Nicotine

1. NAME
   1.1 Substance
   1.2 Group
   1.3 Synonyms
   1.4 Identification numbers
      1.4.1 CAS number
      1.4.2 Other numbers
   1.5 Brand names, Trade names
   1.6 Manufacturers, Importers

2. SUMMARY
   2.1 Main risks and target organs
   2.2 Summary of clinical effects
   2.3 Diagnosis
   2.4 First-aid measures and management principles

3. PHYSICO-CHEMICAL PROPERTIES
   3.1 Origin of the substance
   3.2 Chemical structure
   3.3 Physical properties
   3.4 Other characteristics

4. USES/CIRCUMSTANCES OF POISONING
   4.1 Uses
4.2 High risk circumstance of poisoning
4.3 Occupationally exposed populations

5. ROUTES OF ENTRY

5.1 Oral
5.2 Inhalation
5.3 Dermal
5.4 Eye
5.5 Parenteral
5.6 Others

6. KINETICS

6.1 Absorption by route of exposure
6.2 Distribution by route of exposure
6.3 Biological half-life by route of exposure
6.4 Metabolism
6.5 Elimination by route of exposure

7. TOXICOLOGY

7.1 Mode of Action
7.2 Toxicity

7.2.1 Human data
7.2.1.1 Adults
7.2.1.2 Children
7.2.2 Relevant animal data
7.2.3 Relevant in vitro data
7.2.4 Workplace standards
7.2.5 Acceptable daily intake (ADI) and other guideline levels

7.3 Carcinogenicity
7.4 Teratogenicity
7.5 Mutagenicity

7.6 Interactions

8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS

8.1 Material sampling plan

8.1.1 Sampling and specimen collection

8.1.1.1 Toxicological analyses

8.1.1.2 Biomedical analyses

8.1.1.3 Arterial blood gas analysis

8.1.1.4 Haematological analyses

8.1.1.5 Other (unspecified) analyses

8.1.2 Storage of laboratory samples and specimens

8.1.2.1 Toxicological analyses

8.1.2.2 Biomedical analyses

8.1.2.3 Arterial blood gas analysis

8.1.2.4 Haematological analyses

8.1.2.5 Other (unspecified) analyses

8.1.3 Transport of laboratory samples and specimens

8.1.3.1 Toxicological analyses

8.1.3.2 Biomedical analyses

8.1.3.3 Arterial blood gas analysis

8.1.3.4 Haematological analyses

8.1.3.5 Other (unspecified) analyses

8.2 Toxicological Analyses and Their Interpretation

8.2.1 Tests on toxic ingredient(s) of material

8.2.1.1 Simple Qualitative Test(s)

8.2.1.2 Advanced Qualitative Confirmation Test(s)
8.2.1.3 Simple Quantitative Method(s)

8.2.1.4 Advanced Quantitative Method(s)

8.2.2 Tests for biological specimens

8.2.2.1 Simple Qualitative Test(s)

8.2.2.2 Advanced Qualitative Confirmation Test(s)

8.2.2.3 Simple Quantitative Method(s)

8.2.2.4 Advanced Quantitative Method(s)

8.2.2.5 Other Dedicated Method(s)

8.2.3 Interpretation of toxicological analyses

8.3 Biomedical investigations and their interpretation

8.3.1 Biochemical analysis

8.3.1.1 Blood, plasma or serum

8.3.1.2 Urine

8.3.1.3 Other fluids

8.3.2 Arterial blood gas analyses

8.3.3 Haematological analyses

8.3.4 Interpretation of biomedical investigations

8.4 Other biomedical (diagnostic) investigations and their interpretation

8.5 Overall Interpretation of all toxicological analyses and toxicological investigations

8.6 References

9. CLINICAL EFFECTS

9.1 Acute poisoning

9.1.1 Ingestion

9.1.2 Inhalation

9.1.3 Skin exposure

9.1.4 Eye contact
9.1.5 Parenteral exposure
9.1.6 Other

9.2 Chronic poisoning
9.2.1 Ingestion
9.2.2 Inhalation
9.2.3 Skin exposure
9.2.4 Eye contact
9.2.5 Parenteral exposure
9.2.6 Other

9.3 Course, prognosis, cause of death

9.4 Systematic description of clinical effects
9.4.1 Cardiovascular
9.4.2 Respiratory
9.4.3 Neurological
9.4.3.1 CNS
9.4.3.2 Peripheral nervous system
9.4.3.3 Autonomic nervous system
9.4.3.4 Skeletal and smooth muscle
9.4.4 Gastrointestinal
9.4.5 Hepatic
9.4.6 Urinary
9.4.6.1 Renal
9.4.6.2 Others
9.4.7 Endocrine and reproductive systems
9.4.8 Dermatological
9.4.9 Eye, ears, nose, throat: local effects
9.4.10 Haematological
9.4.11 Immunological

9.4.12 Metabolic

  9.4.12.1 Acid-base disturbances

  9.4.12.2 Fluid and electrolyte disturbances

  9.4.12.3 Others

9.4.13 Allergic reactions

9.4.14 Other clinical effects

9.4.15 Special risks

9.5 Others

9.6 Summary

10. MANAGEMENT

10.1 General principles

10.2 Relevant laboratory analyses and other investigations

  10.2.1 Sample collection

  10.2.2 Biomedical analysis

  10.2.3 Toxicological analysis

  10.2.4 Other investigations

10.3 Life supportive procedures and symptomatic treatment

10.4 Decontamination

10.5 Elimination

10.6 Antidote treatment

  10.6.1 Adults

  10.6.2 Children

10.7 Management discussion

11. ILLUSTRATIVE CASES

11.1 Case reports from literature
11.2 Internally extracted data on cases

11.3 Internal cases

12. ADDITIONAL INFORMATION

12.1 Availability of antidotes

12.2 Specific preventive measures

12.3 Other

13. REFERENCES

14. AUTHOR(S), REVIEWER(S), DATE(S) (INCLUDING UPDATES), COMPLETE ADDRESSES

CHEMICAL SUBSTANCES

1. NAME

1.1 Substance
Nicotine

1.2 Group
Alkaloid of Nicotiana Tabacum

1.3 Synonyms
(S)-3-(1-Methylpyrrolidin-2-yl)pyridine

1.4 Identification numbers

1.4.1 CAS number
54-11-5

1.4.2 Other numbers

1.5 Brand names, Trade names

Nicabate
Nicobrevin
Nicotinell TTS
Nicorette
Nicoret
Cigarette tobacco
Black leaf
Nicocide
Nico-fume

Transdermal patches deliver 5 to 30 mg nicotine over 24 hours; used patch has significant nicotine content

Cigarette tobacco varies in its nicotine content but common blends contain 15 to 25 mg per cigarette with a current trend towards lower levels.

Nicotine insecticides: 40% solution of the sulfate.

Chewing gum - nicotine polacrilex: 2 and 4 mg nicotine bound to an ion exchange resin in a sugar-free flavoured chewing gum base.

1.6 Manufacturers, Importers
2. SUMMARY

2.1 Main risks and target organs
Nicotine is one of the most toxic of all poisons and has a rapid onset of action. Apart from local caustic actions, the target organs are the peripheral and central nervous systems. Nicotine is also a powerfully addictive drug.

2.2 Summary of clinical effects
Burning sensation in the mouth and throat, salivation, nausea, abdominal pain, vomiting and diarrhoea. Gastrointestinal reactions are less severe but can occur even after cutaneous and respiratory exposure.

Systemic effects include: agitation, headache, sweating, dizziness, auditory and visual disturbances, confusion, weakness and lack of coordination.

A transient increase in blood pressure, followed by hypertension, bradycardia, paroxysmal atrial fibrillation, or cardiac standstill may be observed.

In severe poisoning, tremor, convulsions and coma occur. Faintness, prostration, cyanosis and dyspnoea progress to collapse. Death may occur from paralysis of respiratory muscles and/or central respiratory failure.

2.3 Diagnosis
Burning sensation in the mouth and throat, salivation, nausea, abdominal pain, vomiting and diarrhoea. 
Agitation, headache, sweating, dizziness, auditory and visual disturbances, confusion, weakness and lack of coordination.

In severe poisoning, tremor, convulsions and coma occur. Faintness, prostration, cyanosis and dyspnoea progress to collapse.

Plasma nicotine level: nicotine concentrations in the urine are not useful in the management of overdose since these vary according to changes in pH and urine flow.

White cell count: polymorphonuclear leucocytosis

Urinalysis: glycosuria.

2.4 First-aid measures and management principles
There are no known antidotes.

Immediate establishment of an airway, monitoring of breathing patterns, and maintenance of circulation are essential in cases of serious overdose. Preparations for possible seizures or rapid progression to coma and artificial ventilation procedures should be kept ready, oxygen may be required.
If vomiting has not occurred following nicotine ingestion, remove stomach contents by gastric lavage. Induction of emesis is less preferable to lavage since convulsions or coma may intervene.

Single or multiple doses of activated charcoal may be used. Children who ingest more than one cigarette should receive activated charcoal and medical observation for at least several hours.

If nicotine is spilled on the skin, immediately wash thoroughly with running water (avoid warm water).

Seizure activity and agitation can be controlled with diazepam or barbiturates.

Cholinergic symptoms may be ameliorated with atropine.

3. PHYSICO-CHEMICAL PROPERTIES

3.1 Origin of the substance

Nicotine is a natural alkaloid obtained from the dried leaves and stems of the Nicotiana tabacum and Nicotiana rustica, where it occurs in concentrations of 0.5-8%. Cigarette tobacco varies in its nicotine content, but common blends contain 15-25 mg per cigarette, with a current trend towards lower levels.

3.2 Chemical structure

3.3 Physical properties

Molecular weight: 162.26

Nicotine is a liquid alkaloid. It is water soluble and has a pKa of 8.5. It is a bitter-tasting liquid which is strongly alkaline in reaction and forms salts with acids.

3.4 Other characteristics

Store at room temperature, below 86 F (30°C). Protect from light and air.

4. USES/CIRCUMSTANCES OF POISONING

4.1 Uses

Nicotine is most frequently encountered in tobacco products for smoking, chewing, sniffing and tobacco "without smoking”.

As an insecticide (now rare), and as an adjunct to smoking cessation programmes (gums, patches). It is a substance of abuse.

4.2 High risk circumstance of poisoning

Nicotine is most frequently encountered in tobacco products for smoking, chewing, sniffing and tobacco "without smoking”.

As an insecticide (now rare), and as an adjunct to smoking cessation programmes (gums, patches). It is a substance of abuse.

4.3Occupationally exposed populations

People who are involved in the processing and extracting tobacco (green tobacco sickness), as well as mixing, storing
and applying certain insecticides.

5. ROUTES OF ENTRY

5.1 Oral
Poisoning occurs in children who ingest cigarettes or cigars or 2nicotine gum. In adults chewing tobacco or nicotine gum, and people who ingest liquid nicotine in the form of insecticide preparations.

5.2 Inhalation
Inhalation is the most frequent route of entry because of worldwide tobacco smoking.

5.3 Dermal
Dermal exposure to nicotine can lead to intoxication. Such exposure has been reported after spilling or applying nicotine-containing insecticides on the skin or clothes (Loockhart, 1933; Benowitz, 1987), and as a consequence of occupational contact with tobacco leaves (green tobacco sickness) (Weizenecker, 1970; Gehlbach, 1974).

5.4 Eye
No data available.

5.5 Parenteral
No data available.

5.6 Others
Tobacco has been used in enemas and poultices (Gosselin, 1988).

6. KINETICS

6.1 Absorption by route of exposure
Nicotine is a water and lipid soluble drug which, in the free base form, is readily absorbed via respiratory tissues, skin, and the gastrointestinal tract. Nicotine may pass through skin or mucous membranes when in alkaline solution (in which nicotine is largely unionized).

When tobacco smoke reaches the small airways and alveoli of the lung, the nicotine is rapidly absorbed. The rapid absorption of nicotine from cigarette smoke through the lungs occurs because of the huge surface area of the alveoli and small airways, and because of dissolution of nicotine at physiological pH (approximately 7.4) which facilitates transfer across cell membranes.

Chewing tobacco, snuff, and nicotine polacrilex gum are of alkaline pH as a result of the selection of appropriate tobacco and/or buffering with additives by the manufacturers. The alkaline pH facilitates absorption of nicotine through mucous membranes.

6.2 Distribution by route of exposure
After absorption, nicotine enters the blood where, at pH 7.4, it is about 70% ionized. Binding to plasma proteins is less than 5%. Studies showed that, after intravenous administration, the distribution of c^{14}-labeled nicotine is immediate, reaching the brain of mice within 1 min. after injection. Similar findings based on positron emission tomography of the brain, were seen after injection of ^{11}C-nicotine in monkeys. (US Department of Health Report of Surgeon General 1988).
Nicotine inhaled in tobacco smoke enters the blood almost as rapidly as after rapid I.V. injections. Because of delivery into the lung, peak nicotine levels may be higher and lag time between smoking and entry into the brain shorter than after IV injection.

After smoking, the action of nicotine on the brain is expected to occur quickly. Rapid onset of effects after a puff is believed to provide optimal reinforcement for the development of drug dependence. The effect of nicotine declines as it is distributed to other tissues. The distribution half-life, which describes the movement of nicotine from the blood and other rapidly perfused tissues, such as the brain, to other body tissues, is about 9 min. (Feyerabend, 1985). Distribution kinetics, rather than elimination kinetics (half-life about 2 hr) determine the time course of the CNS actions of nicotine after smoking a single cigarette.

The apparent volume of distribution in animals is approximately 1.0 L/kg whereas in one clinical study it was 2.0 L/kg in smokers and 3.0 L/kg in nonsmokers (Ellenhorn, 1988).

6.3 Biological half-life by route of exposure

The elimination half-life of nicotine averages 2 hours (Benowitz, 1982; Feyerabend, 1985). The half-life of a drug is useful in predicting the rate of accumulation of that drug in the body with repetitive dosing and the time course of decline after cessation of dosing. Consistent with a half-life of 2 hours, accumulation of nicotine over 6 to 8 hours during regular smoking and persistence of significant levels of nicotine in the blood for 6 to 8 hours after cessation of smoking, i.e. overnight, has been observed (Benowitz, 1982b). Thus, cigarette smoking represents a situation where the smoker is exposed to significant concentrations and possibly pharmacological effects of nicotine for 24 hours a day.

Apparent acute tolerance to nicotine, determined on the basis of observations of the relationship between venous blood levels and effects, may be due to distribution disequilibrium between venous and arterial blood; venous blood levels substantially underestimate concentrations of nicotine in arterial blood and at potential sites of action. True tolerance does, however, develop rapidly, with a half-life of development and regression of about 35 minutes. The kinetics of tolerance may be another determinant of cigarette smoking particularly when the smoker smokes his next cigarette.

6.4 Metabolism

Nicotine is a tertiary amine which is composed of a pyridine and a pyrrolidine ring. Nicotine undergoes a large first pass effect during which the liver metabolizes 80% to 90%; to a smaller extent, the lung also is able to metabolize nicotine.

The major metabolite of nicotine is cotinine; nicotine-1'-N-
oxide is a minor metabolite. Cotinine is also extensively metabolized and trans-3'-hydroxycotinine is its major metabolite. The most abundant metabolite in the mice is trans-3'-hydroxy-cotinine, accounting for almost 40%, whereas cotinine itself accounts for only about 15% of the dose of nicotine.

Cotinine levels in various biological fluids are widely used to estimate intake of nicotine in tobacco users. The usefulness of cotinine as a quantitative marker of nicotine intake, is limited by individual variability in percentage conversion of nicotine to cotinine and in rate of elimination of cotinine itself. Since it accounts for a much greater percentage of nicotine, trans-3'-hydroxycotinine measurement, either alone or in combination with measurement of other metabolites, may be a superior quantitative marker of nicotine intake.

6.5 Elimination by route of exposure
Nicotine and its metabolites (cotinine and nicotine 1-N-oxide) are excreted in the urine. At a pH of 5.5 or less, 23% is excreted unchanged. At a pH of 8, only 2% is excreted in the urine. The effect of urinary pH on total clearance is due entirely to changes in renal clearance. (Ellenhorn, 1988).

Nicotine is secreted into saliva. Passage of saliva containing nicotine into the stomach, combined with the trapping of nicotine in the acidic gastric fluid and reabsorption from the small bowel, provides a potential route for enteric nicotine recirculation. This recirculation may account for some of the oscillations in the terminal decline phase of nicotine blood levels after i.v. nicotine infusion or cessation of smoking.

Nicotine freely crosses the placenta and has been found in amniotic fluid and the umbilical cord blood of neonates. Nicotine is found in breast milk and the breast fluid of non-lactating women and in cervical mucous secretions (US Department of Health and Human Services, a report of the Surgeon General 1988).

7. TOXICOLOGY
7.1 Mode of Action
Nicotine is an agonist at nicotinic receptors in the peripheral and central nervous system. In man, as in animals, nicotine has been shown to produce both behavioral stimulation and depression. Pharmacodynamic studies indicate a complex dose response relationship, due both to complexity of intrinsic pharmacological actions and to rapid development of tolerance.

7.2 Toxicity
7.2.1 Human data
7.2.1.1 Adults
The mean lethal dose has been estimated to be 30 to 60 mg (0.5-1.0 mg/kg) (Gosselin, 1988).

7.2.1.2 Children
The lethal dose is considered to be about 10 mg of nicotine (Arena, 1974).

http://www.inchem.org/documents/pims/chemical/nicotine.htm
7.2.2 Relevant animal data
- Dog: oral LD50: 9.2 mg/kg
- Mouse: oral LD50: 3.3 mg/kg (RTECS, 1985-86)
- Rat: oral LD50: 50 mg/kg

7.2.3 Relevant in vitro data
- No data available.

7.2.4 Workplace standards
- MSHA standard air: TWA = 0.5 mg/m³ (skin)
- OSHA standard air: TWA = 0.5 mg/m³ (skin)

7.2.5 Acceptable daily intake (ADI) and other guideline levels
- Not relevant.

7.3 Carcinogenicity
- Literature reports indicate that nicotine is neither an initiator nor a promoter of tumours in mice. There is inconclusive evidence to suggest that cotinine, an oxidized metabolite of nicotine, may be carcinogenic in the rat. (PDR, 1987).

7.4 Teratogenicity
- Nicotine rapidly crosses the placenta and enters the fetus. Some investigations have reported teratogenic effects of high doses of nicotine, which interfered with osteogenesis in mice and chick embryos. Chronic nicotine treatments of pregnant rats throughout gestation produced subtle neurological changes which manifested themselves as behavioral or electrophysiological alterations in the offspring. Thus, several studies suggest that nicotine, at least in high doses, may have toxic effects on the fetus. Smoking is associated with impaired growth and development of the fetus. Whether cigarette smoking is associated with increased rates of congenital malformations in humans is controversial. Several studies show no association or a lower incidence of malformations in offspring of smoking mothers, but other reports positive associations. One study has reported an association between paternal smoking and the incidence of congenital malformations (US Department of Health and Human Services (1988)).

7.5 Mutagenicity
- In the Ames Salmonella typhimurium mutagenesis and mammalian cell cytogenic assays, nicotine did not possess any genotoxic activity, although it induced separable DNA damage in the Escherichia coli pol A+/A-system (US Department of Health and Human Services, 1988).

7.6 Interactions
- Smoking increases the metabolism of certain compounds and lowers blood levels of drug such as phenacetin, caffeine, theophylline, imipramine and pentazocine through enzyme induction. Other reported effects of smoking, which do not involve enzyme induction, include reduced diuretic effects of furosemide and decreased cardiac output, and antagonism of the hypotensive effects of propranolol, which may also relate to the normal effects of nicotine. Both smoking and nicotine can increase the level of circulating cortisol and catecholamines. Therapy with adrenergic agonists or with adrenergic blockers may need to be adjusted according to changes in smoking...
status.

8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS

8.1 Material sampling plan
8.1.1 Sampling and specimen collection
  8.1.1.1 Toxicological analyses
  8.1.1.2 Biomedical analyses
  8.1.1.3 Arterial blood gas analysis
  8.1.1.4 Haematological analyses
  8.1.1.5 Other (unspecified) analyses
8.1.2 Storage of laboratory samples and specimens
  8.1.2.1 Toxicological analyses
  8.1.2.2 Biomedical analyses
  8.1.2.3 Arterial blood gas analysis
  8.1.2.4 Haematological analyses
  8.1.2.5 Other (unspecified) analyses
8.1.3 Transport of laboratory samples and specimens
  8.1.3.1 Toxicological analyses
  8.1.3.2 Biomedical analyses
  8.1.3.3 Arterial blood gas analysis
  8.1.3.4 Haematological analyses
  8.1.3.5 Other (unspecified) analyses

8.2 Toxicological Analyses and Their Interpretation
8.2.1 Tests on toxic ingredient(s) of material
  8.2.1.1 Simple Qualitative Test(s)
  8.2.1.2 Advanced Qualitative Confirmation Test(s)
  8.2.1.3 Simple Quantitative Method(s)
  8.2.1.4 Advanced Quantitative Method(s)
8.2.2 Tests for biological specimens
  8.2.2.1 Simple Qualitative Test(s)
  8.2.2.2 Advanced Qualitative Confirmation Test(s)
  8.2.2.3 Simple Quantitative Method(s)
  8.2.2.4 Advanced Quantitative Method(s)
  8.2.2.5 Other Dedicated Method(s)
8.2.3 Interpretation of toxicological analyses

8.3 Biomedical investigations and their interpretation
8.3.1 Biochemical analysis
  8.3.1.1 Blood, plasma or serum
    Not relevant
  8.3.1.2 Urine
    To detect glycosuria
  8.3.1.3 Other fluids
8.3.2 Arterial blood gas analyses
  Not relevant.
8.3.3 Haematological analyses
  White cell count or full blood count.
8.3.4 Interpretation of biomedical investigations

8.4 Other biomedical (diagnostic) investigations and their interpretation
8.5 Overall Interpretation of all toxicological analyses and toxicological investigations
8.6 References

9. CLINICAL EFFECTS
9.1 Acute poisoning
9.1.1 Ingestion
  Symptoms of nicotine poisoning may develop within 15
minutes. The onset of symptoms is much more rapid after the ingestion of liquid nicotine (e.g. insecticide preparations) Death may occur within 5 minutes of ingestion of concentrated nicotine insecticides. Four to eight milligrams orally may produce serious symptoms in individuals not habituated to nicotine. Gastrointestinal signs and symptoms occur first and include mouth and throat burning followed by profuse salivation, nausea, vomiting, abdominal pain and occasionally diarrhoea.

More severe intoxication results in dizziness, weakness and confusion, progressing to convulsions, hypertension and coma. Intense vagal stimulation may cause transient cardiac standstill or paroxysmal atrial fibrillation. Death is usually due to paralysis of respiratory muscles and/or central respiratory failure.

9.1.2 Inhalation
In humans, acute exposure to nicotine even in low doses (similar to the amounts consumed by tobacco users) elicits autonomic and somatic reflex effects. Dizziness, nausea and/or vomiting are commonly experienced by nonsmokers after low doses of nicotine, such as when people try their first cigarette. However cigarette smokers rapidly become tolerant to these effects.

9.1.3 Skin exposure
Dermal exposure to nicotine can also lead to intoxication. Such exposures have been reported after spilling or applying nicotine containing insecticides on the skin or clothes and as consequence of occupational contact with tobacco leaves.

A self-limiting illness known as "green-tobacco sickness" has been described in young man handling uncured tobacco leaves in the field; it consists of pallor, vomiting and prostration and is probably due to the percutaneous absorption of nicotine from wet leaves.

9.1.4 Eye contact
No data available.

9.1.5 Parenteral exposure
No data available.

9.1.6 Other
Serious poisoning has occurred from the use of aqueous infusions of tobacco as enemas (Gosselin, 1988). Nicotine 2 mg administered intranasally as a 2% aqueous thickened solution was better absorbed than the same dose given as a chewing gum (Russell, 1983)

9.2 Chronic poisoning
9.2.1 Ingestion
Chronic poisoning by nicotine is possible by chewing tobacco or nicotine gums.

9.2.2 Inhalation
Smoking causes coronary and peripheral vascular disease, cancer, chronic obstructive lung disease, peptic ulcer and reproductive disturbances, including prematurity. 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.

9.2.3 Skin exposure
Through transdermal nicotine

9.2.4 Eye contact
No data available.

9.2.5 Parenteral exposure
No data available.

9.2.6 Other
Not relevant

9.3 Course, prognosis, cause of death
In fatal cases of nicotine poisoning, death is usually rapid; it occurs nearly always within 1 hour and occasionally within 5 minutes. According to the traditional view, death is due to paralysis of the respiratory muscles; paralysis of medullary centres controlling respiration requires a larger dose. Circulatory failure is not necessarily permanent; if heart action can be initiated by external cardiac massage or intracardiac epinephrine while respiration is maintained, death may be prevented (Franke, 1936). If the patient survives the initial period, the prognosis is good (Gosselin 1988).

9.4 Systematic description of clinical effects
9.4.1 Cardiovascular
The overall effect on the cardiovascular system leads to tachycardia, peripheral vasoconstriction and elevations of blood pressure with an attendant increase in the work of the heart. Nicotine may induce vasospasm and cardiac arrhythmias. Tolerance does not develop to the catecholamine-releasing effects of nicotine.

Acute effects
A transient increase in blood pressure followed by bradycardia, paroxysmal atrial fibrillation, or cardiac standstill is observed.

Chronic effects
Nicotine could contribute both to the atherosclerotic process and to acute coronary events by several mechanisms. Nicotine could promote atherosclerotic disease by its actions on lipid metabolism and coagulation by hemodynamic effects and/or by causing endothelial injury.

Nicotine may act by releasing free fatty acids, enhancing the conversion of VLDL (very low density lipoproteins) to LDL (low density lipoproteins), impairing the clearance of LDL and/or by accelerating the metabolism of HDL (Brischetto, 1983; Gluette Brown, 1986; Grasso, 1986; Hojnacki, 1986.)

Nicotine could affect platelets by increasing the
release of epinephrine, which is known to enhance platelet reactivity by inhibiting prostacyclin, an antiaggregatory hormone secreted by endothelial cells, or perhaps directly (Sonnenfeld, 1980). Alternatively, by increasing heart rate and cardiac output and thereby increasing blood turbulence or by a direct action, nicotine may promote endothelial injury. Cigarette smoking, most likely mediated by nicotine, facilitates AV nodal conduction which could result in an increased ventricular response during atrial fibrillation (Peters, 1987). Nicotine could aggravate peripheral vascular disease by constricting small collateral arteries and/or by inducing local thrombosis. Patients with coronary or peripheral vascular disease are likely to suffer some increase in risk when taken nicotine. Nicotine could contribute to the progression of chronic hypertension by aggravating vasoconstriction either in sympathetic activation or inhibition of prostaglandin synthesis.

Based on its pharmacological actions, it is likely that nicotine plays a role in causing or aggravating acute coronary events. Myocardial infarction can be due to one or more of these precipitating factors: excessive demand for oxygen and substrates; thrombosis; and coronary spasm. Nicotine increases heart rate and blood pressure and, therefore, myocardial oxygen consumption.

Nicotine consumed in the form of nicotine gum has been studied in patients with coronary artery disease. Nicotine gum (4mg) increased myocardial contractility in healthy people, but in patients with coronary artery disease, nicotine gum decreased contractility in the ischaemic regions of the myocardium, consistent with aggravation of ischaemia (Bayer, 1985). In the most severe cases of coronary artery disease, overall contractility decreased after nicotine gum. This study supports the idea that nicotine contributes to the induction of myocardial ischaemia in susceptible smokers.

In addition to creating an imbalance between myocardial oxygen supply and demand, nicotine may promote thrombosis. Nicotine may also induce coronary spasm by sympathetic activation or inhibition of prostacyclin. Coronary spasm has been observed during cigarette smoking (Maouad, 1984).

Sudden cardiac death in smokers might result from ischaemia, combined with the arrhythmogenic effects of increased amounts of circulating catecholamines released by nicotine.

9.4.2 Respiratory

Acute effects

Initial tachypnoea, but later dyspnoea, decreased
respiratory rate, and cyanosis may be seen. Respiratory arrest may occur within minutes, and resultant death within 1 hour.

**Chronic effects**

Nicotine may directly or indirectly influence the development of emphysema in smokers, but further research is needed to define the magnitude of the contribution of nicotine to the pathogenesis of smoking including chronic lung disease. Nicotine can also worsen pulmonary function in smokers who already have lung disease. Acute exposure to nicotine induces constriction of both central and peripheral airways (Yamatake, 1978). The increase in airways resistance by nicotine involves vagal reflexes and stimulation or parasympathetic ganglia in the bronchial wall (Nakamme, 1986). The magnitude of bronchoconstriction observed in experimental animals and humans following acute inhalation of cigarette smoke is correlated with the level of nicotine in the smoke (Beck, 1986) suggesting that nicotine may be an important factor in the increased airways resistance of smokers.

### 9.4.3 Neurological

#### 9.4.3.1 CNS

The effects of nicotine are generally dose-dependent and extremely high doses can produce toxic symptoms such as delirium. These effects also occur in nicotine tolerant individuals. Nicotine first stimulates and later depresses the CNS. Headache, confusion, dizziness, agitation, restlessness and incoordination develop initially after serious nicotine overdose; 30 minutes later, convulsions and coma occur.

#### 9.4.3.2 Peripheral nervous system

Neuromuscular symptoms include hypotonia, decreased deep tendon reflexes, weakness, fasciculations and paralysis of muscles (including respiratory muscles).

#### 9.4.3.3 Autonomic nervous system

Cholinergic symptoms often observed initially include diaphoresis, salivation, lacrimation, increased bronchial secretions, miosis and later mydriasis.

Nicotine has actions at the sympathetic ganglia and on the chemoreceptors of the aorta and carotid bodies. Nicotine also affects the adrenal medulla, releasing catecholamines.

#### 9.4.3.4 Skeletal and smooth muscle

Weakness, fasciculations and paralysis of muscles (including respiratory muscles)

### 9.4.4 Gastrointestinal

**Acute effects**
Gastrointestinal symptoms occur first and include burning of the mouth and throat followed by profuse salivation, nausea, vomiting, abdominal pain and occasionally diarrhoea.

Chronic effects

Cigarette smoking is a risk factor for peptic ulcer disease and an even stronger risk factor for delayed healing, failure to respond to therapy and relapse (Kikendall, 1984). In animals, nicotine potentiates peptic ulcer formation induced by histamine or pentagastrin (Konturek, 1971).

9.4.5 Hepatic
No data available.

9.4.6 Urinary
9.4.6.1 Renal
9.4.6.2 Others

9.4.7 Endocrine and reproductive systems
The action of nicotine on the adrenal medulla (release of catecholamines) does not appear to be affected by tolerance, and may aggravate patients with hyperthyroidism, phaeochromocytoma or insulin-dependent diabetes.

9.4.8 Dermatological
No data available.

9.4.9 Eye, ears, nose, throat: local effects
No data available.

9.4.10 Haematological
No data available.

9.4.11 Immunological
No data available.

9.4.12 Metabolic
9.4.12.1 Acid-base disturbances
Not relevant.
9.4.12.2 Fluid and electrolyte disturbances
Not relevant.
9.4.12.3 Others
Action on lipids.

Nicotine may act by releasing free fatty acids, enhancing the conversion of VLDL (very low density lipoproteins) to LDL (low density lipoproteins), impairing the clearance of LDL and/or by accelerating the metabolism of HDL. (Brischetto, 1983; Gluette Brown, 1986; Grasso, 1986; Hojnacki, 1986).

9.4.13 Allergic reactions
No data available.

9.4.14 Other clinical effects
No data available.

9.4.15 Special risks
Pregnancy

Nicotine in any form may be harmful to the fetus.
Exposure to nicotine during the last trimester has been associated with a decrease in breathing movements. These effects may be the result of decreased placental perfusion caused by nicotine. One miscarriage during nicotine therapy has been reported. Studies of pregnant rhesus monkeys have shown that maternal nicotine administration produced acidosis, hypoxia and hypercarbia in the fetus. Nicotine has been shown to be teratogenic in mice treated cutaneously with 25 mg/kg, which is approximately 300 times the human oral dose. Studies in rats and monkeys have not demonstrated a teratogenic effect of nicotine in newborns which occur during cigarette smoking. Cigarette smoking is associated with impaired fetal growth and development.

Breast feeding

Nicotine passes freely into the breast milk in small quantities, which are not clinically significant, averaging 91ppb in one study. Heavy smoking (20-30 cigarettes per day) may alter the supply of milk and cause nausea and vomiting in the infant.

9.5 Others
Withdrawal Syndrome. Need for oral gratification and other psychological problems may result in the production of symptoms of withdrawal including anxiety, impaired concentration and memory, depression, hostility, sleep disturbances, and increased appetite (Ellenhorn 1988).

9.6 Summary

10. MANAGEMENT

10.1 General principles
There is no known antidote. Immediate establishment of an airway, monitoring of breathing patterns, and maintenance of circulation are essential in serious overdose cases. Preparations for possible seizures of rapid progressing to coma must be initiated in serious overdose cases by establishment of an intravenous line, supplemental oxygen, cardiac monitoring, and direct observation.

Artificial ventilation procedures should be kept ready; oxygen may be required.

10.2 Relevant laboratory analyses and other investigations

10.2.1 Sample collection
Plasma

10.2.2 Biomedical analysis
Full blood count
Urinalysis (glycosuria)

10.2.3 Toxicological analysis
Plasma nicotine levels and metabolites in urine.

10.2.4 Other investigations
No data available.

10.3 Life supportive procedures and symptomatic treatment
Artificial ventilation and oxygen therapy until spontaneous breathing is adequate. Keeps the airways clear.
Profuse salivation may require continuous oral suction. Bronchial secretions, excess salivation, and diarrhoea may be ameliorated by atropine. If severe or persistent convulsions occur, they may be controlled with small intravenous doses of barbiturates or diazepam.

10.4 Decontamination
If contact was with the skin, remove contaminated clothing and wash the skin thoroughly with water without rubbing (avoid warm water). If the patient has swallowed nicotine, induce emesis if there are no convulsions and respiration is normal. Wash out the stomach. Activated charcoal may be left in the stomach.

Children who ingest more than one cigarette should receive activated charcoal and medical observation for at least several hours.

10.5 Elimination
Haemodialysis and haemoperfusion have not been evaluated in acute nicotine poisoning. Acidification of urine may increase excretion of nicotine but although pharmacologically sound, its clinical value remains to be established and could be harmful.

10.6 Antidote treatment
10.6.1 Adults
10.6.2 Children

10.7 Management discussion

11. ILLUSTRATIVE CASES
11.1 Case reports from literature
Malizia (1983) described four children who ingested two cigarettes each and developed salivation, vomiting, diarrhoea, tachypnoea, tachycardia, and hypotension within 30 minutes and depressed respiration and cardiac arrhythmias within 40 minutes. Convulsions occurred within 60 minutes of ingestion. All recovered after gastric lavage, activated charcoal, intermittent positive pressure ventilation, and 5 mg diazepam intravenously for convulsions.

A 23 year old woman who had smoked two packs per day for several years chewed a single piece of nicotine gum (2 mg nicotine) after which she developed nausea, tremor, flushing, palpitations, paresthesias, pruritus, vomiting, diarrhoea, confusion and abdominal pain. She recovered after treatment and with prochlorperazine, morphine and atropine (Mensch, 1984).

11.2 Internally extracted data on cases
11.3 Internal cases

12. ADDITIONAL INFORMATION
12.1 Availability of antidotes
No data available.

12.2 Specific preventive measures
Preventative measures for occupational exposure to nicotine
include adequate ventilation, chemical goggles, mechanical filter respirator, rubber gloves, aprons and boots.

12.3 Other

No data available.

13. REFERENCES


Hospital de Clinicas San Martin
Cordoba 2351
Capital Federal
Buenos Aires
Argentina

Date:          March 1991

Peer Review:   Adelaide, April 1991

See Also:
Toxicological Abbreviations
Nicotine (ICSC)