (prior to World War I) about 14,000 kg seeds and 7000 kg of dried leaves as a drug. The tinctures and extracts of the plants were used because of their sedative, anodyne and antispasmodic effects (in the cases of asthma, epilepsy, whooping cough, angina, chorea, stomach pains). The drug has to be administrated with care, as narcotic poisoning may result from internal use, overdoses producing paralysis. There are contra-dictionary opinions about the possibility of care use of hemlock in the medicine. Hemlock remains a classic homeopathic agent with various uses (Zdanevich and Belodubrovskaya, 1997). Said to be a long-acting remedy, it is of special value in old age when the vital powers of the body are failing. It has been used against a serious type of malignant tumour. The mother homeopathic tincture is prepared from the fresh flowering plant.

3. Botanical characterisation

Conium maculatum is a tall, branched plant with white flowers. It is a biennial plants, usually 120–180 (200) cm high (Fig. 1). The root, described as a taproot, is long, forked and pale yellow. As a biennial *Conium maculatum* produces a basal rosette in the first year, and then produces the flowering stems during the second year. The stem is erect, smooth, slightly ridged, stout below, much branched above and hollow, and is bright green. It is distinctively mottled with small irregular

Fig. 1. Poison hemlock (*Conium maculatum* L.).

purple spots. The leaves are numerous, alternate, long-stalked, tripinnate (i.e. divided along the midrib into opposite pairs of leaflets and these again divided and subdivided). The upper leaves are much smaller, sometimes nearly stalkless, dipinnate or pinnate, quite smooth. The umbels are small, numerous, have a terminal position, with 12–16 rays to the umbel. At the base of the main umbel one can see 4–8 lance-shaped bracts. The petals of the small flowers are white with an inflexed point. The stamens of the flowers are longer than the petals and have white anthers. The inflorescence is produced mainly from June to September. The fruit is a broadly ovoid, double achene (it is a schizocarp), and is composed of two greyish-brown seeds with five wavy, longitudinal ridges. At germination the cotyledons are narrow and lanceolate, the first true leaves have two or more leaflets along an axis and are hairless. The plant has a bitter taste and a mousy odour. Where plants are numerous, the odour can be very pervasive. The seeds or fruits do not a have very marked odour, but if crushed or mixed with an alkali as potassium hydroxide solution, the same characteristic, odour of mouse urine is produced.

Conium maculatum resembles water hemlock (*Cicuta virosa*). The two plants, however, may be distinguished on the basis of characteristic morphological properties:

Conium maculatum	*Cicuta virosa*
Single taproot	Branched root system, with a lateral tuber
Purple spotted stem	Absence of such spots
Mousy odour	Absence of the odour

Conium maculatum damp ground, hedgerows, banks of streams and rivers, roadsides and woodland, pastures, meadows, and waste ground. The plant is reported as a very common weed in Europe, North and South America, North Africa, Australia and New Zealand, and there are data about its occurrence in Ethiopia (Mekkonen, 1994), and in Pakistan (Ahmed et al., 1989). It was brought to the United States from Europe as a garden plant. In other countries the presence of the plant is a consequence of the transport of grain, for example in Norway (Kielland and Anders, 1998). In Hungary, the plant is one of the commonest weeds and poisonous plants (Vetter, 1999), with cases of poisonings occurring mainly in the spring or summer. *Conium maculatum* prefers moist soils with high nitrogen level (i.e. it is a nitrophile plant). A single plant may produce about 35,000–40,000 seeds, which usually fall near the parent plant but can be spread by water and animals (Mitich, 1998). *Conium maculatum* belongs to a group of very common, wide spreaded weed species; therefore its germination (mainly the ecological conditions) is an important target of investigations. In north-central Kentucky (USA) seeds of *Conium maculatum* are dispersed from mid-September to mid-February. Studies showed (Baskin and Baskin, 1990), that 40–85% of the freshly matured seeds had morphological dormancy (needing only a moist substrate, a photoperiod of 14 h light and alternating thermoperiods of 30/15 °C) for normal germination. *Conium maculatum* can be a tenacious weed species particularly in moist habitats. It may act as a pioneer species quickly colonizing disturbed sites.

4. Occurrence and chemistry of poisonous agents of hemlock

Conium maculatum contains piperidine alkaloids: coniine (2-propylpiperidine), *N*-methyl-coniine (1-methyl-2-propylpiperidine), conhydrine 2-(1-hydroxypropyl)-piperidine, pseudoconhydrine (5-hydroxypropyl)-piperidine (these are saturated piperidine alkaloids) and γ-coniceine (2*n*-propyl-1Δ-piperidine), a partially unsaturated one (see Fig. 2). Conhydrinone and *N*-methyl-pseudoconhydrine were later isolated (Leete and Olson, 1972; Roberts and Brown, 1981). The piperidine alkaloids (numbering several hundred) in

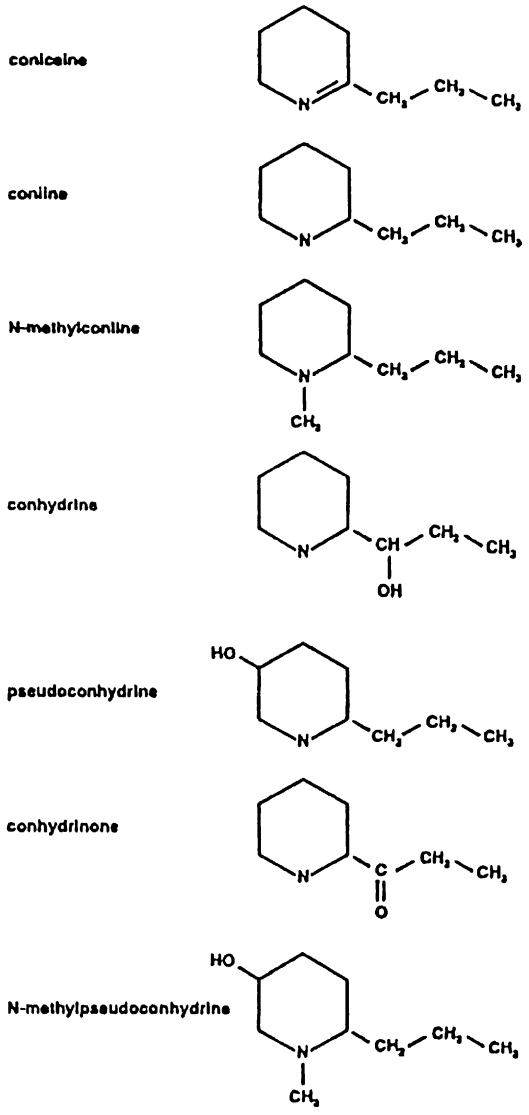

Fig. 2. The alkaloids of *Conium maculatum* (according to Lopez et al., 1999).

general are derived biosynthetically from lysine, acetate or mevalonate as the precursor. The piperidine alkaloids found in *Conium maculatum* are acetate-derived. The results of chemical and biochemical investigations suggested, that *Conium* piperidine alkaloids are formed by the cyclisation of an eight-carbon chain derived from four acetate units. Nitrogen was incorporated at some stage in the pathway to give the piperidine nucleus. Experiments with N-labelled amino acids showed, that L-alanine provided the N in a transaminase catalysed enzymatic reaction (the presence of such a aminotransferase which produces γ-coniceine from 5-oxooctanal, was established). After the transamination, the 5-oxooctylamine is formed, there is a non-enzymatic cyclisation producing γ-coniceine (the biogenetic pathway is shown in Fig. 3). γ-Coniceine is the precursor of the other *Conium* alkaloids. The observation, that when the concentration of coniine was higher, the concentration of γ-coniceine was low, and vice versa supported the precursor role of γ-coniceine in the biosynthesis of coniine.

The interconversion of coniine and γ-coniceine in *Conium* plants indicated that these compounds are members of an oxidation-reduction system. The γ-coniceine was reduced to coniine by a γ-coniceine reductase but the reverse reaction also occurred. The reduction of γ-coniceine, however, is stochiometrically preferred. The formation of conhydrine and conhydrinone from γ-coniceine has been demonstrated. It was suggested (Leete and Olson, 1972) the allylic oxidation of γ-coniceine gives 1′-hydroxy-γ-coniceine. It produces the enol of conhydrinone by a tautomeric shift of the double bond, which is reduced to conhydrine. Similarly γ-coniceine can function as a direct precursor to pseudoconhydrine. A mechanism for the biosynthesis of pseudoconhydrine has been proposed whereby γ-coniceine undergoes a tautomeric shift of the double bond, producing an intermediate which is then oxidised at C5 to a second intermediate, which is finally reduced to pseudoconhydrine (Panter and Keeler, 1989).

The majority of the Apiaceae (Umbelliferae) plants produce different volatile oils in clearly delimited tissues of the fruits. It is known that *Conium maculatum* produces and contains piperidine alkaloids but the synthesis and accumulation sites have not yet been unequivocally identified. The location of secretory structures and the presence of essential oils and alkaloids were investigated (Corsi and Biasci, 1998). In seedlings positive histochemical reactions to alkaloids were made both in the root and the shoot tips. In more mature plants these positive reactions tended to disappear, whereas the cells of elongations's zones reacted very positively. All vegetative organs and flowers showed strong, positive reactions at the secretory duct level. Positive reactions were shown in fruits only by secretory ducts. Ten days after fertilisation the presence of alkaloids was demonstrated in different layers of the fruit wall (in the endocarp, in the inner layer of the mesocarp and in the exocarp). The histochemical findings suggest that the secretory structures either produce alkaloid themselves or that they are supplied continuously with alkaloids from root and shoot tips. According to the earlier conclusions (for example, Cromwell, 1956) the alkaloid synthesis in *Conium maculatum* took place more readily in tissues of the shoot than the root. These findings (Corsi and Biasci, 1998) suggest, the *Conium maculatum* is similar to other members of the Apiaceae family, having secretory ducts in vegetative organs and fruits.

The concentrations and the relative proportions of the different *Conium* alkaloids appear to depend on different factors (temperature, moisture, time and age of the plant). According to earlier experiments (Fairbairn and Challen, 1959) γ-coniceine was the predominant

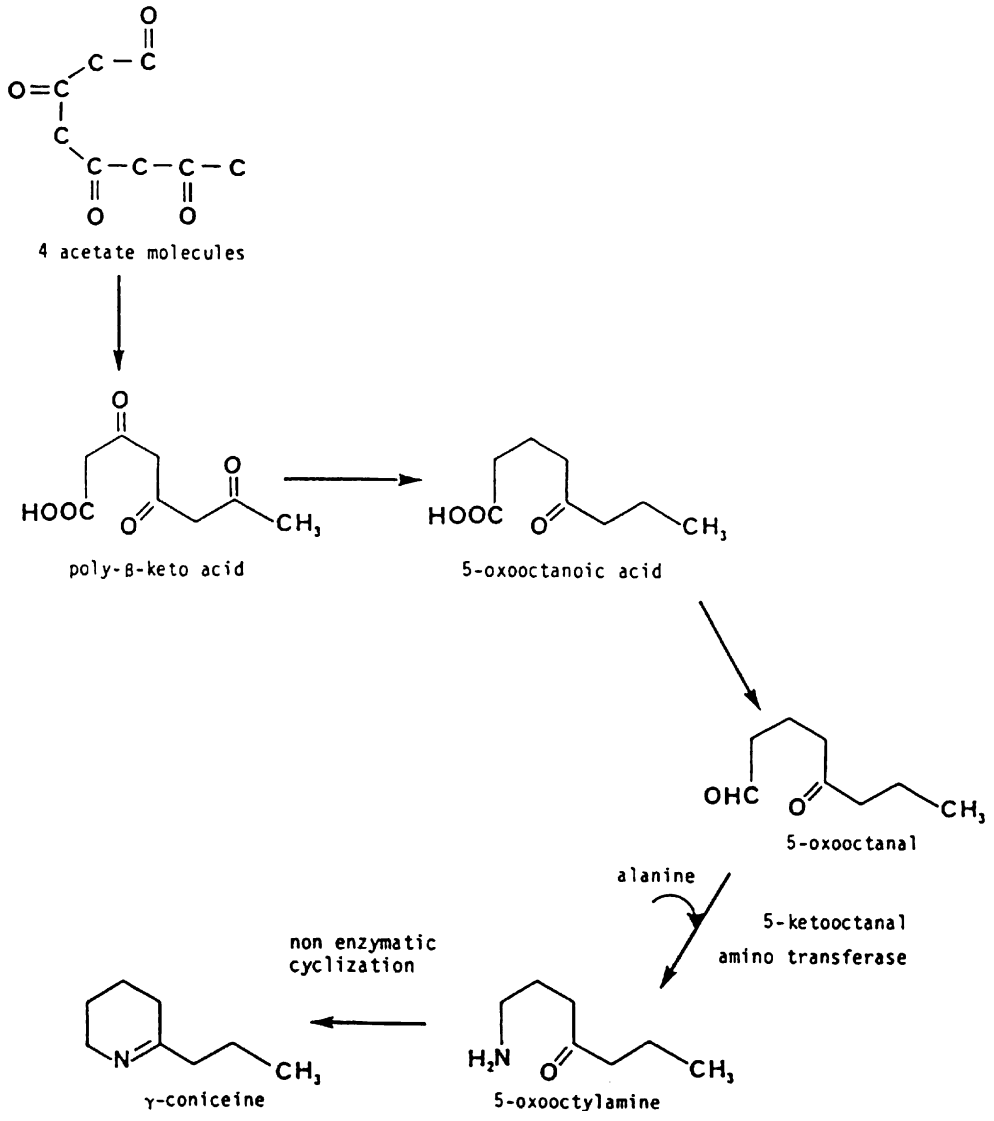

Fig. 3. Biosynthetic pathway of γ-coniceine started from acetate (according to Panter and Keeler, 1989).

alkaloid component during the rainy season and coniine was predominant during the dry period. The γ-coniceine content decreased, the coniine content increased markedly during the fruit ripening phase (Fairbairn and Challen, 1959). The relative concentration of the alkaloids changes with the stage of development and is varied in different plants. The seedlings contained low total alkaloid content, mainly γ-coniceine (Cromwell, 1956). In the leaves of the young plants (i.e. in the phase of the active growth) γ-coniceine was the major alkaloid component with small amounts of conhydrine. The roots contained only traces of alkaloids, in the dormant stage however, they have higher proportion of γ-coniceine and coniine than roots of the young plants with great metabolic activity. The phases of flowering, pollination and fertilisation show a sharp change in distribution of alkaloids. The coniine content increases rapidly, the amount of γ-coniceine decreases. When the fruits are riped, the *N*-methyl-coniine is the predominant component. The concentration of coniine and γ-coniceine fluctuated very rapidly during the day (diurnal changes), the increase of the first corresponds to a decrease of the second (Fairbairn and Suwal, 1961).

The data on total alkaloid content in different organs of *Conium maculatum* has been summarised (Lopez et al., 1999), roots contain 0–0.5%, shoots 0.02–0.7%, leaves 0.3–1.5%, flowers 1.0%, unripe fruits 1.6–3.0, ripe fruits 0.2–1.0% and seeds 0.02–0.9%, respectively.

5. Biological effects of *Conium maculatum* alkaloids

The consumption of varying parts of the plants (leaves, fruits) can cause different degrees of clinical effects and there appears to be different susceptibility to toxicity between species.

5.1. Cattle

Hemlock is more poisonous to cows than to other animals. Fresh plant collected at the same site was lethal to cows at the dosage 5.3 g plant/kg body weight (Keeler and Balls, 1978). The general symptoms of poisoning of cattle are: arthrogryposis, breathing, carpal joint, elbow joint, depression, diarrhoea, gait, incoordination, lateral rotation of limbs, muscle spasms, salivation, teeth grinding, torticollis, trembling, coffee-coloured urine, vomiting (Penny, 1953; Keeler, 1977; Cooper and Johnson, 1984). Cattle in two herds developed signs of bloating, increased salivation and lacrimation, depression, respiratory distress, ataxia and death after ingestion of hay that contained larger amount of the plant (Galey et al., 1992). The *Conium* alkaloids (coniine, γ-coniceine) were determined in the hay, the plants of the hayfield and the urine of affected animals. Congenital skeletal malformations in calves from ingestion of hemlock have been reported. Skeletal malformations were induced in calves both with fresh plants and with pure coniine (Keeler, 1977; Keeler and Balls, 1978; Keeler et al., 1980). According to the latest experiments: clinical signs of toxicity became evident about 30–40 min after orally dosing. Animals first became nervous and shortly developed tremors and the animals had an ataxic gait. These signs lasted each day for 6–7 h in cows. After three to four days of administration of coniine the animals developed persistent signs of depression. Terata induced in calves included severe carpal flexure, rotation of the forelimbs elbow joint rigidity and curvature of the vertebral column. Elimination of plant toxicants via milk by lactating animals is considered a minor route of excretion, however, it may be important when the health of the neonate or food safety in humans is considered. The alkaloids of *Conium maculatum* can be excreted via the milk in cattle (Panter and James, 1990).

5.2. Sheep

Fresh plant material administrated to sheep (Panter et al., 1988a,b) at doses 10 g/kg body weight was lethal, pure coniine (injected i.m.) was lethal at 240 mg/kg BW (Keeler et al., 1980). The general symptoms of poisoning for sheep are: ataxia, carpal joint, frequent urination and defecation, salivation, kinked tail, trembling, weakness, death. Fetal movements in pregnant ewes gavaged with hemlock twice daily for 30 days (5–10 g/kg body weight) were reduced significantly, but temporarily (Panter et al., 1988a). Fetal movement was observed by sonography on days 45, 54 and 60 of gestation, immediately before and 1 h following hemlock feeding. The fetal movement was significantly reduced after hemlock administration, but returned to normal level within 18 h after treatment. Seven of eleven lambs born to seven treated ewes had varying degrees of front limb abnormalities (moderate flexure of the carpal joints, lateral deviation in the front limbs, etc.) but these malformations were resolved spontaneously by eight weeks after lambing. The maternal effects of hemlock treatment (Panter et al., 1988b) included trembling, muscular weakness in the neck initially, then progressing to the limbs, ataxia, frequent urination, defecation and death.

5.3. Goat

The effect of *Conium maculatum* on adult goats was published in a classical work (Copithorne, 1937). The degree of acute toxicity of fresh plant to goats: cattle > sheep = goats > pigs (Lopez et al., 1999). Fetal movement was significantly reduced in pregnant goats gavaged with seeds and was temporarily reduced with fresh *Conium* plants (Panter et al., 1990a). *Conium* seed induced cleft palate and multiple congenital contractures in all kids born to pregnant, with hemlock treated goats (Panter et al., 1990b). Multiple congenital contractures included torticollis, scoliosis, lordosis, arthrogryposis, rib cage anomalies, over extension and flexure and rigidity of the joints. However, in animals gavaged with fresh plants, fetal movement was inhibited for only about 5 h after each individual dosage and gradually returned to control levels 12 h after treatment.

5.4. Swine

The ingestion of hemlock by pigs causes toxicosis. The clinical signs included ataxia, tremors, severe lacrimation, mydriasis, tachycardia, polypnea and fever (Widmer, 1984). The boar was recumbent and exhibiting tonic/clonic movements in both rear legs. The faeces were well-formed and dark green. The symptoms of hemlock toxicosis in the pig was described (Hannam, 1985). Two sows were ataxic and trembling. Both recovered, but 10 days later one suffered a relapse. These two sows subsequently farrowed and produced litters of 18 and 17 piglets. In the first litter, six animals showed tremors but were able to walk, the seventh showed congenital articular rigidity in all four limbs or in the hindlimbs only. In the second litter, four pigs could walk and the others were malformed. All the malformed piglets showed tremors. Five gilts and two more sows had also been exposed to hemlock during pregnancy. One of the gilts produced a normal litter, but the other five suffered 50% malformation in their litter. Skeletal malformations were induced in newborn pigs from gilts fed poisonous hemlock seed or plant during gestation days 43–53 and 51–61 (Panter et al., 1985). The teratogenic effects in the first group were more severe than those in the second one, with many newly born pigs showing arthrogryposis and twisted and maligned bones in the limb. One of the pigs shows scoliosis and defor-

mity of the thoractic cage. It is suggested the γ-coniceine is the teratogenic alkaloid.

5.5. Rabbit

The literature has only limited information on toxicity of *Conium maculatum* in the rabbit. Of four rabbits accidentally fed large amount of hemlock, two died within 3 h, one became weak and ataxic, and the last was not affected (Short and Edwards, 1989). Pregnant rabbits were given coniine (40 mg/kg BW) by oral gavage at 8-h intervals on gestation days 20–24 (Forsyth and Frank, 1993). The animals were killed on day 29, fetuses were immediately removed, weighed and examined for external abnormalities. Animals treated with coniine appeared to lose more weight and eat less than controls. The only statistically significant visceral or skeletal malformation was a reduction in cranial ossification of rabbit fetuses. Coniine-treated rabbit litters tended to be affected by artrogryposis more than controls.

5.6. Elk

Sixteen (16) tule elk of the 120 residents died from hemlock poisoning (Jessup et al., 1986). Symptoms included depression, recumbence, paralysis, groaning, tooth grinding, reduced heart rate, dyspnoea, hypersalivation. Some died suddenly, others struggled for one or two days. The cytological and the chemical composition of blood were normal apart from increased packed cell volume, aspartate transaminase, alanine transaminase, lactic dehydrogenase activities, and total protein concentration. The animals had eaten roots, stems and leaves. The rumen contents in general and the carrot-like roots in particular had the strong aromatic mousy odour associated with *Conium maculatum*. Percentages of forages types consumed by three elk were 38–84% (!) hemlock. The total alkaloid concentration was greater in roots (5 mg/g DW) than in green parts of the plant (0.2 mg/g DW). The alkaloids in the hemlock leaves and stems consisted of 22% coniine, 76% γ-coniceine and 1.9% other type; in the roots were 6% coniine and 94% other type.

5.7. Poultry and insects

The effect of coniine (concentrations: 0.015%, 0.030%, 0.075%, 0.15%, 0.75%, 1.5%, 3% and 6%) was investigated on the developing chick (Frank and Reed, 1990). The deformations caused by coniine were excessive flexion or extension of one or more toes. No histopathological differences or alterations in bone formation were seen in the limbs or toes from any group. The chick embryo provides a simple experimental animal model of coniine-induced arthrogryopsis. Coniine was administrated (Frank and Reed, 1987) to three-week-old chickens, turkeys and six-week-old quails at 0, 25, 50 and 100 mg/kg BW respectively. At 25 mg/kg coniine treatment clinical signs were observed only in some quails (excitement, depression, hypermetria, seizures, opisthonus and flaccid paralysis). Chickens (9/10) and quails (8/10) dosed at 50 mg/kg BW were affected and several animals of each species died (2/10 and 5/10). The most resistant were the turkeys because they were affected only when dosed at 100 mg/kg BW, 4 of 10 animals died. Coniine was detected in skeletal muscle and liver of birds and was present in some survivors seven days after coniine treatment. The general symptoms of hemlock poisoning at turkeys are weakness, diarrhoea, enteritis, paralysis, salivation congestion of kidney, liver and lungs, and death. Skylarks, chaffinches and robins are not susceptible to coniine (Scatizzi et al., 1993).

Some insects attack the plant *Conium maculatum*. *Agonopterix alstroemeriana* (*Oecophoridae*) has been reported infesting poison *hemlock* (Berenbaum and Harrison, 1994). In addition, the plant was recorded as a food plant of *Polyphagous lepidopterans*, *Eupitheca miserulata*, *Spilosoma virginica*, and others.

One of the *Conium* alkaloids, coniine was bioassayed for toxicity, growth inhibition and feeding deterrency in the polyphagous insect species *Heliothis zea* (Nitao, 1987). Contrary to expectations, coniine showed no biological activity toward *Heliothis zea* at the concentrations tested.

5.8. Human toxicosis

The plant *Conium maculatum* was famous as a poison and its extract was used often to execute criminals or political prisoners in ancient Greece (Holm, 1997; Scutchfield and Genovese, 1997). Symptoms described by Socrates were: a rapid loss of power of the lower extremities (muscular weakness) ataxia, staggering and trembling. As the effects ascended, there was loss of control of the upper extremities. Total paralysis of the legs and arms followed. There was loss of the power to chew and loss of sensation and the pupils became fixed. Finally, death was due to paralysis of respiration and asphyxia; the intellect was clear until death occurred (Panter and Keeler, 1989). A hemlock poisoning is recorded in humans who have mistakenly eaten the leaves of the plants for parsley (*Petroselinum crispum*) or the roots for parsnips (*Pastinaca sativa*), or the seeds for anise (*Pimpinella anisum*). The primary action on hemlock is on the central nervous system. The effect of the plant is similar to poisoning with nicotine. The general symptoms of hemlock poisoning are nervousness, trembling, problems in movement, particularly in the legs of humans, dilation of pupils, slow and weak pulse (becoming later rapid), rapid respiration, heavy

salivation, frequent urination, nausea, convulsions, decrease of the body temperature. Severe poisoning may cause coma and the death from respiratory failure (Mitich, 1998; Biberci et al., 2002). The symptoms of human poisoning are in general the same as of the animals, but the acute renal failure seems to be a symptom only of the human poisoning. The history of the cases of human poisoning is very interested and instructive. The deaths of two young men and one three-year-old boy was described (Drummer et al., 1995). These two men were found dead in Australia, on New Year's Day 1993. Both had consumed large amount of alcohol and they returned at midnight carrying a quantity of green plants. They were seen boiling this leaf material in a pot full of water and they were not seen until their discovery. Both men showed moderate to marked congestion of the lungs and in one of the men there was a small amount of mucus in the left main bronchus, and both showed liver congestion. According to the results of the toxicological examinations: the presence of ethanol, and 11-carboxy-tetrahydrocannabinol in blood and of γ-coniceine in blood and urine was confirmed. The γ-coniceine was also detected in the gastric content of one patient. The second case: four children ate the green leaf of a plant known locally as "carrot weed". A three-year-old boy consumed a quantity of leaf material, the others spat out the leaves. One hour and 10 min after consuming he appeared to wake and to fall asleep. Ninety minutes later the boy was found dead, all attempts to resuscitate being unsuccessful. The post-mortem examination established that the stomach contained 142 g of partly digested plant material, which was also present in the oesophagus. The plant material in the stomach was found to contain the γ-coniceine and the conhydrinone the first was also detected in the blood of the boy. Eleven patients showed characteristic symptoms, including nicotine-like effects and intense muscle pain, with rapid swelling and stiffening of muscles (Rizzi et al., 1989). Histological examination established coarse vacuolisations of myocyte sarcoplasma, multifocal necrosis of myocytes and macrophage infiltration. Three of the eleven patients died. Another case of hemlock poisoning of children was described (Frank et al., 1995). A four-year-old boy and his father ingested the green leaves of a "wild carrot". Within 30 min the child became sleepy and took a nap. Two hours later the patient had vomited green material. The patient's pulse was 100 beats per minute the respiratory rate was 26 per minute. His pupils were small and reactive. The lungs, heart and abdomen were unremarkable; there were no signs of trauma. On neurological examination there was semi-purposeful response to noxious stimuli in the upper extremities and withdrawal in the lower extremities. The parameters of the blood were within the normal limits the toxicological screen was negative. Due to the therapy (lavage of stomach, activated charcoal-treatment, infusions) within 4 h he was awake and talking to his parents. Later, the plant was identified as a poison hemlock, and 850 μg/g fresh w. of γ-coniceine content was established. Nowadays in Turkey, the incidence of plant poisoning is about 6% and especially high among the children between ages 2 and 11 living in rural areas. The plant *Conium maculatum* is standing on the third place in the frequency often the plant poisonings (Oztekin, 1994).

The human hemlock poisonings were studied (Rizzi et al., 1991). In the non-rapidly fatal cases they tested myoglobinuria, serum muscle enzymes and renal function. In the patients with acute renal failure were performed microscopic examination of kidney; immunohistochemistry was performed to identify myoglobin and actin in tubules. The alkaloid coniine was detected in urine, serum or tissues. Neurological features were presented in all of the cases coniine had a curare-like effect on the neuromuscular junction. Acute renal failure was observed in five patients (5/17).

The mechanism of action of *Conium* alkaloids is twofold. The most problematical effect occurs at the neuromuscular junction where they act as non-depolarizing blockers, similar to curare (Bowman and Snaghvi, 1963). Death is usually caused by respiratory failure. The *Conium* alkaloids produce a biphasic nicotine-like effect, including salivation, mydriasis and tachycardia followed by brachycardia. Coniine can produce rhabdomyolysis by either a direct toxic effect on skeletal muscle or a strychnine-like pro-consulvant action on the central nervous system (Scatizzi et al., 1993).

6. Structure–activity relationship of *Conium* alkaloids

The chemical structure determines the teratogenic effect of hemlock. The side chain of the molecule must be at least a propyl-group. According to the experiments (Keeler and Balls, 1978) coniine, γ-coniceine and *N*-methyl-coniine were teratogenic, other homologous substances were not. No information has been found considering the acute toxicity and the structure of the alkaloids.

7. Management and control of the plant

The hemlock belongs to the invasive weed species, has wide adaptations ability. The biological control of the plant is a theoretical possibility only. The hemlock is infected often by one or more virus strains such as ringspot virus, carrot thin leaf virus (CTLV), alfalfa mosaic virus (AMV) or celery mosaic virus (CeMV) (Howell and Mink, 1981). The methods of using viral infection or phytophagous insects to control and remove the plant need more research. The mechanical control of

the plant means hand pulling or grubbing. Hand pulling works are easier with wet soils and with small infestations. It is best to pull or grub out the plant prior to flowering (Parsons, 1973). If extensive areas are covered by hemlock, chemical control is simpler. In this case one can use a synthetic auxin-like compound, such as 2,4-D (2,4-dichloro-phenoxy-acetic acid), which practically does not kill grasses (few exceptions are only). However, hemlock is a prolific seed producer, and a repeated in next year may be needed to achieve complete control. In alfalfa the poison hemlock can be controlled with other selective herbicide such as hexazone (Panter and Keeler, 1989).

Some management guidelines can be followed to minimalize chance and probability of plant toxicosis. One should prevent the pregnant animals from grazing the plant prior to day 70 of gestation in the cow or day 60 in the pig, because these are the critical stages when developmental problems may occur.

8. Economic importance

Poisoning of animals by poison hemlock can cause great losses. The losses can be direct (death, performance and reproduction losses; Panter et al., 2002) and indirect ones (costs incurred by a livestock enterprise in trying to prevent poisoning or costs incident to poisoning). The economic losses can only be estimated, because most deaths from plants go undiagnosed and unreported. *Conium maculatum* contributes to the overall livestock loss from poisonous plants, estimated to be over $100 million annually in the United States (Nielsen and James, 1985; James et al., 1992).

9. Conclusions

(1) *Conium maculatum* is a very common weed species of invasive character, i.e. the habitat of the plant is increasing. The plant grows first of all on soil with higher or nitrogen content, it is said to be a nitrophile species. Its chemical control (for example by auxin-like compounds) seems to be the most economic and relative safe method.

(2) *Conium maculatum* has a very significant capacity to synthesize the alkaloids of piperidine type. The main component is coniine the production of which is localized in different types of plant tissues.

(3) There are two types of animal poisoning: the acute and the chronic ones. The acute type is observed when the animals ingest some vegetative parts or seeds of plant. The alkaloids produce a neuromusculare blockage which can stop the function of the respiratory muscles. The chronic toxicity affect the pregnant animals only, the offspring is born with different malformations (mainly with MCC = multiple congenital contractures).

(4) The cause of a human toxicosis is probably usually the mistaken ingestion of the plant (fresh leaves or seeds). The seriousness of hemlock poisoning and the prospects of recovery are determined by ingested quality, alkaloid concentration and the general condition of the organism. The probability of a mistaken ingestion of the plant can minimised by better management and control as well as by a better identification of the plant.

(5) The economic (direct and indirect) losses, caused by hemlock poisoning, are not negligible, there are numerous tasks for the experts.

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