

Review

FACTS ABOUT NICOTINE TOXICITY

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Nicotine is an alkaloid obtained from the leaves of the tobacco plant, and it is the main constituent of tobacco smoke. This review opens with physical and chemical properties of nicotine and with general considerations about the methods for determining nicotine and its metabolite cotinine. It summarises the data about acute and long-term toxicity of nicotine and also reviews its metabolism and kinetic data, types of exposure and the main recognised health effects, with special attention to reproductive, cardiovascular, pulmonary, gastrointestinal, immunological and genetic toxicity. The main focus is on hazardous exposure and risk estimation.

KEY WORDS: *acute toxicity, exposure, long-term toxicity, NOAEL, risk estimation, risk evaluation*

Nicotine is a naturally occurring alkaloid found primarily in the members of the *Solanaceae* family, which includes tobacco, potato, tomato, green pepper, and eggplant. Nicotine was first isolated and determined to be the major constituent of tobacco in 1828 (1). In commercial tobaccos, the major alkaloid is nicotine, accounting for about 95 % of the total alkaloid content (2). Tobacco use is the leading cause of death in the world today. With 4.9 million tobacco-related deaths per year, no other consumer product is as dangerous or kills as many people as tobacco (3).

PHYSICAL AND CHEMICAL DATA (4)

Chemical formula: $C_{10}H_{14}N_2$

IUPAC name: 3-[2-(N-methylpyrrolidinyl)]pyridine

Appearance: oily, colourless hygroscopic liquid, with characteristic odour, turns brown on exposure to air

Boiling point (decomposes): 247 °C

Density: 1.01 g cm⁻³

Solubility in water: miscible

Vapour pressure at 20 °C: 0.006 kPa

Octanol/water partition coefficient as log P_{ow} : 1.2

TOXICOKINETICS

Absorption of nicotine

Nicotine absorption can occur through the oral cavity, skin, lung, urinary bladder, and gastrointestinal tract (5). Absorption of nicotine across biological membranes depends on pH (5). In its ionised state, such as in acidic environments, nicotine does not rapidly cross membranes. The respiratory absorption of nicotine is 60 % to 80 % (6). The rapid absorption of nicotine from cigarette smoke through the lung occurs because of the huge surface area of the alveoli and because of dissolution of nicotine at physiological pH (approximately 7.4), which facilitates transfer across cell membranes. Absorption through the alveoli is also dependent on the nicotine concentration in the smoke. Nicotine is poorly absorbed from the stomach due to the acidity of the gastric fluid, but is well absorbed in the small intestine, which has a more alkaline pH and a large surface area (5). Nicotine base can be absorbed through the skin, and there have been cases of poisoning after skin contact with pesticides containing nicotine (7, 8). Likewise, there is evidence of cutaneous absorption of and toxicity from nicotine in tobacco field workers (6).

Metabolism of nicotine

In most people nicotine is 70 % to 80 % metabolised to cotinine by C-oxidation. The proposed mechanism of conversion of nicotine to cotinine involves hydroxylation of nicotine by cytochrome P450-dependent monooxygenases (CYP) and conversion to the corresponding aldehyde and production of cotinine by a cytosolic enzyme (5). The enzymes involved in the C-oxidation of nicotine have mostly been identified. The most important enzyme in the C-oxidation of nicotine leading to cotinine formation is CYP2A6 (9, 10). Other pathways of nicotine metabolism involve formation of nornicotine, demethyl cotinine, trans-3-hydroxy-cotinine and δ -(3-pyridyl)- γ -methylaminobutyric acid, N-oxidation and N-methylation of nicotine. The phase II metabolism involves N- and O-glucuronidation of nicotine and its metabolites (5).

Distribution of nicotine in body tissues

The pattern of tissue uptake, examined in tissues of rabbits by measuring concentrations of nicotine in various tissues after 24-hr constant i.v. infusion of nicotine, showed that spleen, liver, lungs, and brain have high affinity for nicotine, whereas the affinity of adipose tissue is relatively low (11). Nicotine readily crosses the placenta and the foetuses of mothers who smoke are exposed to higher nicotine concentrations than their mothers (12).

Nicotine excretion

It has been demonstrated that nicotine is excreted through urine, faeces, bile, saliva, gastric juice, sweat, and breast fluid (13, 14). When ^{14}C -nicotine is given to an animal, it has been shown that about 55 % of the radioactivity is excreted in the urine. However, only 1 % of the radioactivity was observed in the form of unchanged nicotine. This result demonstrates that nicotine is excreted following extensive metabolism. Nicotine disappears rapidly from the blood, with a half-life of 2 h to 3 h in humans (6). Nicotine and cotinine are also detected in the urine of infants whose mothers smoke, indicating that exposure of mothers to tobacco smoke reaches the infant (15). In another study, researchers reported that the daily nicotine intake was 18 % higher in persons with increased nicotine excretion and concluded that the rate of elimination of nicotine affects the rate of consumption (16). The rate of nicotine excretion is also influenced

by the pH of the urine. When the pH of the urine is made alkaline, the proportion of uncharged nicotine increases and reabsorption of nicotine occurs and as a result, less nicotine is excreted (17).

METHOD OF ANALYSIS IN BIOLOGICAL SAMPLES

Several biological markers have been proposed for nicotine exposure assessment. The most widely used markers are nicotine in the urine, hair, saliva and plasma; and cotinine, a major nicotine metabolite, in the urine, saliva and plasma (18). Urine cotinine is currently one of the most widely used biomarkers for nicotine exposure, but the main disadvantages are inter-individual variability in cotinine excretion levels for similar exposures and a relatively short half-life (19). Nicotine and cotinine in body fluids indicate only recent exposure because of their rapid elimination (the half life of cotinine in body fluids is about 15 h, compared with 2 h for nicotine) (20). Their concentrations from hair, by contrast, can provide measures of cumulative, long-term exposure (20).

A wide variety of methods for the analysis of nicotine and cotinine in biological samples have been published: gas chromatography coupled by nitrogen-phosphorus detector or mass-spectrometer, high-performance liquid chromatography, radioimmunoassay and enzyme linked immunosorbent assay (21).

TOXICITY DATA AND TOXICITY EVALUATION

General toxicity

Acute toxicity

In experimental animals, the dose of nicotine which is lethal to 50 % of the animals (LD_{50}) varies widely, depending on the route of administration and the species used. The intravenous (i.v.) LD_{50} dose of nicotine in mice is 7.1 mg kg^{-1} body weight (22). By direct i.v. administration the LD_{50} to rats was determined to 1 mg kg^{-1} (23). The intraperitoneal (i.p.) LD_{50} values for nicotine in mice and rats have been found to be 5.9 mg kg^{-1} and 14.6 mg kg^{-1} , respectively (22). The oral LD_{50} dose for nicotine in rats is 50 mg kg^{-1} to 60 mg kg^{-1} (24). The wide variation in sensitivity to the toxic effects of nicotine in rodents appears to be genetically determined (25). Dermal acute toxicity

(LD₅₀) in rabbits is 140 mg kg⁻¹ (26). In interpreting animal toxicity data it is important to recognise that the route of administration is an important determinant of toxicity. Rapid i.v. injections result in the highest blood and brain concentrations and produce toxicity at the lowest doses. In contrast, oral or i.p. administration require higher doses to produce toxicity. This is due in part to pre-systemic ("first pass") metabolism of nicotine whereby, after absorption into the portal venous circulation, nicotine is metabolised by the liver before it reaches the systemic venous circulation.

Probable oral lethal dose in humans is less than 5 mg kg⁻¹ or a taste (less than 7 drops) for a 70 kg person (27). It may be assumed that ingestion of 40 mg to 60 mg of nicotine is lethal to humans (27). No inhalation toxicity data are available on which to base an *immediately dangerous to life or health concentration* (IDLH) for nicotine. Therefore, the revised IDLH for nicotine is 5 mg m⁻³ based on acute oral toxicity data in humans and animals (28).

A number of poisonings and deaths from ingestion of nicotine, primarily involving nicotine-containing pesticides, have been reported in humans (6). Nicotine poisoning produces nausea, vomiting, abdominal pain, diarrhoea, headaches, sweating, and pallor. More severe poisoning results in dizziness, weakness, and confusion, progressing to convulsions, hypotension, and coma. Death is usually due to paralysis of respiratory muscles and/or central respiratory failure. Dermal exposure to nicotine can also lead to poisoning. Such exposures have been reported after spilling or applying nicotine-containing insecticides on the skin or clothes and as a consequence of occupational contact with tobacco leaves (6, 8). Acute intoxication may occur in children following ingestion of tobacco materials. Four children, each of whom ingested two cigarettes, developed salivation, vomiting, diarrhoea, tachypnoea, tachycardia, and hypertension within 30 min, followed by depressed respiration and cardiac arrhythmia within 40 min and convulsions within 60 min (29). All recovered and suffered no complication. Although ingestions of tobacco are common, deaths due to ingestion of tobacco are extremely rare, due to early vomiting and first pass metabolism of the nicotine that is absorbed.

Long-term toxicity

As attested to in the U.S. Surgeon General's reports since 1964, smoking causes coronary and peripheral vascular disease, cancer, chronic obstructive lung

disease, peptic ulcer disease, and reproductive disturbances, including prematurity (30). Nicotine may contribute to tobacco-related disease, but direct causation has not been determined because nicotine is taken up simultaneously with a multitude of other potentially harmful substances that occur in tobacco smoke and smokeless tobacco. However, particularly now that nicotine may be prescribed in the form of gum or other delivery systems, the potential health consequences of chronic nicotine exposure deserve careful consideration.

Reproductive toxicity

Teratogenicity

Nicotine rapidly crosses the placenta and enters the foetus (12). *Khan et al.* (31) have described teratogenic effects of high doses of nicotine, which interfered with skeletogenesis in mice and chick embryos. In animal studies designed to investigate neurotoxic effects, nicotine was found to target neurotransmitter receptors in the foetal brain, leading to reduced cell proliferation and, consequently, altered synaptic activity. *Sandberg et al.* (32) found that prenatal exposure to nicotine (1.5 mg kg⁻¹ per day during the last foetal trimester) induced structural changes in the lungs of foetal lamb.

On the basis of animal studies, it appears that nicotine acts on the respiratory and central nervous systems of the foetus and concentrates in maternal and foetal blood, amniotic fluid, and breast milk (33). Nicotine may have a direct toxic effect on the foetal cardiovascular system resulting in reduced blood flow (34).

Pregnancy

Exposure to nicotine in rhesus monkeys has been shown to decrease tubal motility, which may increase the chance of tubal implantation and ectopic pregnancy (35). In rats, nicotine caused pregnancy failure after dermal application of relatively low levels (1.75 mg kg⁻¹ bw per day) throughout gestation (6).

A likely mechanism for the reproductive problems in pregnant cigarette smokers is placental insufficiency, which is supported by the evidence of placental hypoperfusion in cigarette smoking mothers (36). Nicotine may have a direct toxic effect on the foetal cardiovascular system resulting in reduced blood flow (34). Maternal smoking during pregnancy is a major risk factor for sudden infant death syndrome

(SIDS), with nicotine likely to be the active agent (37). Foetal hypoxemia has also been considered as a contributory cause of behavioural abnormalities, such as hyperactivity, short attention span, lower scores on spelling and reading tests, which occurred at a higher frequency in children whose mothers had smoked throughout pregnancy than in those born to nonsmoking mothers (37).

Genotoxicity and carcinogenicity

Studies evaluated the genotoxic potentials of nicotine by Salmonella mutagenicity assay and in the Chinese hamster ovary sister-chromatid exchange (SCE) assay (38). All assays were conducted with and without S9 metabolic activation. Nicotine was not able to induce mutations or sister chromatid exchange in these experimental systems. However, opposite results were established in another study using Chinese hamster ovary cells (39). Nicotine was reported to increase chromosome aberrations and sister chromatid exchange frequency in a dose- and time-dependent manner in Chinese hamster ovary cells, and it was concluded that nicotine acted as a clastogen. It was also reported that nicotine was genotoxic at the concentrations found in saliva achieved during tobacco chewing (39). Nicotine was found as a co-carcinogen in animals (27).

Cardiovascular disease

Nicotine plays an important role in the development of cardiovascular disease. It could promote atherosclerotic disease by its actions on lipid metabolism and coagulation, by haemodynamic effects, and/or by causing endothelial injury. Compared to nonsmokers, cigarette smokers have elevated low-density (LDL) and very-low-density lipoproteins (VLDL), as well as reduced high-density lipoprotein (HDL) levels, a profile associated with an increased risk of atherosclerosis (40). Lipid peroxidation and generation of free radicals, increased in smokers, are the processes associated with the pathogenesis of atherosclerosis. The products of lipid peroxidation may cause irreversible damage to the membrane structure of the cells. Some studies show that nicotine administration to animals results in endothelial cell abnormalities and decreases the synthesis of prostacyclin (an inhibitor of platelet aggregation) (41). Nicotine increases heart rate through the activation of the sympathetic nervous system (40).

Pulmonary toxicity

Cigarette smoking is the major cause of chronic obstructive lung disease (30). Nicotine, which is readily absorbed from the lung and distributed to tissue, including bone marrow, increases the expression of the elastase gene, leading to increased elastase protein concentration per cell, suggesting a pathophysiologic mechanism for emphysema (42). Inhaled nicotine produces a concentration-dependent cough and airway obstruction in healthy subjects, probably because of stimulation of afferent nerve endings in the bronchial mucosa and mediated through parasympathetic cholinergic pathways (43).

Immunotoxicity

There is some evidence that nicotine administration *in vitro* can produce changes in immunocytes. Although the majority of the above studies suggest an *in vitro* effect of nicotine on immunocytes, little direct evidence exists regarding the *in vivo* action of nicotine on the immune system (44). Regarding the possible mechanisms that might mediate the effects of nicotine on the immune function, some have suggested that one consequence of the glucocorticoid hypersecretion produced by nicotine exposure, such as that experienced by habitual smokers, is the suppression of the immune system (45).

Gastrointestinal toxicity

Normally, the gastrointestinal mucosa is protected from injury by a layer of mucus and by the secretion of bicarbonate by gastric and duodenal epithelial cells to neutralize gastric acid. If these protective mechanisms are impaired, or if there is an increase in the levels of damaging factors, then ulceration may occur. Nicotine and other components of cigarette increase the reflux of duodenal contents into the stomach and mouth, decrease the secretion of pancreatic bicarbonate, decrease the production of gastric mucus and cytoprotective prostaglandins, and perhaps increase the production of free radicals and the release of vasopressin, a potent vasoconstrictor (46, 47).

EXPOSURE

Tobacco smoke is the main source of nicotine exposure. According to European Community Directive 2001/37/EC, nicotine content is limited to a

Table 1 Nicotine content in common vegetables

Vegetable	Highest reported mean nicotine content / ng g ⁻¹	Reference	Amount of vegetable required to obtain 1 µg of nicotine* / g
Cauliflower	3.8	Domino <i>et al.</i> (49)	263.4
Eggplant	100.0	Castro and Morji (50)	10.0
Potatoes	7.1	Domino <i>et al.</i> (49)	140.4
Green tomatoes	42.8	Castro and Morji (50)	23.4
Red tomatoes	10.7	Sheen (51)	93.5

*One microgram of nicotine is the amount a passive smoker would absorb in about three hours in a room with a minimal amount of tobacco smoke.

maximum of 1 mg per cigarette from 1 January 2004. Seventy five percent or more of nicotine emitted from a cigarette is emitted into the air as sidestream smoke, which contributes substantially to environmental tobacco smoke (ETS). Nicotine in ETS is inhaled into the lungs by nonsmokers. The data of *Jarvis et al.* (48) on adults attending London hospital are an example of estimating daily nicotine intake from ETS. Using urine concentrations, the estimated daily intake of nicotine by nonsmokers was 100 µg for those reporting passive exposure and 20 µg for those reporting no exposure to ETS.

As already mentioned, nicotine is present in certain human foods, especially plants from the family *Solanaceae* (potatoes, tomatoes, and eggplant) (Table 1.).

HAZARDOUS EXPOSURE AND RISK ESTIMATION

Human data

A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20 °C resulting in nausea, vomiting, convulsions, abdominal pain, diarrhoea, headache, sweating, weakness, dizziness and confusion. Nicotine irritates the eyes and the skin and may cause effects on the cardiovascular system and central nervous system, resulting in convulsions and respiratory failure. Exposure far above the observed effect level may result in death. The effects of nicotine may be delayed, so medical monitoring is indicated. Acute toxic effects from nicotine generally result from oral exposure (4). Nicotine is highly toxic with nausea occurring from exposure to 2 mg to 5 mg and deaths were reported in adults from ingested quantities of 40 mg to 60 mg.

Infants are especially susceptible to nicotine toxicity. The ingestion of one or more fresh cigarettes is considered potentially toxic.

Chronic toxicity that may be caused by prolonged exposure to small doses occurs in smoking (27). Maternal smoking during pregnancy is associated with increased risk of spontaneous abortion, low birth weight and stillbirth (6). Mechanisms include the reduction of uteroplacental blood flow and direct effects on developing foetal brain. In case-control studies, there was no association between spraying nicotine and the incidence of multiple myeloma in farmers; neither was there a convincing association between spraying nicotine and the incidence of leukaemia (6).

Workplace level of nicotine in the air due to ETS is 20 µg m⁻³. The dose of nicotine inhaled is equal to the product of air concentration and ventilation rate. A typical ventilation rate for an adult during light activity is 1 m³ per hour. Thus, the intake of nicotine would be about 20 µg per hour. About 71 % of nicotine that is inhaled is absorbed, so the systemic dose of nicotine is estimated to be about 14 µg per hour. Assuming an eight-hour workplace exposure, this would be equivalent to 112 µg per day (52). Air nicotine levels measured by *Hammond et al.* (53) over nine hours at 11 Massachusetts office worksites that allowed smoking, indicated a median level of 8.6 µg m⁻³. The estimated absorption of nicotine from this level of exposure over nine hours is 55 µg. In office workplaces that banned smoking, the median air nicotine level was 0.3 µg m⁻³. The National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL) and the American Conference of Governmental Industrial Hygienists' (ACGIH) Threshold Limit Value (TLV) for nicotine are 500 µg m⁻³ (27). A model used to derive a health-based standard for ETS has shown that an

eight-hour, time-weighted average exposure to 2.3 $\mu\text{g m}^{-3}$ of nicotine would correspond to three lung cancer deaths among 10,000 exposed people over a working lifetime (54).

Average nicotine daily intake (i. e. absorbed dose) from significant ETS plus dietary exposure is about 80 μg and even a diet rich in nicotine-containing food is only 10 % of the total nicotine exposure (55).

RISK EVALUATION

In 2004, The Committee on Updating of Occupational Exposure Limits (6) considered the no-observed-adverse-effect level (NOAEL) of 0.5 mg m^{-3} from a two-year inhalation rat study as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). The Committee noted that the actual NOAEL might be higher since exposure was for 20 h a day and only one concentration was tested. Since workers are supposed to be exposed for maximally eight hours a day, this NOAEL is adjusted, resulting in a 1.25 mg m^{-3} . For the extrapolation to a HBROEL, the Committee established an overall assessment factor of 9. This factor covered intra- and interspecies variation. Thus, applying this factor of 9 and the preferred-value approach, a health-based occupational exposure limit of 0.1 mg m^{-3} was recommended for nicotine. The Committee recommended a health-based occupational exposure limit for nicotine of 0.1 mg m^{-3} , as an eight-hour time-weighted average (TWA). Because of the high skin absorption potential of nicotine, the committee advised a skin notation. After the final report was published in March 2004, the Health Council received comments which were taken into account in deciding on revised version published in 2005. The committee considered NOAEL of 0.5 mg m^{-3} , implying that this two-year inhalation rat study does not provide information on the lowest exposure level at which adverse effects are becoming manifest. Therefore, the committee considered this study inappropriate for deriving a health-based occupational exposure limit (56). The current occupational exposure limit for nicotine in Croatia is 0.5 mg m^{-3} (57).

The risk of occupational exposure is low if protective measures are applied (eye protection in combination with breathing protection, protective gloves and clothing, and ventilation). The human health risk from environmental exposure to nicotine is high because

nicotine is widespread in the environment through tobacco smoke.

It is very important to point out that with intermittent dosing, such as practiced by smokers, the total dose of nicotine absorbed per day could exceed the toxic or even lethal dose of a single injection.

As previously described, food is a source of low-level nicotine exposure and for most people it represents an insignificant exposure compared with exposure to ETS.

CONCLUSION

Tobacco smoke contains more than 3,800 different compounds. Although all of these substances affect exposed humans to some degree, nicotine is generally considered to be the primary substance responsible for the pharmacological responses to smoking. In many countries tobacco smoking is recognised as a serious health hazard and a major contributing factor to deaths from a number of common diseases. Because of that, knowledge of the toxicity of nicotine is important to help understand tobacco-induced human disease as well as to assess the potential risks associated with the therapeutic use of nicotine as an aid in quitting smoking. Nicotine as a biomarker is very important for quantifying human exposure to environmental tobacco smoke (ETS) and for predicting potential health risks for exposed individuals. Passive smoking is a real and significant threat to public health. The first step is the promotion of effective measures protecting from indoor exposure to tobacco smoke at the workplace, in public transport, and other public places.

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Sažetak

TOKSIČNOST NIKOTINA

Nikotin je alkaloid iz lišća duhana i glavni sastojak duhanskog dima. U prvom dijelu rada opisana su fizička i kemijska svojstva nikotina, metode određivanja nikotina i kotinina, glavnog i specifičnog metabolita nikotina u biološkim uzorcima, apsorpcija, raspodjela, biotransformacija i izlučivanje nikotina. Navedeni su podaci za akutnu i kroničnu toksičnost nikotina te podaci o zdravstvenim učincima nikotina na reprodukcijski, krvožilni, dišni, gastrointestinalni i imunosni sustav. Opisan je rizik izloženosti ljudi kao posljedica udisanja duhanskog dima i uzimanja hrane koja sadržava nikotin. Na kraju je opisano donošenje pravilnika kojim se propisuje maksimalno dopuštena koncentracija nikotina u zraku radnih prostorija i prostora, koja prema sadašnjem stupnju saznanja ne izaziva oštećenje zdravlja zaposlenih.

KLJUČNE RIJEČI: *akutna toksičnost, izloženost, kronična toksičnost, NOAEL, ocjenjivanje rizika, procjena rizika*

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