

SECTION-1: Identification of the substance / mixture and the company / undertaking

Catalogue Number	CS-IP-00442
Product Name	Salicylic Acid
CAS No.	69-72-7
Category	IP Standards
Synonyms	Ortho Hydroxybenzoic Acid; 2-Hydroxybenzoic acid (ACI); Salicylic acid (6CI, 8CI); Advanced Pain Relief Callus Removers; Dr. Scholl's Callus Removers; Salicylic acid collodion
Brand	Clearsynth Labs Ltd.
Identified uses	Laboratory Chemicals
Uses advised against	Not available
Company	Clearsynth Labs Ltd. Mumbai, India
Emergency Phone #	+91-22-245045900
REACH No.	Not available

SECTION 2: Hazards identification

Disclaimer: This is sample MSDS. Please email sales@clearsynth.com for more details.

2.1 Classification of the substance or mixture-Regulation (EC) No 1272/2008:

- Skin irritation (Category 2)
- Serious eye damage/eye irritation (Category 2)
- Acute toxicity (Category 4)

2.2 Label Elements

Signal Word: Warning



Hazard Statement(s)

Code	Statement
H302	Harmful if swallowed.

H318	Causes serious eye damage.
H312	Harmful in contact with skin.
H319	Causes serious eye irritation.
H315	Causes skin irritation.
H317	May cause an allergic skin reaction.
H361	Not available
H370	Not available
H372	Not available
H402	Not available

Precautionary Statement(s)

Code	Statement
P203	Not available
P264	Wash hands thoroughly after handling.
P264+P265	Not available
P270	Not available
P280	Wear protective gloves/protective clothing/eye protection/face protection.
P301+P317	Not available
P305+P354+P338	Not available
P317	Not available
P318	Not available
P330	Not available
P405	Store locked up.
P501	Dispose of contents/container in accordance with local/regional/national/international regulation
P302+P352	IF ON SKIN: Wash with plenty of water and soap.
P305+P351+P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present
P321	Specific treatment (see ... on this label).
P337+P317	If eye irritation persists: Get medical help.
P362+P364	Take off contaminated clothing and wash it before reuse.
P260	Not available

P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
P272	Not available
P273	Not available
P308+P316	Not available
P319	Get medical help if you feel unwell.
P332+P317	If skin irritation occurs: Get medical help.
P333+P317	Not available

SECTION 3: Composition / information on ingredients

3.1 Substance

Component : Salicylic Acid

CAS Number : 69-72-7

Molecular Formula : C7H6O3

Molecular Weight : 138.12

Parent Chemical : Salicylic Acid

Synonyms : Ortho Hydroxybenzoic Acid; 2-Hydroxybenzoic acid (ACI); Salicylic acid (6CI, 8CI); Advanced Pain Relief Callus Removers; Dr. Scholl's Callus Removers; Salicylic acid collodion

Concentration : Not available

SECTION 4: First aid measures

Not available

SECTION 5: Firefighting measures

Not available

SECTION 6: Accidental release measures

Not available

SECTION-7: Handling and storage

Not available

SECTION 8: Exposure controls / personal protection

Not available

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties

Test	Result
Appearance	No data available
IR spectrum	No data available
pH	No data available
Solubility	No data available

Property	Value
a) Physical State	No data available
b) Color	No data available
c) Odor	No data available
d) pH	2.7
e) Vapour Pressure	No data available
f) Viscosity	No data available
g) Initial Boiling Point and boiling range	No data available
h) Melting Point / Freezing Point	No data available
i) Auto Ignition Temperature	No data available
j) Flash Point	No data available
k) Explosion Limit, Lower	No data available
l) Explosion Limit, Upper	No data available
m) Decomposition Temperature	No data available
n) Loss on Drying	No data available
o) Relative Density	No data available
p) Solubility (in DMSO)	No data available
q) Oxidizing Properties	No data available

SECTION 10: Stability and reactivity

Not available

SECTION 11: Toxicological information

11.1 Information on toxicological effects

- Acute toxicity: IDENTIFICATION: Salicylic acid is an analgesic and antipyretic medication. Salicylic acid in the form of esters was found in several plants, notably in wintergreen leaves and the bark of sweet birch. It was made synthetically by heating sodium phenolate with carbon dioxide under pressure and microbial oxidation of naphthalene. Salicylic acid is colorless or white crystals. Colourless acicular crystals or a white crystalline powder. The synthetic form is white but if prepared from natural methyl salicylate, it may have a slightly yellow or pink tint. Salicylic acid is a white crystalline powder with a sweetish acrid taste. If prepared from natural methyl salicylate, it may have a faint mint like odor. It is available in forms of ointments, cream, gel, transdermal patches, liquids and plaster. Salicylic acid is soluble in water, boiling water, alcohol, ether and chloroform. Salicylic acid has keratinolytic properties and is applied topically in the treatment of hyperkeratotic and scaling conditions such as dandruff, ichthyosis and psoriasis. Initially a concentration of 2% is used increasing to about 6% if necessary. It is often used in conjunction with many other agents, such as benzoic acid, coal tar, resorcinol and sulfur. Salicylic acid is also used in the form of paint and in the form of collodion basis (10 to 17%) or as a plaster (20 to 50%) to destroy warts and corns. It also possesses fungicidal properties and is used topically in the treatment of fungal skin infections such as tinea. HUMAN EXPOSURE: Main risks and target organs: The toxic effects of salicylic acid and salicylates are complex. Main risks with oral therapeutic doses are mostly gastrointestinal irritation. Hepatic encephalopathy (Reye's Syndrome) has been reported in children who had taken aspirin for treatment of viral infections such as influenza. Toxic doses of salicylate stimulate the respiratory centre leading to respiratory alkalosis. In severe intoxication, metabolic acidosis, water and electrolyte loss occur as the principle secondary consequences. Central nervous system toxicity includes, tinnitus, hearing loss and in very severe cases particularly in children convulsions and coma. Target organs are central nervous system, lungs, kidneys and liver. Summary of clinical effects: Following oral ingestion of salicylic acid and or any other salicylate, nausea, vomiting, epigastric discomfort, tinnitus, loss of hearing, sweating, flushing (vasodilatation) tachypnea and hyperpnea are commonly observed. Local gastrointestinal (GI) irritation of SA is more marked than ASA (acetylsalicylic acid). In severe intoxication irritability, tremor, blurred vision, mental confusion, delirium, stupor, coma, fever, cerebral edema and cardiorespiratory arrest may occur. Central nervous system toxicity and gastrointestinal haemorrhage are more common after chronic (therapeutic) intoxication. A marked alteration of acid base balance from respiratory alkalosis to metabolic acidosis may be observed. In severe salicylate intoxication in adults, non cardiogenic pulmonary edema, nonfocal neurological abnormalities, unexplained ketosis and a prolonged prothrombin time can occur. Skin eruption and subconjunctival hemorrhage may be seen but marked thrombocytopenia is rare. Methyl salicylate poisoning has the odor of the drug which can be detected on the breath and in the urine and vomit. Central nervous system stimulation, intense hyperpnea and hyperpyrexia are prominent features. Diagnosis: Symptoms and signs of oral ingestion of salicylic acid overdose usually commence by nausea, vomiting and epigastric discomfort. However, in mild salicylism particularly with therapeutic intoxication, tinnitus, loss of hearing, dizziness, sweating, and flushing are more common. Severe salicylate poisoning is associated with marked respiratory and nervous system toxicity. Hyperventilation and respiratory alkalosis are more common in adults, whereas hypoventilation and metabolic acidosis are more commonly observed in children. A rapid screening test for the presence of salicylate in the urine may indicate the use of the drug. Estimation of salicylate concentration in plasma/serum can confirm the diagnosis and reveals the severity of intoxication. Due to the severe gastric irritation which salicylic acid causes, it is no longer used orally. However, when used topically it may cause an allergic contact rash in some people. If applied to large areas of skin, it may be absorbed into the blood stream and induce salicylism. Routes of entry: Oral: Salicylic acid causes gastric irritation and thus, there is no oral pharmaceutical available. However, Chinese medicated oil which contains 67% methyl salicylate has been taken orally. Dermal: Salicylic acid is readily absorbed from the skin and

may induce toxicity (salicylism). Kinetics: Absorption by route of exposure: Salicylic acid is readily absorbed from the skin and may cause toxicity, particularly in children and the newborn. Herbal products such as the chinese medicated oil which contains methyl salicylate is also absorbed through gastrointestinal mucosa following ingestion. Distribution by route of exposure: About 50 to 80% of salicylate in the blood is bound to plasma proteins, while the rest remains in the active ionized state; protein binding is concentration dependent. Saturation of binding sites lead to more free salicylate and increased toxicity. The apparent volume of distribution is 0.1 to 0.2 L/kg. Acidosis increases the volume of distribution because of the enhancement of tissue penetration of salicylate. Biological half-life by route of exposure: The plasma salicylate half-life following therapeutic doses is 2 to 4.5 hours, but in over-dosage, increases to 18 to 36 hours. When the metabolic pathway is saturated (conjugation with glycine), zero order kinetics apply and thus the elimination half-life cannot be derived correctly. Metabolism: At low dosage, approximately 80% of salicylic acid is metabolized in the liver. Conjugation with glycine, forms salicyluric acid and when conjugated with glucuronic acid, acyl and phenolic glucuronide are formed. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large doses, the kinetics switch from first order to zero order (Michaelis-Menten) kinetics. Elimination and excretion: Salicylates are excreted mainly by the kidney as salicylic acid, salicyluric acid, salicylic glucuronides and gentisic acid. The proportion excreted of each metabolite, depends upon urinary pH. With urinary alkalinisation, salicylic acid excretion is enhanced. Mode of action: Toxicodynamics: Marked hyperventilation occurs as a result of direct stimulation of the respiratory centre. Indirect stimulation of respiration is caused by an increased production of CO₂ as a result of salicylate-induced uncoupling of oxidative phosphorylation. Respiratory alkalosis develops as a result of the direct and indirect stimulation of the respiratory centre. In an attempt to compensate, bicarbonate accompanied by sodium, potassium and water, is excreted in the urine. Dehydration and hypokalemia result, but more importantly, the loss of bicarbonate diminishes the buffering capacity of the body and allows the development of a metabolic acidosis. The pyretic effect of toxic doses of salicylate is a direct result of the uncoupling of oxidative phosphorylation. High doses of salicylate have additional toxic effects on the central nervous system consisting of stimulation(including convulsions) followed by depression, confusion, dizziness, asterixis, delirium, psychosis, stupor and coma. Very high doses have depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse secondary to vasomotor depression. The loss of buffering capacity and the effects of salicylate on carbohydrate, lipid and protein metabolism lead to the development of a metabolic acidosis or, more commonly in practice, a mixed acid base disturbance. Both hypo-and hyperglycemia may occur in salicylate poisoning. The former most probably due to an increased tissue demand for glucose oxidation due to the uncoupling of oxidative phosphorylation. Neuroglycopenia can occur in the presence of normal blood glucose concentrations. If hepatic glycogen stores are adequate, catecholamines production stimulates glycogenolysis leading to hyperglycemia which can persist for several days. Salicylate intoxication is often accompanied by hypothermia due to a warfarin like action of salicylate on the vitamin K1 epoxide cycle, which rarely causes clinical problems. Pharmacodynamics: Salicylic acid alleviates pain, lowers an elevated body temperature and inflammation by inhibiting the synthesis of prostaglandins that occur in inflamed tissues. Salicylate inhibits the conversion of arachidonic acid to the unstable endoperoxide intermediate PG G₂, which is catalyzed by the enzyme cyclo oxygenase. Platelets are especially susceptible to this action as they are incapable of regenerating the enzyme, presumably they have little or no capacity for protein biosynthesis. Cyclooxygenase(COX) is present in two main isoforms. COX-1 is the isoform of the enzyme and is present under normal physiological conditions. COX-2 is the inducible isoform of the enzyme and is induced in settings of inflammation (production of eicosanoids and kinins). Inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcer. Adults: Since salicylic acid is available only in topical preparations, human data on toxicity have not been reported. However, the chinese medicated oil, which contains 67% methyl salicylate induced severe salicylate poisoning. Salicylic acid concentrations above 800 mg/L after 6 hours post exposure is severely toxic and may be lethal. Children: Salicylate intoxication is often more serious in small children (1-4 years) than in older children, due to an early development of a metabolic acidosis rather than a respiratory alkalosis.

Teratogenicity: There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have a significantly reduced mass at birth. In addition, there is an increase in prenatal mortality, anemia, antepartum and postpartum haemorrhage, prolonged gestation and complicated deliveries. These effects occur when salicylates are administered during the third trimester, and thus its use during this period of pregnancy should be avoided.

Interactions: Salicylic acid is highly protein-bound and may increase the unbound or free drug concentrations of other drugs such as hypoglycemics, anticoagulants and methotrexate (an antimetabolite chemotherapeutic drug), reaching toxic levels of these agents. The uricosuric activity of phenylbutazone, probenecid and sulphapyrazone is strongly antagonized by salicylate and maybe completely diminished by small doses due to decreased tubular reabsorption of uric acid. In a report of two cases of severe salicylate poisoning, asystole occurred shortly after the intravenous administration of diazepam. Main adverse effects: Salicylic acid is a gastric irritant and because of the serious damage it may cause to the stomach lining, it has not been used orally. Topical use of salicylic acid may induce allergic contact dermatitis. Salicylic acid may cause excessive drying and irritation in some people. Some individuals, especially asthmatics exhibit sensitivity to salicylates. Urticaria, angioneurotic oedema, rhinitis, severe and even fatal paroxysmal, bronchospasm and dyspnea may occur.

Acute poisoning: Ingestion: Initial symptoms of salicylate poisoning may be nausea and vomiting, epigastric pain and occasionally haematemesis. Hyperventilation, sweating, flushing, fever, irritability, tinnitus and loss of hearing are the common clinical features of mild to moderate salicylate intoxication. In severe intoxication, hypoventilation, stupor, hallucination, convulsions, papilledema and coma particularly in children may occur. Metabolic acidosis, non-cardiogenic pulmonary edema, hepatotoxicity and cardiac dysrhythmias may also occur.

Skin exposure: Severe poisoning has been reported as a result of the use of salicylic acid ointment for dermatological problems and in the treatment of skin burns.

Chronic poisoning: Ingestion: Chronic salicylate poisoning occurred as a result of excessive therapeutic administration over a period of 12 hours or more were reported. Metabolic pathways of salicylic acid become saturated and thus plasma concentration increases, producing toxicity. Small children are at particular risk of overdose especially when fever, sweating and tachycardia of salicylate intoxication are attributed to the underlying illness and are used as indications for increasing the dose. Children may become intoxicated through breast milk. The presenting signs of chronic salicylate poisoning can include metabolic acidosis, hypoglycemia, lethargy, coma and fits.

Skin exposure: Chronic usage of salicylic acid and or methyl salicylate in skin and rheumatic diseases may cause intoxication through percutaneous absorption. Life threatening salicylate poisoning caused by percutaneous absorption of salicylic acid (10% ointment) in a 7-year old boy with ichthyosis vulgaris was reported. Application of teething gels containing salicylic acid induced intoxication.

Course, prognosis, cause of death: If a large quantity of a salicylate has been taken, nausea, vomiting, tinnitus, deafness, sweating, vasodilatation and hyperventilation may develop. Acid-base disturbances, electrolyte imbalance, non cardiogenic pulmonary edema, hypoventilation and hallucination, stupor, irritability, coma and convulsions particularly in children and older patients can proceed death. Loss of consciousness in adults is very rare and when occurs indicates poor prognosis. A review of 51 fatal cases of acute salicylate poisoning in Ontario during 1983 and 1984, discovered that salicylate was the most common cause of death, due to the ingestion of single drugs. Autopsy results showed that 50% of the patients had pulmonary abnormalities, 28% had lesions of the gastrointestinal tract, 18% had nervous system abnormalities and 25.6% had no pathological changes. Mortality from chronic salicylate intoxication is considerably higher (25%) than from acute overdose (1 to 2%). Death is often due to sudden cardiac arrest or occasionally due to multiple complications following severe brain damage.

Systemic description of clinical effects: Cardiovascular: Sudden cardiovascular collapse is a recognized complication of salicylate poisoning. Two patients with severe salicylate intoxication developed asystole shortly after intravenous diazepam administration. Transient myocardial dysfunction (global left ventricular shortening fraction of 23%) with pulmonary edema was found in a 13-month-old boy with salicylate poisoning.

Respiratory: Non-cardiogenic pulmonary edema may occur in salicylate intoxicated patients who are over 30 years of age. Cigarette smoking, chronic salicylate ingestion, metabolic acidosis and the presence of neurological symptoms and signs on admission

are strong risk factors for the subsequent development of pulmonary edema. The exact mechanism is unknown. Three possible explanations are: (1) A direct toxic effect on pulmonary microvasculature; (2) Interaction with endogenous mediators such as prostaglandins; and (3) A central nervous system mediated effect. Neurological: Central Nervous System (CNS): In moderate to severe salicylate intoxication, CNS stimulation (irritability and convulsions) followed by depression, confusion, dizziness, delirium, psychosis, asterixis, stupor and coma occur usually when metabolic acidosis is the dominant acid-base abnormality. These features are thought to be due to reduced ionisation of salicylic acid and a shift of salicylate from the plasma into the brain. Very high doses of salicylate have a depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse, secondary to vasomotor depression. Gastrointestinal: Ingestion of salicylate may result in epigastric discomfort, nausea and vomiting. Salicylic acid has more irritant effects on gastric mucosa than acetylsalicylic acid and thus has been withdrawn from oral administration for many years. Acetylsalicylic acid may also cause gastric irritation. Perforated peptic ulcer also occurs extremely rarely. Hepatic: Hepatotoxicity may occur both after the therapeutic use of salicylate or following its over-dosage. Liver biopsy revealed acute hepatocellular necrosis with periportal inflammation and fatty changes in hepatocytes. Hepatic encephalopathy (Reye's Syndrome) has been reported in children taking aspirin for treatment of viral infections such as influenza. Urinary: Renal: Oliguria sometimes occurs, which is mostly due to dehydration. Renal failure may rarely occur in individuals without volume depletion, pre-existing renal and or systemic diseases. Endocrine and reproductive systems: High doses of salicylate cause release of adrenaline from the adrenal medulla; this is thought to be partly responsible for the observed hypoglycaemia due to glycogenolysis that sometimes occurs. Large doses of salicylate stimulate corticosteroids secretion by the adrenal cortex. Dermatological: Toxic epidermal necrosis in 13 patients associated with the use of salicylate have been reported. Eye, ear, nose, throat: local effects: Eye: Transient myopia occurred in a patient following ingestion of acetylsalicylic acid. Bilateral subconjunctival hemorrhage has been reported. Ear: Tinnitus and hearing loss caused by salicylate in overdose are due to increased labyrinthine pressure. It may also be due to an effect on the hair cells of the cochlea. There is a relationship between the hearing loss and the plasma salicylate concentration. Hematological: Salicylates prolong the bleeding time due to inhibition of collagen glucosyltransferase present in membranes of platelets. As a result, the adherence of platelets to connective tissue or collagen fibres is diminished. Salicylate overdose reduces the concentration of vitamin K-dependent coagulation factors, particularly prothrombin. Immunological: Salicylates have the capacity to suppress a variety of antigen-antibody reactions such as: the inhibition of antibody production, of antigen-antibody aggregation and of antigen induced release of histamine. Salicylates also induce a non specific stabilization of capillary permeability during immunological insults. The concentration of salicylate causing this effect is high, and their relationship to the antirheumatic efficacy of salicylates is yet to be determined. Metabolic: Acid-base disturbances: Respiratory alkalosis is more often observed in adults than in children. Metabolic acidosis develops sooner in children than in adults. However, in severe salicylate poisoning in adults, metabolic acidosis may also occur. The acidosis is not therefore due to the presence of salicylic acid itself. The principle cause is competitive inhibition of NAD⁺-dependent dehydrogenases including lactate and oxoglutarate dehydrogenase and the other oxidative enzymes such as succinate dehydrogenase. Salicylate enhances entry and oxidation of fatty acids in liver cells, leading to increased ketogenesis. Competitive inhibition of amino acyl-tRNA synthetases in pairs and amino acid incorporation results in amino-acidemia. Dehydration and vasomotor depression results in poor renal perfusion and accumulation of sulfuric and phosphoric acids. Fluid and electrolyte disturbances: Increased renal secretion of sodium, potassium and water accompanies loss of bicarbonate in the urine. Fluid loss also results from vomiting, sweating and hyperventilation. Dehydration is commonly associated with hypernatremia. (1) Oxidative Phosphorylation: The uncoupling of oxidative phosphorylation by salicylate results in the inhibition of a number of ATP-dependent reactions and an increase in O₂ uptake and CO₂ production. (2) Nitrogen compound metabolism: Toxic doses of salicylate cause a significant nitrogen imbalance, characterized by amino aciduria, though this is due in part to stimulation of active tubular absorption because of reduced ATP formation. Fat metabolism: Salicylates enhance oxidation of fatty acids in

muscle, liver and other tissues together with a decrease of concentrations of plasma, free fatty acids, phospholipids and cholesterol. Allergic reactions: Some people particularly asthmatics, exhibit marked sensitivity to salicylate, resulting in various reactions including urticaria and other skin eruptions, angioneuritis, oedema, rhinitis and severe and even fatal paroxysmal bronchospasm and dyspnea, hypotension, shock and syncope. Despite the fact that the symptoms (such as the ones mentioned above) resemble anaphylaxis, this reaction does not appear to be immunological in nature. It may be a shunt towards the lipoxygenase pathway leading to an increased production of leukotrienes and other inflammatory mediators. Although, this hypothesis is unproved and it does not explain why only a minority of patients with asthma or other predisposing conditions display the reaction. Even so, results in a small number of patients suggest that blockade of 5-lipoxygenase with the drug zileuton may prevent symptoms and signs of aspirin intolerance. Other clinical effects: The relationship between the use of salicylate and Reye's syndrome in children and adolescents (mostly 5 to 15 years) has been demonstrated by epidemiological studies.

Special risks: Salicylate intoxication may occur through placental transfer and breast milk. LC50 (mammals) > 300mg/m³; [ChemIDplus]

- Skin corrosion/irritation: No data available.
- Serious eye damage/eye irritation: No data available.
- Respiratory or skin sensitization: No data available.
- Germ cell mutagenicity: Investigated as a mutagen and reproductive effector.
- Carcinogenicity: No data available.
- Reproductive toxicity: IDENTIFICATION: Salicylic acid is an analgesic and antipyretic medication. Salicylic acid in the form of esters was found in several plants, notably in wintergreen leaves and the bark of sweet birch. It was made synthetically by heating sodium phenolate with carbon dioxide under pressure and microbial oxidation of naphthalene. Salicylic acid is colorless or white crystals. Colourless acicular crystals or a white crystalline powder. The synthetic form is white but if prepared from natural methyl salicylate, it may have a slightly yellow or pink tint. Salicylic acid is a white crystalline powder with a sweetish acrid taste. If prepared from natural methyl salicylate, it may have a faint mint like odor. It is available in forms of ointments, cream, gel, transdermal patches, liquids and plaster. Salicylic acid is soluble in water, boiling water, alcohol, ether and chloroform. Salicylic acid has keratolytic properties and is applied topically in the treatment of hyperkeratotic and scaling conditions such as dandruff, ichthyosis and psoriasis. Initially a concentration of 2% is used increasing to about 6% if necessary. It is often used in conjunction with many other agents, such as benzoic acid, coal tar, resorcinol and sulfur. Salicylic acid is also used in the form of paint and in the form of collodion basis (10 to 17%) or as a plaster (20 to 50%) to destroy warts and corns. It also possesses fungicidal properties and is used topically in the treatment of fungal skin infections such as tinea. HUMAN EXPOSURE: Main risks and target organs: The toxic effects of salicylic acid and salicylates are complex. Main risks with oral therapeutic doses are mostly gastrointestinal irritation. Hepatic encephalopathy (Reye's Syndrome) has been reported in children who had taken aspirin for treatment of viral infections such as influenza. Toxic doses of salicylate stimulate the respiratory centre leading to respiratory alkalosis. In severe intoxication, metabolic acidosis, water and electrolyte loss occur as the principle secondary consequences. Central nervous system toxicity includes, tinnitus, hearing loss and in very severe cases particularly in children convulsions and coma. Target organs are central nervous system, lungs, kidneys and liver. Summary of clinical effects: Following oral ingestion of salicylic acid and or any other salicylate, nausea, vomiting, epigastric discomfort, tinnitus, loss of hearing, sweating, flushing (vasodilatation) tachypnea and hyperpnea are commonly observed. Local gastrointestinal (GI) irritation of SA is more marked than ASA (acetylsalicylic acid). In severe intoxication irritability, tremor, blurred vision, mental confusion, delirium, stupor, coma, fever, cerebral edema and cardiorespiratory arrest may occur. Central nervous system toxicity and gastrointestinal haemorrhage are more common after chronic (therapeutic) intoxication. A marked alteration of acid base balance from respiratory alkalosis to metabolic acidosis may be observed. In severe salicylate intoxication in adults, non cardiogenic pulmonary edema, nonfocal neurological abnormalities, unexplained ketosis and a prolonged prothrombin time can occur. Skin eruption and

subconjunctival hemorrhage may be seen but marked thrombocytopenia is rare. Methyl salicylate poisoning has the odor of the drug which can be detected on the breath and in the urine and vomit. Central nervous system stimulation, intense hyperpnea and hyperpyrexia are prominent features. Diagnosis: Symptoms and signs of oral ingestion of salicylic acid overdose usually commence by nausea, vomiting and epigastric discomfort. However, in mild salicylism particularly with therapeutic intoxication, tinnitus, loss of hearing, dizziness, sweating, and flushing are more common. Severe salicylate poisoning is associated with marked respiratory and nervous system toxicity. Hyperventilation and respiratory alkalosis are more common in adults, whereas hypoventilation and metabolic acidosis are more commonly observed in children. A rapid screening test for the presence of salicylate in the urine may indicate the use of the drug. Estimation of salicylate concentration in plasma/serum can confirm the diagnosis and reveals the severity of intoxication. Due to the severe gastric irritation which salicylic acid causes, it is no longer used orally. However, when used topically it may cause an allergic contact rash in some people. If applied to large areas of skin, it may be absorbed into the blood stream and induce salicylism. Routes of entry: Oral: Salicylic acid causes gastric irritation and thus, there is no oral pharmaceutical available. However, Chinese medicated oil which contains 67% methyl salicylate has been taken orally. Dermal: Salicylic acid is readily absorbed from the skin and may induce toxicity (salicylism). Kinetics: Absorption by route of exposure: Salicylic acid is readily absorbed from the skin and may cause toxicity, particularly in children and the newborn. Herbal products such as the chinese medicated oil which contains methyl salicylate is also absorbed through gastrointestinal mucosa following ingestion. Distribution by route of exposure: About 50 to 80% of salicylate in the blood is bound to plasma proteins, while the rest remains in the active ionized state; protein binding is concentration dependent. Saturation of binding sites lead to more free salicylate and increased toxicity. The apparent volume of distribution is 0.1 to 0.2 L/kg. Acidosis increases the volume of distribution because of the enhancement of tissue penetration of salicylate. Biological half-life by route of exposure: The plasma salicylate half-life following therapeutic doses is 2 to 4.5 hours, but in over-dosage, increases to 18 to 36 hours. When the metabolic pathway is saturated (conjugation with glycine), zero order kinetics apply and thus the elimination half-life cannot be derived correctly. Metabolism: At low dosage, approximately 80% of salicylic acid is metabolized in the liver. Conjugation with glycine, forms salicyluric acid and when conjugated with glucuronic acid, acyl and phenolic glucuronide are formed. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large doses, the kinetics switch from first order to zero order (Michaelis-Menten) kinetics. Elimination and excretion: Salicylates are excreted mainly by the kidney as salicylic acid, salicyluric acid, salicylic glucuronides and gentisic acid. The proportion excreted of each metabolite, depends upon urinary pH. With urinary alkalinisation, salicylic acid excretion is enhanced. Mode of action: Toxicodynamics: Marked hyperventilation occurs as a result of direct stimulation of the respiratory centre. Indirect stimulation of respiration is caused by an increased production of CO₂ as a result of salicylate-induced uncoupling of oxidative phosphorylation. Respiratory alkalosis develops as a result of the direct and indirect stimulation of the respiratory centre. In an attempt to compensate, bicarbonate accompanied by sodium, potassium and water, is excreted in the urine. Dehydration and hypokalemia result, but more importantly, the loss of bicarbonate diminishes the buffering capacity of the body and allows the development of a metabolic acidosis. The pyretic effect of toxic doses of salicylate is a direct result of the uncoupling of oxidative phosphorylation. High doses of salicylate have additional toxic effects on the central nervous system consisting of stimulation(including convulsions) followed by depression, confusion, dizziness, asterixis, delirium, psychosis, stupor and coma. Very high doses have depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse secondary to vasomotor depression. The loss of buffering capacity and the effects of salicylate on carbohydrate, lipid and protein metabolism lead to the development of a metabolic acidosis or, more commonly in practice, a mixed acid base disturbance. Both hypo- and hyperglycemia may occur in salicylate poisoning. The former most probably due to an increased tissue demand for glucose oxidation due to the uncoupling of oxidative phosphorylation. Neuroglycopenia can occur in the presence of normal blood glucose concentrations. If hepatic glycogen stores are adequate, catecholamines production stimulates glycogenolysis leading to hyperglycemia which can persist for several days. Salicylate

intoxication is often accompanied by hypothermia due to a warfarin like action of salicylate on the vitamin K1 epoxide cycle, which rarely causes clinical problems. Pharmacodynamics: Salicylic acid alleviates pain, lowers an elevated body temperature and inflammation by inhibiting the synthesis of prostaglandins that occur in inflamed tissues. Salicylate inhibits the conversion of arachidonic acid to the unstable endoperoxide intermediate PG G₂, which is catalyzed by the enzyme cyclo oxygenase. Platelets are especially susceptible to this action as they are incapable of regenerating the enzyme, presumably they have little or no capacity for protein biosynthesis. Cyclooxygenase(COX) is present in two main isoforms. COX-1 is the isoform of the enzyme and is present under normal physiological conditions. COX-2 is the inducible isoform of the enzyme and is induced in settings of inflammation (production of eicosanoids and kinins). Inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcer. Adults: Since salicylic acid is available only in topical preparations, human data on toxicity have not been reported. However, the chinese medicated oil, which contains 67% methyl salicylate induced severe salicylate poisoning. Salicylic acid concentrations above 800 mg/L after 6 hours post exposure is severely toxic and may be lethal. Children: Salicylate intoxication is often more serious in small children (1-4 years) than in older children, due to an early development of a metabolic acidosis rather than a respiratory alkalosis. Teratogenicity: There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have a significantly reduced mass at birth. In addition, there is an increase in prenatal mortality, anemia, antepartum and postpartum haemorrhage, prolonged gestation and complicated deliveries. These effects occur when salicylates are administered during the third trimester, and thus its use during this period of pregnancy should be avoided. Interactions: Salicylic acid is highly protein-bound and may increase the unbound or free drug concentrations of other drugs such as hypoglycemics, anticoagulants and methotrexate(an antimetabolite chemotherapeutic drug), reaching toxic levels of these agents. The uricosuric activity of phenylbutazone, probenecid and sulphinpyrazone is strongly antagonized by salicylate and maybe completely diminished by small doses due to decreased tubular reabsorption of uric acid. In a report of two cases of severe salicylate poisoning, asystole occurred shortly after the intravenous administration of diazepam. Main adverse effects: Salicylic acid is a gastric irritant and because of the serious damage it may cause to the stomach lining, it has not been used orally. Topical use of salicylic acid may induce allergic contact dermatitis. Salicylic acid may cause excessive drying and irritation in some people. Some individuals, especially asthmatics exhibit sensitivity to salicylates. Urticaria, angioneurotic oedema, rhinitis, severe and even fatal paroxysmal, bronchospasm and dyspnea may occur. Acute poisoning: Ingestion: Initial symptoms of salicylate poisoning may be nausea and vomiting, epigastric pain and occasionally haematemesis. Hyperventilation, sweating, flushing, fever, irritability, tinnitus and loss of hearing are the common clinical features of mild to moderate salicylate intoxication. In severe intoxication, hypoventilation, stupor, hallucination, convulsions, papilledema and coma particularly in children may occur. Metabolic acidosis, non-cardiogenic pulmonary edema, hepatotoxicity and cardiac dysrhythmias may also occur. Skin exposure: Severe poisoning has been reported as a result of the use of salicylic acid ointment for dermatological problems and in the treatment of skin burns. Chronic poisoning: Ingestion: Chronic salicylate poisoning occurred as a result of excessive therapeutic administration over a period of 12 hours or more were reported. Metabolic pathways of salicylic acid become saturated and thus plasma concentration increases, producing toxicity. Small children are at particular risk of overdose especially when fever, sweating and tachycardia of salicylate intoxication are attributed to the underlying illness and are used as indications for increasing the dose. Children may become intoxicated through breast milk. The presenting signs of chronic salicylate poisoning can include metabolic acidosis, hypoglycemia, lethargy, coma and fits. Skin exposure: Chronic usage of salicylic acid and or methyl salicylate in skin and rheumatic diseases may cause intoxication through percutaneous absorption. Life threatening salicylate poisoning caused by percutaneous absorption of salicylic acid (10% ointment) in a 7-year old boy with ichthyosis vulgaris was reported. Application of teething gels containing salicylic acid induced intoxication. Course, prognosis, cause of death: If a large quantity of a salicylate has been taken, nausea, vomiting, tinnitus, deafness, sweating, vasodilatation and hyperventilation may develop. Acid-base disturbances,

electrolyte imbalance, non cardiogenic pulmonary edema, hypoventilation and hallucination, stupor, irritability, coma and convulsions particularly in children and older patients can proceed death. Loss of consciousness in adults is very rare and when occurs indicates poor prognosis. A review of 51 fatal cases of acute salicylate poisoning in Ontario during 1983 and 1984, discovered that salicylate was the most common cause of death, due to the ingestion of single drugs. Autopsy results showed that 50% of the patients had pulmonary abnormalities, 28% had lesions of the gastrointestinal tract, 18% had nervous system abnormalities and 25.6% had no pathological changes. Mortality from chronic salicylate intoxication is considerably higher (25%) than from acute overdose (1 to 2%). Death is often due to sudden cardiac arrest or occasionally due to multiple complications following severe brain damage. Systemic description of clinical effects: Cardiovascular: Sudden cardiovascular collapse is a recognized complication of salicylate poisoning. Two patients with severe salicylate intoxication developed asystole shortly after intravenous diazepam administration. Transient myocardial dysfunction (global left ventricular shortening fraction of 23%) with pulmonary edema was found in a 13-month-old boy with salicylate poisoning. Respiratory: Non-cardiogenic pulmonary edema may occur in salicylate intoxicated patients who are over 30 years of age. Cigarette smoking, chronic salicylate ingestion, metabolic acidosis and the presence of neurological symptoms and signs on admission are strong risk factors for the subsequent development of pulmonary edema. The exact mechanism is unknown. Three possible explanations are: (1) A direct toxic effect on pulmonary microvasculature; (2) Interaction with endogenous mediators such as prostaglandins; and (3) A central nervous system mediated effect. Neurological: Central Nervous System (CNS): In moderate to severe salicylate intoxication, CNS stimulation (irritability and convulsions) followed by depression, confusion, dizziness, delirium, psychosis, asterixis, stupor and coma occur usually when metabolic acidosis is the dominant acid-base abnormality. These features are thought to be due to reduced ionisation of salicylic acid and a shift of salicylate from the plasma into the brain. Very high doses of salicylate have a depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse, secondary to vasomotor depression. Gastrointestinal: Ingestion of salicylate may result in epigastric discomfort, nausea and vomiting. Salicylic acid has more irritant effects on gastric mucosa than acetylsalicylic acid and thus has been withdrawn from oral administration for many years. Acetylsalicylic acid may also cause gastric irritation. Perforated peptic ulcer also occurs extremely rarely. Hepatic: Hepatotoxicity may occur both after the therapeutic use of salicylate or following its over-dosage. Liver biopsy revealed acute hepatocellular necrosis with periportal inflammation and fatty changes in hepatocytes. Hepatic encephalopathy (Reye's Syndrome) has been reported in children taking aspirin for treatment of viral infections such as influenza. Urinary: Renal: Oliguria sometimes occurs, which is mostly due to dehydration. Renal failure may rarely occur in individuals without volume depletion, pre-existing renal and or systemic diseases. Endocrine and reproductive systems: High doses of salicylate cause release of adrenaline from the adrenal medulla; this is thought to be partly responsible for the observed hypoglycaemia due to glycogenolysis that sometimes occurs. Large doses of salicylate stimulate corticosteroids secretion by the adrenal cortex. Dermatological: Toxic epidermal necrosis in 13 patients associated with the use of salicylate have been reported. Eye, ear, nose, throat: local effects: Eye: Transient myopia occurred in a patient following ingestion of acetylsalicylic acid. Bilateral subconjunctival hemorrhage has been reported. Ear: Tinnitus and hearing loss caused by salicylate in overdose are due to increased labyrinthine pressure. It may also be due to an effect on the hair cells of the cochlea. There is a relationship between the hearing loss and the plasma salicylate concentration. Hematological: Salicylates prolong the bleeding time due to inhibition of collagen glucosyltransferase present in membranes of platelets. As a result, the adherence of platelets to connective tissue or collagen fibres is diminished. Salicylate overdose reduces the concentration of vitamin K-dependent coagulation factors, particularly prothrombin. Immunological: Salicylates have the capacity to suppress a variety of antigen-antibody reactions such as: the inhibition of antibody production, of antigen-antibody aggregation and of antigen induced release of histamine. Salicylates also induce a non specific stabilization of capillary permeability during immunological insults. The concentration of salicylate causing this effect is high, and their relationship to the antirheumatic efficacy of salicylates is yet to be determined. Metabolic: Acid-base disturbances: Respiratory

alkalosis is more often observed in adults than in children. Metabolic acidosis develops sooner in children than in adults. However, in severe salicylate poisoning in adults, metabolic acidosis may also occur. The acidosis is not therefore due to the presence of salicylic acid itself. The principle cause is competitive inhibition of NAD⁺-dependent dehydrogenases including lactate and oxoglutarate dehydrogenase and the other oxidative enzymes such as succinate dehydrogenase. Salicylate enhances entry and oxidation of fatty acids in liver cells, leading to increased ketogenesis. Competitive inhibition of amino acyl-tRNA synthetases in pairs and amino acid incorporation results in amino-acidemia. Dehydration and vasomotor depression results in poor renal perfusion and accumulation of sulfuric and phosphoric acids. Fluid and electrolyte disturbances: Increased renal secretion of sodium, potassium and water accompanies loss of bicarbonate in the urine. Fluid loss also results from vomiting, sweating and hyperventilation. Dehydration is commonly associated with hypernatremia. (1) Oxidative Phosphorylation: The uncoupling of oxidative phosphorylation by salicylate results in the inhibition of a number of ATP-dependent reactions and an increase in O₂ uptake and CO₂ production. (2) Nitrogen compound metabolism: Toxic doses of salicylate cause a significant nitrogen imbalance, characterized by amino aciduria, though this is due in part to stimulation of active tubular absorption because of reduced ATP formation. Fat metabolism: Salicylates enhance oxidation of fatty acids in muscle, liver and other tissues together with a decrease of concentrations of plasma, free fatty acids, phospholipids and cholesterol. Allergic reactions: Some people particularly asthmatics, exhibit marked sensitivity to salicylate, resulting in various reactions including urticaria and other skin eruptions, angioneuritis, oedema, rhinitis and severe and even fatal paroxysmal bronchospasm and dyspnea, hypotension, shock and syncope. Despite the fact that the symptoms (such as the ones mentioned above) resemble anaphylaxis, this reaction does not appear to be immunological in nature. It may be a shunt towards the lipoxygenase pathway leading to an increased production of leukotrienes and other inflammatory mediators. Although, this hypothesis is unproved and it does not explain why only a minority of patients with asthma or other predisposing conditions display the reaction. Even so, results in a small number of patients suggest that blockade of 5-lipoxygenase with the drug zileuton may prevent symptoms and signs of aspirin intolerance. Other clinical effects: The relationship between the use of salicylate and Reye's syndrome in children and adolescents (mostly 5 to 15 years) has been demonstrated by epidemiological studies. Special risks: Salicylate intoxication may occur through placental transfer and breast milk. Investigated as a mutagen and reproductive effector.

- STOT-single exposure: IDENTIFICATION: Salicylic acid is an analgesic and antipyretic medication. Salicylic acid in the form of esters was found in several plants, notably in wintergreen leaves and the bark of sweet birch. It was made synthetically by heating sodium phenolate with carbon dioxide under pressure and microbial oxidation of naphthalene. Salicylic acid is colorless or white crystals. Colourless acicular crystals or a white crystalline powder. The synthetic form is white but if prepared from natural methyl salicylate, it may have a slightly yellow or pink tint. Salicylic acid is a white crystalline powder with a sweetish acrid taste. If prepared from natural methyl salicylate, it may have a faint mint like odor. It is available in forms of ointments, cream, gel, transdermal patches, liquids and plaster. Salicylic acid is soluble in water, boiling water, alcohol, ether and chloroform. Salicylic acid has keratolytic properties and is applied topically in the treatment of hyperkeratotic and scaling conditions such as dandruff, ichthyosis and psoriasis. Initially a concentration of 2% is used increasing to about 6% if necessary. It is often used in conjunction with many other agents, such as benzoic acid, coal tar, resorcinol and sulfur. Salicylic acid is also used in the form of paint and in the form of collodion basis (10 to 17%) or as a plaster (20 to 50%) to destroy warts and corns. It also possesses fungicidal properties and is used topically in the treatment of fungal skin infections such as tinea. HUMAN EXPOSURE: Main risks and target organs: The toxic effects of salicylic acid and salicylates are complex. Main risks with oral therapeutic doses are mostly gastrointestinal irritation. Hepatic encephalopathy (Reye's Syndrome) has been reported in children who had taken aspirin for treatment of viral infections such as influenza. Toxic doses of salicylate stimulate the respiratory centre leading to respiratory alkalosis. In severe intoxication, metabolic acidosis, water and electrolyte loss occur as the principle secondary consequences. Central nervous system toxicity includes, tinnitus, hearing loss and in very severe cases particularly in children convulsions

and coma. Target organs are central nervous system, lungs, kidneys and liver. Summary of clinical effects: Following oral ingestion of salicylic acid and or any other salicylate, nausea, vomiting, epigastric discomfort, tinnitus, loss of hearing, sweating, flushing (vasodilatation) tachypnea and hyperpnea are commonly observed. Local gastrointestinal (GI) irritation of SA is more marked than ASA (acetylsalicylic acid). In severe intoxication irritability, tremor, blurred vision, mental confusion, delirium, stupor, coma, fever, cerebral edema and cardiorespiratory arrest may occur. Central nervous system toxicity and gastrointestinal haemorrhage are more common after chronic (therapeutic) intoxication. A marked alteration of acid base balance from respiratory alkalosis to metabolic acidosis may be observed. In severe salicylate intoxication in adults, non cardiogenic pulmonary edema, nonfocal neurological abnormalities, unexplained ketosis and a prolonged prothrombin time can occur. Skin eruption and subconjunctival hemorrhage may be seen but marked thrombocytopenia is rare. Methyl salicylate poisoning has the odor of the drug which can be detected on the breath and in the urine and vomit. Central nervous system stimulation, intense hyperpnea and hyperpyrexia are prominent features. Diagnosis: Symptoms and signs of oral ingestion of salicylic acid overdose usually commence by nausea, vomiting and epigastric discomfort. However, in mild salicylism particularly with therapeutic intoxication, tinnitus, loss of hearing, dizziness, sweating, and flushing are more common. Severe salicylate poisoning is associated with marked respiratory and nervous system toxicity. Hyperventilation and respiratory alkalosis are more common in adults, whereas hypoventilation and metabolic acidosis are more commonly observed in children. A rapid screening test for the presence of salicylate in the urine may indicate the use of the drug. Estimation of salicylate concentration in plasma/serum can confirm the diagnosis and reveals the severity of intoxication. Due to the severe gastric irritation which salicylic acid causes, it is no longer used orally. However, when used topically it may cause an allergic contact rash in some people. If applied to large areas of skin, it may be absorbed into the blood stream and induce salicylism. Routes of entry: Oral: Salicylic acid causes gastric irritation and thus, there is no oral pharmaceutical available. However, Chinese medicated oil which contains 67% methyl salicylate has been taken orally. Dermal: Salicylic acid is readily absorbed from the skin and may induce toxicity (salicylism). Kinetics: Absorption by route of exposure: Salicylic acid is readily absorbed from the skin and may cause toxicity, particularly in children and the newborn. Herbal products such as the chinese medicated oil which contains methyl salicylate is also absorbed through gastrointestinal mucosa following ingestion. Distribution by route of exposure: About 50 to 80% of salicylate in the blood is bound to plasma proteins, while the rest remains in the active ionized state; protein binding is concentration dependent. Saturation of binding sites lead to more free salicylate and increased toxicity. The apparent volume of distribution is 0.1 to 0.2 L/kg. Acidosis increases the volume of distribution because of the enhancement of tissue penetration of salicylate. Biological half-life by route of exposure: The plasma salicylate half-life following therapeutic doses is 2 to 4.5 hours, but in over-dosage, increases to 18 to 36 hours. When the metabolic pathway is saturated (conjugation with glycine), zero order kinetics apply and thus the elimination half-life cannot be derived correctly. Metabolism: At low dosage, approximately 80% of salicylic acid is metabolized in the liver. Conjugation with glycine, forms salicyluric acid and when conjugated with glucuronic acid, acyl and phenolic glucuronide are formed. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large doses, the kinetics switch from first order to zero order (Michaelis-Menten) kinetics. Elimination and excretion: Salicylates are excreted mainly by the kidney as salicylic acid, salicyluric acid, salicylic glucuronides and gentisic acid. The proportion excreted of each metabolite, depends upon urinary pH. With urinary alkalinisation, salicylic acid excretion is enhanced. Mode of action: Toxicodynamics: Marked hyperventilation occurs as a result of direct stimulation of the respiratory centre. Indirect stimulation of respiration is caused by an increased production of CO₂ as a result of salicylate-induced uncoupling of oxidative phosphorylation. Respiratory alkalosis develops as a result of the direct and indirect stimulation of the respiratory centre. In an attempt to compensate, bicarbonate accompanied by sodium, potassium and water, is excreted in the urine. Dehydration and hypokalemia result, but more importantly, the loss of bicarbonate diminishes the buffering capacity of the body and allows the development of a metabolic acidosis. The pyretic effect of toxic doses of salicylate is a direct result of the uncoupling of oxidative phosphorylation. High doses of salicylate have additional

toxic effects on the central nervous system consisting of stimulation(including convulsions) followed by depression, confusion, dizziness, asterixis, delirium, psychosis, stupor and coma. Very high doses have depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse secondary to vasomotor depression. The loss of buffering capacity and the effects of salicylate on carbohydrate, lipid and protein metabolism lead to the development of a metabolic acidosis or, more commonly in practice, a mixed acid base disturbance. Both hypo-and hyperglycemia may occur in salicylate poisoning. The former most probably due to an increased tissue demand for glucose oxidation due to the uncoupling of oxidative phosphorylation. Neuroglycopenia can occur in the presence of normal blood glucose concentrations. If hepatic glycogen stores are adequate, catecholamines production stimulates glycogenolysis leading to hyperglycemia which can persist for several days. Salicylate intoxication is often accompanied by hypothermia due to a warfarin like action of salicylate on the vitamin K1 epoxide cycle, which rarely causes clinical problems. Pharmacodynamics: Salicylic acid alleviates pain, lowers an elevated body temperature and inflammation by inhibiting the synthesis of prostaglandins that occur in inflamed tissues. Salicylate inhibits the conversion of arachidonic acid to the unstable endoperoxide intermediate PG G₂, which is catalyzed by the enzyme cyclo oxygenase. Platelets are especially susceptible to this action as they are incapable of regenerating the enzyme, presumably they have little or no capacity for protein biosynthesis. Cyclooxygenase(COX) is present in two main isoforms. COX-1 is the isoform of the enzyme and is present under normal physiological conditions. COX-2 is the inducible isoform of the enzyme and is induced in settings of inflammation (production of eicosanoids and kinins). Inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcer. Adults: Since salicylic acid is available only in topical preparations, human data on toxicity have not been reported. However, the chinese medicated oil, which contains 67% methyl salicylate induced severe salicylate poisoning. Salicylic acid concentrations above 800 mg/L after 6 hours post exposure is severely toxic and may be lethal. Children: Salicylate intoxication is often more serious in small children (1-4 years) than in older children, due to an early development of a metabolic acidosis rather than a respiratory alkalosis. Teratogenicity: There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have a significantly reduced mass at birth. In addition, there is an increase in prenatal mortality, anemia, antepartum and postpartum haemorrhage, prolonged gestation and complicated deliveries. These effects occur when salicylates are administered during the third trimester, and thus its use during this period of pregnancy should be avoided. Interactions: Salicylic acid is highly protein-bound and may increase the unbound or free drug concentrations of other drugs such as hypoglycemics, anticoagulants and methotrexate(an antimetabolite chemotherapeutic drug), reaching toxic levels of these agents. The uricosuric activity of phenylbutazone, probenecid and sulphinpyrazone is strongly antagonized by salicylate and maybe completely diminished by small doses due to decreased tubular reabsorption of uric acid. In a report of two cases of severe salicylate poisoning, asystole occurred shortly after the intravenous administration of diazepam. Main adverse effects: Salicylic acid is a gastric irritant and because of the serious damage it may cause to the stomach lining, it has not been used orally. Topical use of salicylic acid may induce allergic contact dermatitis. Salicylic acid may cause excessive drying and irritation in some people. Some individuals, especially asthmatics exhibit sensitivity to salicylates. Urticaria, angioneurotic oedema, rhinitis, severe and even fatal paroxysmal, bronchospasm and dyspnea may occur. Acute poisoning: Ingestion: Initial symptoms of salicylate poisoning may be nausea and vomiting, epigastric pain and occasionally haematemesis. Hyperventilation, sweating, flushing, fever, irritability, tinnitus and loss of hearing are the common clinical features of mild to moderate salicylate intoxication. In severe intoxication, hypoventilation, stupor, hallucination, convulsions, papilledema and coma particularly in children may occur. Metabolic acidosis, non-cardiogenic pulmonary edema, hepatotoxicity and cardiac dysrhythmias may also occur. Skin exposure: Severe poisoning has been reported as a result of the use of salicylic acid ointment for dermatological problems and in the treatment of skin burns. Chronic poisoning: Ingestion: Chronic salicylate poisoning occurred as a result of excessive therapeutic administration over a period of 12 hours or more were reported. Metabolic pathways of salicylic acid become saturated and thus plasma concentration

increases, producing toxicity. Small children are at particular risk of overdose especially when fever, sweating and tachycardia of salicylate intoxication are attributed to the underlying illness and are used as indications for increasing the dose. Children may become intoxicated through breast milk. The presenting signs of chronic salicylate poisoning can include metabolic acidosis, hypoglycemia, lethargy, coma and fits. Skin exposure: Chronic usage of salicylic acid and or methyl salicylate in skin and rheumatic diseases may cause intoxication through percutaneous absorption. Life threatening salicylate poisoning caused by percutaneous absorption of salicylic acid (10% ointment) in a 7-year old boy with ichthyosis vulgaris was reported. Application of teething gels containing salicylic acid induced intoxication. Course, prognosis, cause of death: If a large quantity of a salicylate has been taken, nausea, vomiting, tinnitus, deafness, sweating, vasodilatation and hyperventilation may develop. Acid-base disturbances, electrolyte imbalance, non cardiogenic pulmonary edema, hypoventilation and hallucination, stupor, irritability, coma and convulsions particularly in children and older patients can proceed death. Loss of consciousness in adults is very rare and when occurs indicates poor prognosis. A review of 51 fatal cases of acute salicylate poisoning in Ontario during 1983 and 1984, discovered that salicylate was the most common cause of death, due to the ingestion of single drugs. Autopsy results showed that 50% of the patients had pulmonary abnormalities, 28% had lesions of the gastrointestinal tract, 18% had nervous system abnormalities and 25.6% had no pathological changes. Mortality from chronic salicylate intoxication is considerably higher (25%) than from acute overdose (1 to 2%). Death is often due to sudden cardiac arrest or occasionally due to multiple complications following severe brain damage. Systemic description of clinical effects: Cardiovascular: Sudden cardiovascular collapse is a recognized complication of salicylate poisoning. Two patients with severe salicylate intoxication developed asystole shortly after intravenous diazepam administration. Transient myocardial dysfunction (global left ventricular shortening fraction of 23%) with pulmonary edema was found in a 13-month-old boy with salicylate poisoning. Respiratory: Non-cardiogenic pulmonary edema may occur in salicylate intoxicated patients who are over 30 years of age. Cigarette smoking, chronic salicylate ingestion, metabolic acidosis and the presence of neurological symptoms and signs on admission are strong risk factors for the subsequent development of pulmonary edema. The exact mechanism is unknown. Three possible explanations are: (1) A direct toxic effect on pulmonary microvasculature; (2) Interaction with endogenous mediators such as prostaglandins; and (3) A central nervous system mediated effect. Neurological: Central Nervous System (CNS): In moderate to severe salicylate intoxication, CNS stimulation (irritability and convulsions) followed by depression, confusion, dizziness, delirium, psychosis, asterixis, stupor and coma occur usually when metabolic acidosis is the dominant acid-base abnormality. These features are thought to be due to reduced ionisation of salicylic acid and a shift of salicylate from the plasma into the brain. Very high doses of salicylate have a depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse, secondary to vasomotor depression. Gastrointestinal: Ingestion of salicylate may result in epigastric discomfort, nausea and vomiting. Salicylic acid has more irritant effects on gastric mucosa than acetylsalicylic acid and thus has been withdrawn from oral administration for many years. Acetylsalicylic acid may also cause gastric irritation. Perforated peptic ulcer also occurs extremely rarely. Hepatic: Hepatotoxicity may occur both after the therapeutic use of salicylate or following its over-dosage. Liver biopsy revealed acute hepatocellular necrosis with periportal inflammation and fatty changes in hepatocytes. Hepatic encephalopathy (Reye's Syndrome) has been reported in children taking aspirin for treatment of viral infections such as influenza. Urinary: Renal: Oliguria sometimes occurs, which is mostly due to dehydration. Renal failure may rarely occur in individuals without volume depletion, pre-existing renal and or systemic diseases. Endocrine and reproductive systems: High doses of salicylate cause release of adrenaline from the adrenal medulla; this is thought to be partly responsible for the observed hypoglycaemia due to glycogenolysis that sometimes occurs. Large doses of salicylate stimulate corticosteroids secretion by the adrenal cortex. Dermatological: Toxic epidermal necrosis in 13 patients associated with the use of salicylate have been reported. Eye, ear, nose, throat: local effects: Eye: Transient myopia occurred in a patient following ingestion of acetylsalicylic acid. Bilateral subconjunctival hemorrhage has been reported. Ear: Tinnitus and hearing loss caused by salicylate in overdose are due to increased labyrinthine pressure. It may also be

due to an effect on the hair cells of the cochlea. There is a relationship between the hearing loss and the plasma salicylate concentration. Hematological: Salicylates prolong the bleeding time due to inhibition of collagen glucosyltransferase present in membranes of platelets. As a result, the adherence of platelets to connective tissue or collagen fibres is diminished. Salicylate overdose reduces the concentration of vitamin K-dependent coagulation factors, particularly prothrombin. Immunological: Salicylates have the capacity to suppress a variety of antigen-antibody reactions such as: the inhibition of antibody production, of antigen-antibody aggregation and of antigen induced release of histamine. Salicylates also induce a non specific stabilization of capillary permeability during immunological insults. The concentration of salicylate causing this effect is high, and their relationship to the antirheumatic efficacy of salicylates is yet to be determined. Metabolic: Acid-base disturbances: Respiratory alkalosis is more often observed in adults than in children. Metabolic acidosis develops sooner in children than in adults. However, in severe salicylate poisoning in adults, metabolic acidosis may also occur. The acidosis is not therefore due to the presence of salicylic acid itself. The principle cause is competitive inhibition of NAD⁺-dependent dehydrogenases including lactate and oxoglutarate dehydrogenase and the other oxidative enzymes such as succinate dehydrogenase. Salicylate enhances entry and oxidation of fatty acids in liver cells, leading to increased ketogenesis. Competitive inhibition of amino acyl-tRNA synthetases in pairs and amino acid incorporation results in amino-acidemia. Dehydration and vasomotor depression results in poor renal perfusion and accumulation of sulfuric and phosphoric acids. Fluid and electrolyte disturbances: Increased renal secretion of sodium, potassium and water accompanies loss of bicarbonate in the urine. Fluid loss also results from vomiting, sweating and hyperventilation. Dehydration is commonly associated with hypernatremia. (1) Oxidative Phosphorylation: The uncoupling of oxidative phosphorylation by salicylate results in the inhibition of a number of ATP-dependent reactions and an increase in O₂ uptake and CO₂ production. (2) Nitrogen compound metabolism: Toxic doses of salicylate cause a significant nitrogen imbalance, characterized by amino aciduria, though this is due in part to stimulation of active tubular absorption because of reduced ATP formation. Fat metabolism: Salicylates enhance oxidation of fatty acids in muscle, liver and other tissues together with a decrease of concentrations of plasma, free fatty acids, phospholipids and cholesterol. Allergic reactions: Some people particularly asthmatics, exhibit marked sensitivity to salicylate, resulting in various reactions including urticaria and other skin eruptions, angioneuritis, oedema, rhinitis and severe and even fatal paroxysmal bronchospasm and dyspnea, hypotension, shock and syncope. Despite the fact that the symptoms (such as the ones mentioned above) resemble anaphylaxis, this reaction does not appear to be immunological in nature. It may be a shunt towards the lipoxygenase pathway leading to an increased production of leukotrienes and other inflammatory mediators. Although, this hypothesis is unproved and it does not explain why only a minority of patients with asthma or other predisposing conditions display the reaction. Even so, results in a small number of patients suggest that blockade of 5-lipoxygenase with the drug zileuton may prevent symptoms and signs of aspirin intolerance. Other clinical effects: The relationship between the use of salicylate and Reye's syndrome in children and adolescents (mostly 5 to 15 years) has been demonstrated by epidemiological studies. Special risks: Salicylate intoxication may occur through placental transfer and breast milk. /AQUATIC SPECIES/ Metabolic products are often more toxic than their pharmacological parent compounds. Therefore, the acute and chronic effects of the main metabolites--salicylic acid (SAL), gentisic acid (GEN), and o-hydroxyhippuric acid (HDP)--of acetylsalicylic acid (ASA), the active ingredient in Aspirin and many other pharmaceuticals, were assessed using standard (*Daphnia magna*) and autochthonous (*Daphnia longispina*) cladocerans. The sequence of decreasing levels of acute and chronic toxicity of ASA metabolites to daphnids was GEN > SAL > HDP. HDP did not present acute toxicity, but chronic exposures enabled the production of abnormal neonates and, in particular, egg abortion. Thus, reproduction was the end point most susceptible to HDP. On the other hand, SAL and GEN induced changes in the normal patterns of reproduction and growth of both species. In general, *D. longispina* was more sensitive than was *D. magna*, although the population growth of the autochthonous species was superior under SAL exposures than that of the standard test species. Although the concentrations that were determined to have a toxic effect were above the levels detected in aquatic environmental samples, exposure to low levels of pharmacologically

active substances for a duration longer than the test period may induce changes in nontarget organisms.

- STOT-repeated exposure: IDENTIFICATION: Salicylic acid is an analgesic and antipyretic medication. Salicylic acid in the form of esters was found in several plants, notably in wintergreen leaves and the bark of sweet birch. It was made synthetically by heating sodium phenolate with carbon dioxide under pressure and microbial oxidation of naphthalene. Salicylic acid is colorless or white crystals. Colourless acicular crystals or a white crystalline powder. The synthetic form is white but if prepared from natural methyl salicylate, it may have a slightly yellow or pink tint. Salicylic acid is a white crystalline powder with a sweetish acrid taste. If prepared from natural methyl salicylate, it may have a faint mint like odor. It is available in forms of ointments, cream, gel, transdermal patches, liquids and plaster. Salicylic acid is soluble in water, boiling water, alcohol, ether and chloroform. Salicylic acid has keratolytic properties and is applied topically in the treatment of hyperkeratotic and scaling conditions such as dandruff, ichthyosis and psoriasis. Initially a concentration of 2% is used increasing to about 6% if necessary. It is often used in conjunction with many other agents, such as benzoic acid, coal tar, resorcinol and sulfur. Salicylic acid is also used in the form of paint and in the form of collodion basis (10 to 17%) or as a plaster (20 to 50%) to destroy warts and corns. It also possesses fungicidal properties and is used topically in the treatment of fungal skin infections such as tinea. HUMAN EXPOSURE: Main risks and target organs: The toxic effects of salicylic acid and salicylates are complex. Main risks with oral therapeutic doses are mostly gastrointestinal irritation. Hepatic encephalopathy (Reye's Syndrome) has been reported in children who had taken aspirin for treatment of viral infections such as influenza. Toxic doses of salicylate stimulate the respiratory centre leading to respiratory alkalosis. In severe intoxication, metabolic acidosis, water and electrolyte loss occur as the principle secondary consequences. Central nervous system toxicity includes, tinnitus, hearing loss and in very severe cases particularly in children convulsions and coma. Target organs are central nervous system, lungs, kidneys and liver. Summary of clinical effects: Following oral ingestion of salicylic acid and or any other salicylate, nausea, vomiting, epigastric discomfort, tinnitus, loss of hearing, sweating, flushing (vasodilatation) tachypnea and hyperpnea are commonly observed. Local gastrointestinal (GI) irritation of SA is more marked than ASA (acetylsalicylic acid). In severe intoxication irritability, tremor, blurred vision, mental confusion, delirium, stupor, coma, fever, cerebral edema and cardiorespiratory arrest may occur. Central nervous system toxicity and gastrointestinal haemorrhage are more common after chronic (therapeutic) intoxication. A marked alteration of acid base balance from respiratory alkalosis to metabolic acidosis may be observed. In severe salicylate intoxication in adults, non cardiogenic pulmonary edema, nonfocal neurological abnormalities, unexplained ketosis and a prolonged prothrombin time can occur. Skin eruption and subconjunctival hemorrhage may be seen but marked thrombocytopenia is rare. Methyl salicylate poisoning has the odor of the drug which can be detected on the breath and in the urine and vomit. Central nervous system stimulation, intense hyperpnea and hyperpyrexia are prominent features. Diagnosis: Symptoms and signs of oral ingestion of salicylic acid overdose usually commence by nausea, vomiting and epigastric discomfort. However, in mild salicylism particularly with therapeutic intoxication, tinnitus, loss of hearing, dizziness, sweating, and flushing are more common. Severe salicylate poisoning is associated with marked respiratory and nervous system toxicity. Hyperventilation and respiratory alkalosis are more common in adults, whereas hypoventilation and metabolic acidosis are more commonly observed in children. A rapid screening test for the presence of salicylate in the urine may indicate the use of the drug. Estimation of salicylate concentration in plasma/serum can confirm the diagnosis and reveals the severity of intoxication. Due to the severe gastric irritation which salicylic acid causes, it is no longer used orally. However, when used topically it may cause an allergic contact rash in some people. If applied to large areas of skin, it may be absorbed into the blood stream and induce salicylism. Routes of entry: Oral: Salicylic acid causes gastric irritation and thus, there is no oral pharmaceutical available. However, Chinese medicated oil which contains 67% methyl salicylate has been taken orally. Dermal: Salicylic acid is readily absorbed from the skin and may induce toxicity (salicylism). Kinetics: Absorption by route of exposure: Salicylic acid is readily absorbed from the skin and may cause toxicity, particularly in children and the newborn. Herbal products such as the chinese medicated oil which contains methyl salicylate is also absorbed through gastrointestinal mucosa following ingestion.

Distribution by route of exposure: About 50 to 80% of salicylate in the blood is bound to plasma proteins, while the rest remains in the active ionized state; protein binding is concentration dependent. Saturation of binding sites lead to more free salicylate and increased toxicity. The apparent volume of distribution is 0.1 to 0.2 L/kg. Acidosis increases the volume of distribution because of the enhancement of tissue penetration of salicylate. Biological half-life by route of exposure: The plasma salicylate half-life following therapeutic doses is 2 to 4.5 hours, but in over-dosage, increases to 18 to 36 hours. When the metabolic pathway is saturated (conjugation with glycine), zero order kinetics apply and thus the elimination half-life cannot be derived correctly. Metabolism: At low dosage, approximately 80% of salicylic acid is metabolized in the liver. Conjugation with glycine, forms salicyluric acid and when conjugated with glucuronic acid, acyl and phenolic glucuronide are formed. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large doses, the kinetics switch from first order to zero order (Michaelis-Menten) kinetics. Elimination and excretion: Salicylates are excreted mainly by the kidney as salicylic acid, salicyluric acid, salicylic glucuronides and gentisic acid. The proportion excreted of each metabolite, depends upon urinary pH. With urinary alkalinisation, salicylic acid excretion is enhanced. Mode of action: Toxicodynamics: Marked hyperventilation occurs as a result of direct stimulation of the respiratory centre. Indirect stimulation of respiration is caused by an increased production of CO₂ as a result of salicylate-induced uncoupling of oxidative phosphorylation. Respiratory alkalosis develops as a result of the direct and indirect stimulation of the respiratory centre. In an attempt to compensate, bicarbonate accompanied by sodium, potassium and water, is excreted in the urine. Dehydration and hypokalemia result, but more importantly, the loss of bicarbonate diminishes the buffering capacity of the body and allows the development of a metabolic acidosis. The pyretic effect of toxic doses of salicylate is a direct result of the uncoupling of oxidative phosphorylation. High doses of salicylate have additional toxic effects on the central nervous system consisting of stimulation(including convulsions) followed by depression, confusion, dizziness, asterixis, delirium, psychosis, stupor and coma. Very high doses have depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse secondary to vasomotor depression. The loss of buffering capacity and the effects of salicylate on carbohydrate, lipid and protein metabolism lead to the development of a metabolic acidosis or, more commonly in practice, a mixed acid base disturbance. Both hypo-and hyperglycemia may occur in salicylate poisoning. The former most probably due to an increased tissue demand for glucose oxidation due to the uncoupling of oxidative phosphorylation. Neuroglycopenia can occur in the presence of normal blood glucose concentrations. If hepatic glycogen stores are adequate, catecholamines production stimulates glycogenolysis leading to hyperglycemia which can persist for several days. Salicylate intoxication is often accompanied by hypofibrinogenemia due to a warfarin like action of salicylate on the vitamin K1 epoxide cycle, which rarely causes clinical problems. Pharmacodynamics: Salicylic acid alleviates pain, lowers an elevated body temperature and inflammation by inhibiting the synthesis of prostaglandins that occur in inflamed tissues. Salicylate inhibits the conversion of arachidonic acid to the unstable endoperoxide intermediate PG G₂, which is catalyzed by the enzyme cyclo oxygenase. Platelets are especially susceptible to this action as they are incapable of regenerating the enzyme, presumably they have little or no capacity for protein biosynthesis. Cyclooxygenase(COX) is present in two main isoforms. COX-1 is the isoform of the enzyme and is present under normal physiological conditions. COX-2 is the inducible isoform of the enzyme and is induced in settings of inflammation (production of eicosanoids and kinins). Inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcer. Adults: Since salicylic acid is available only in topical preparations, human data on toxicity have not been reported. However, the chinese medicated oil, which contains 67% methyl salicylate induced severe salicylate poisoning. Salicylic acid concentrations above 800 mg/L after 6 hours post exposure is severely toxic and may be lethal. Children: Salicylate intoxication is often more serious in small children (1-4 years) than in older children, due to an early development of a metabolic acidosis rather than a respiratory alkalosis. Teratogenicity: There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have a significantly reduced mass at birth. In addition, there is an increase in prenatal mortality, anemia, antepartum and postpartum

haemorrhage, prolonged gestation and complicated deliveries. These effects occur when salicylates are administered during the third trimester, and thus its use during this period of pregnancy should be avoided.

Interactions: Salicylic acid is highly protein-bound and may increase the unbound or free drug concentrations of other drugs such as hypoglycemics, anticoagulants and methotrexate (an antimetabolite chemotherapeutic drug), reaching toxic levels of these agents. The uricosuric activity of phenylbutazone, probenecid and sulphinyprazone is strongly antagonized by salicylate and maybe completely diminished by small doses due to decreased tubular reabsorption of uric acid. In a report of two cases of severe salicylate poisoning, asystole occurred shortly after the intravenous administration of diazepam. Main adverse effects: Salicylic acid is a gastric irritant and because of the serious damage it may cause to the stomach lining, it has not been used orally. Topical use of salicylic acid may induce allergic contact dermatitis. Salicylic acid may cause excessive drying and irritation in some people. Some individuals, especially asthmatics exhibit sensitivity to salicylates. Urticaria, angioneurotic oedema, rhinitis, severe and even fatal paroxysmal, bronchospasm and dyspnea may occur. Acute poisoning: Ingestion: Initial symptoms of salicylate poisoning may be nausea and vomiting, epigastric pain and occasionally haematemesis. Hyperventilation, sweating, flushing, fever, irritability, tinnitus and loss of hearing are the common clinical features of mild to moderate salicylate intoxication. In severe intoxication, hypoventilation, stupor, hallucination, convulsions, papilledema and coma particularly in children may occur. Metabolic acidosis, non-cardiogenic pulmonary edema, hepatotoxicity and cardiac dysrhythmias may also occur. Skin exposure: Severe poisoning has been reported as a result of the use of salicylic acid ointment for dermatological problems and in the treatment of skin burns. Chronic poisoning: Ingestion: Chronic salicylate poisoning occurred as a result of excessive therapeutic administration over a period of 12 hours or more were reported. Metabolic pathways of salicylic acid become saturated and thus plasma concentration increases, producing toxicity. Small children are at particular risk of overdose especially when fever, sweating and tachycardia of salicylate intoxication are attributed to the underlying illness and are used as indications for increasing the dose. Children may become intoxicated through breast milk. The presenting signs of chronic salicylate poisoning can include metabolic acidosis, hypoglycemia, lethargy, coma and fits. Skin exposure: Chronic usage of salicylic acid and or methyl salicylate in skin and rheumatic diseases may cause intoxication through percutaneous absorption. Life threatening salicylate poisoning caused by percutaneous absorption of salicylic acid (10% ointment) in a 7-year old boy with ichthyosis vulgaris was reported. Application of teething gels containing salicylic acid induced intoxication. Course, prognosis, cause of death: If a large quantity of a salicylate has been taken, nausea, vomiting, tinnitus, deafness, sweating, vasodilatation and hyperventilation may develop. Acid-base disturbances, electrolyte imbalance, non cardiogenic pulmonary edema, hypoventilation and hallucination, stupor, irritability, coma and convulsions particularly in children and older patients can proceed death. Loss of consciousness in adults is very rare and when occurs indicates poor prognosis. A review of 51 fatal cases of acute salicylate poisoning in Ontario during 1983 and 1984, discovered that salicylate was the most common cause of death, due to the ingestion of single drugs. Autopsy results showed that 50% of the patients had pulmonary abnormalities, 28% had lesions of the gastrointestinal tract, 18% had nervous system abnormalities and 25.6% had no pathological changes. Mortality from chronic salicylate intoxication is considerably higher (25%) than from acute overdose (1 to 2%). Death is often due to sudden cardiac arrest or occasionally due to multiple complications following severe brain damage. Systemic description of clinical effects: Cardiovascular: Sudden cardiovascular collapse is a recognized complication of salicylate poisoning. Two patients with severe salicylate intoxication developed asystole shortly after intravenous diazepam administration. Transient myocardial dysfunction (global left ventricular shortening fraction of 23%) with pulmonary edema was found in a 13-month-old boy with salicylate poisoning. Respiratory: Non-cardiogenic pulmonary edema may occur in salicylate intoxicated patients who are over 30 years of age. Cigarette smoking, chronic salicylate ingestion, metabolic acidosis and the presence of neurological symptoms and signs on admission are strong risk factors for the subsequent development of pulmonary edema. The exact mechanism is unknown. Three possible explanations are: (1) A direct toxic effect on pulmonary microvasculature; (2) Interaction with endogenous mediators such as prostaglandins; and (3) A central nervous system mediated effect. Neurological:

Central Nervous System (CNS): In moderate to severe salicylate intoxication, CNS stimulation (irritability and convulsions) followed by depression, confusion, dizziness, delirium, psychosis, asterixis, stupor and coma occur usually when metabolic acidosis is the dominant acid-base abnormality. These features are thought to be due to reduced ionisation of salicylic acid and a shift of salicylate from the plasma into the brain. Very high doses of salicylate have a depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse, secondary to vasomotor depression. Gastrointestinal: Ingestion of salicylate may result in epigastric discomfort, nausea and vomiting. Salicylic acid has more irritant effects on gastric mucosa than acetylsalicylic acid and thus has been withdrawn from oral administration for many years. Acetylsalicylic acid may also cause gastric irritation. Perforated peptic ulcer also occurs extremely rarely. Hepatic: Hepatotoxicity may occur both after the therapeutic use of salicylate or following its over-dosage. Liver biopsy revealed acute hepatocellular necrosis with periportal inflammation and fatty changes in hepatocytes. Hepatic encephalopathy (Reye's Syndrome) has been reported in children taking aspirin for treatment of viral infections such as influenza. Urinary: Renal: Oliguria sometimes occurs, which is mostly due to dehydration. Renal failure may rarely occur in individuals without volume depletion, pre-existing renal and or systemic diseases. Endocrine and reproductive systems: High doses of salicylate cause release of adrenaline from the adrenal medulla; this is thought to be partly responsible for the observed hypoglycaemia due to glycogenolysis that sometimes occurs. Large doses of salicylate stimulate corticosteroids secretion by the adrenal cortex. Dermatological: Toxic epidermal necrosis in 13 patients associated with the use of salicylate have been reported. Eye, ear, nose, throat: local effects: Eye: Transient myopia occurred in a patient following ingestion of acetylsalicylic acid. Bilateral subconjunctival hemorrhage has been reported. Ear: Tinnitus and hearing loss caused by salicylate in overdose are due to increased labyrinthine pressure. It may also be due to an effect on the hair cells of the cochlea. There is a relationship between the hearing loss and the plasma salicylate concentration. Hematological: Salicylates prolong the bleeding time due to inhibition of collagen glucosyltransferase present in membranes of platelets. As a result, the adherence of platelets to connective tissue or collagen fibres is diminished. Salicylate overdose reduces the concentration of vitamin K-dependent coagulation factors, particularly prothrombin. Immunological: Salicylates have the capacity to suppress a variety of antigen-antibody reactions such as: the inhibition of antibody production, of antigen-antibody aggregation and of antigen induced release of histamine. Salicylates also induce a non specific stabilization of capillary permeability during immunological insults. The concentration of salicylate causing this effect is high, and their relationship to the antirheumatic efficacy of salicylates is yet to be determined. Metabolic: Acid-base disturbances: Respiratory alkalosis is more often observed in adults than in children. Metabolic acidosis develops sooner in children than in adults. However, in severe salicylate poisoning in adults, metabolic acidosis may also occur. The acidosis is not therefore due to the presence of salicylic acid itself. The principle cause is competitive inhibition of NAD⁺-dependent dehydrogenases including lactate and oxoglutarate dehydrogenase and the other oxidative enzymes such as succinate dehydrogenase. Salicylate enhances entry and oxidation of fatty acids in liver cells, leading to increased ketogenesis. Competitive inhibition of amino acyl-tRNA synthetases in pairs and amino acid incorporation results in amino-acidemia. Dehydration and vasomotor depression results in poor renal perfusion and accumulation of sulfuric and phosphoric acids. Fluid and electrolyte disturbances: Increased renal secretion of sodium, potassium and water accompanies loss of bicarbonate in the urine. Fluid loss also results from vomiting, sweating and hyperventilation. Dehydration is commonly associated with hypernatremia. (1) Oxidative Phosphorylation: The uncoupling of oxidative phosphorylation by salicylate results in the inhibition of a number of ATP-dependent reactions and an increase in O₂ uptake and CO₂ production. (2) Nitrogen compound metabolism: Toxic doses of salicylate cause a significant nitrogen imbalance, characterized by amino aciduria, though this is due in part to stimulation of active tubular absorption because of reduced ATP formation. Fat metabolism: Salicylates enhance oxidation of fatty acids in muscle, liver and other tissues together with a decrease of concentrations of plasma, free fatty acids, phospholipids and cholesterol. Allergic reactions: Some people particularly asthmatics, exhibit marked sensitivity to salicylate, resulting in various reactions including urticaria and other skin eruptions, angioneuritis, oedema, rhinitis and severe

and even fatal paroxysmal bronchospasm and dyspnea, hypotension, shock and syncope. Despite the fact that the symptoms (such as the ones mentioned above) resemble anaphylaxis, this reaction does not appear to be immunological in nature. It may be a shunt towards the lipoxygenase pathway leading to an increased production of leukotrienes and other inflammatory mediators. Although, this hypothesis is unproved and it does not explain why only a minority of patients with asthma or other predisposing conditions display the reaction. Even so, results in a small number of patients suggest that blockade of 5-lipoxygenase with the drug zileuton may prevent symptoms and signs of aspirin intolerance. Other clinical effects: The relationship between the use of salicylate and Reye's syndrome in children and adolescents (mostly 5 to 15 years) has been demonstrated by epidemiological studies. Special risks: Salicylate intoxication may occur through placental transfer and breast milk. /AQUATIC SPECIES/ Ten acidic and two neutral pharmaceuticals were detected in the effluents of eight sewage treatment plants (STPs) from across Atlantic Canada. ...Six compounds (caffeine, naproxen, salicylic acid, carbamazepine, metoprolol, and sotolol) were found to persist in a small stream for a distance of at least 17 km, suggesting that small stream exposure to pharmaceutically active residues may be relatively greater than that in large bodies of water. Bioassays assessing acute and chronic effects on four organisms were conducted on four high-use drugs: Acetaminophen, ibuprofen, naproxen, and salicylic acid (metabolite of acetyl salicylic acid). Results indicated no negative effects except for the chronic algal (*Selenastrum capricornutum*) growth test on ibuprofen (no-observed-effect concentration, 10 ug/L; lowest-observed-effect concentration, 32 ug/L). Effects of these four compounds on invertebrates and plants in the receiving environments are unlikely based on the concentrations measured. - Aspiration hazard: No data available.

Likely routes of exposure

- IDENTIFICATION: Salicylic acid is an analgesic and antipyretic medication. Salicylic acid in the form of esters was found in several plants, notably in wintergreen leaves and the bark of sweet birch. It was made synthetically by heating sodium phenolate with carbon dioxide under pressure and microbial oxidation of naphthalene. Salicylic acid is colorless or white crystals. Colourless acicular crystals or a white crystalline powder. The synthetic form is white but if prepared from natural methyl salicylate, it may have a slightly yellow or pink tint. Salicylic acid is a white crystalline powder with a sweetish acid taste. If prepared from natural methyl salicylate, it may have a faint mint like odor. It is available in forms of ointments, cream, gel, transdermal patches, liquids and plaster. Salicylic acid is soluble in water, boiling water, alcohol, ether and chloroform. Salicylic acid has keratinolytic properties and is applied topically in the treatment of hyperkeratotic and scaling conditions such as dandruff, ichthyosis and psoriasis. Initially a concentration of 2% is used increasing to about 6% if necessary. It is often used in conjunction with many other agents, such as benzoic acid, coal tar, resorcinol and sulfur. Salicylic acid is also used in the form of paint and in the form of collodion basis (10 to 17%) or as a plaster (20 to 50%) to destroy warts and corns. It also possesses fungicidal properties and is used topically in the treatment of fungal skin infections such as tinea. HUMAN EXPOSURE: Main risks and target organs: The toxic effects of salicylic acid and salicylates are complex. Main risks with oral therapeutic doses are mostly gastrointestinal irritation. Hepatic encephalopathy (Reye's Syndrome) has been reported in children who had taken aspirin for treatment of viral infections such as influenza. Toxic doses of salicylate stimulate the respiratory centre leading to respiratory alkalosis. In severe intoxication, metabolic acidosis, water and electrolyte loss occur as the principle secondary consequences. Central nervous system toxicity includes, tinnitus, hearing loss and in very severe cases particularly in children convulsions and coma. Target organs are central nervous system, lungs, kidneys and liver. Summary of clinical effects: Following oral ingestion of salicylic acid and or any other salicylate, nausea, vomiting, epigastric discomfort, tinnitus, loss of hearing, sweating, flushing (vasodilatation) tachypnea and hyperpnea are commonly observed. Local gastrointestinal (GI) irritation of SA is more marked than ASA (acetylsalicylic acid). In severe intoxication irritability, tremor, blurred vision, mental confusion, delirium, stupor, coma, fever, cerebral edema and cardiorespiratory arrest may occur. Central nervous system toxicity and gastrointestinal haemorrhage are more common after chronic (therapeutic) intoxication. A marked alteration of acid base balance from respiratory alkalosis to metabolic acidosis may be observed. In severe

salicylate intoxication in adults, non cardiogenic pulmonary edema, nonfocal neurological abnormalities, unexplained ketosis and a prolonged prothrombin time can occur. Skin eruption and subconjunctival hemorrhage may be seen but marked thrombocytopenia is rare. Methyl salicylate poisoning has the odor of the drug which can be detected on the breath and in the urine and vomit. Central nervous system stimulation, intense hyperpnea and hyperpyrexia are prominent features. Diagnosis: Symptoms and signs of oral ingestion of salicylic acid overdose usually commence by nausea, vomiting and epigastric discomfort. However, in mild salicylism particularly with therapeutic intoxication, tinnitus, loss of hearing, dizziness, sweating, and flushing are more common. Severe salicylate poisoning is associated with marked respiratory and nervous system toxicity. Hyperventilation and respiratory alkalosis are more common in adults, whereas hypoventilation and metabolic acidosis are more commonly observed in children. A rapid screening test for the presence of salicylate in the urine may indicate the use of the drug. Estimation of salicylate concentration in plasma/serum can confirm the diagnosis and reveals the severity of intoxication. Due to the severe gastric irritation which salicylic acid causes, it is no longer used orally. However, when used topically it may cause an allergic contact rash in some people. If applied to large areas of skin, it may be absorbed into the blood stream and induce salicylism. Routes of entry: Oral: Salicylic acid causes gastric irritation and thus, there is no oral pharmaceutical available. However, Chinese medicated oil which contains 67% methyl salicylate has been taken orally. Dermal: Salicylic acid is readily absorbed from the skin and may induce toxicity (salicylism). Kinetics: Absorption by route of exposure: Salicylic acid is readily absorbed from the skin and may cause toxicity, particularly in children and the newborn. Herbal products such as the chinese medicated oil which contains methyl salicylate is also absorbed through gastrointestinal mucosa following ingestion. Distribution by route of exposure: About 50 to 80% of salicylate in the blood is bound to plasma proteins, while the rest remains in the active ionized state; protein binding is concentration dependent. Saturation of binding sites lead to more free salicylate and increased toxicity. The apparent volume of distribution is 0.1 to 0.2 L/kg. Acidosis increases the volume of distribution because of the enhancement of tissue penetration of salicylate. Biological half-life by route of exposure: The plasma salicylate half-life following therapeutic doses is 2 to 4.5 hours, but in over-dosage, increases to 18 to 36 hours. 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Indirect stimulation of respiration is caused by an increased production of CO₂ as a result of salicylate-induced uncoupling of oxidative phosphorylation. Respiratory alkalosis develops as a result of the direct and indirect stimulation of the respiratory centre. In an attempt to compensate, bicarbonate accompanied by sodium, potassium and water, is excreted in the urine. Dehydration and hypokalemia result, but more importantly, the loss of bicarbonate diminishes the buffering capacity of the body and allows the development of a metabolic acidosis. The pyretic effect of toxic doses of salicylate is a direct result of the uncoupling of oxidative phosphorylation. High doses of salicylate have additional toxic effects on the central nervous system consisting of stimulation(including convulsions) followed by depression, confusion, dizziness, asterixis, delirium, psychosis, stupor and coma. Very high doses have depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse secondary to vasomotor depression. The loss of buffering capacity and the effects of salicylate on carbohydrate, lipid and protein metabolism lead to the development of a metabolic acidosis or, more commonly in practice, a mixed acid base disturbance. Both hypo-and hyperglycemia may occur in salicylate poisoning. The former most probably due to an increased tissue demand for glucose oxidation due to the uncoupling of oxidative phosphorylation. Neuroglycopenia can occur in the presence of normal blood glucose

concentrations. If hepatic glycogen stores are adequate, catecholamines production stimulates glycogenolysis leading to hyperglycemia which can persist for several days. Salicylate intoxication is often accompanied by hypothermia due to a warfarin like action of salicylate on the vitamin K1 epoxide cycle, which rarely causes clinical problems. Pharmacodynamics: Salicylic acid alleviates pain, lowers an elevated body temperature and inflammation by inhibiting the synthesis of prostaglandins that occur in inflamed tissues. Salicylate inhibits the conversion of arachidonic acid to the unstable endoperoxide intermediate PG G₂, which is catalyzed by the enzyme cyclooxygenase. Platelets are especially susceptible to this action as they are incapable of regenerating the enzyme, presumably they have little or no capacity for protein biosynthesis. Cyclooxygenase(COX) is present in two main isoforms. COX-1 is the isoform of the enzyme and is present under normal physiological conditions. 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Teratogenicity: There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have a significantly reduced mass at birth. In addition, there is an increase in prenatal mortality, anemia, antepartum and postpartum haemorrhage, prolonged gestation and complicated deliveries. These effects occur when salicylates are administered during the third trimester, and thus its use during this period of pregnancy should be avoided. Interactions: Salicylic acid is highly protein-bound and may increase the unbound or free drug concentrations of other drugs such as hypoglycemics, anticoagulants and methotrexate(an antimetabolite chemotherapeutic drug), reaching toxic levels of these agents. 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Small children are at particular risk of overdose especially when fever, sweating and tachycardia of salicylate intoxication are attributed to the underlying illness and are used as indications for increasing the dose. Children may become intoxicated through breast milk. The presenting signs of chronic salicylate poisoning can include metabolic acidosis, hypoglycemia, lethargy, coma and fits. Skin exposure: Chronic usage of salicylic acid and or methyl salicylate in skin and rheumatic diseases may cause intoxication through percutaneous absorption. Life threatening salicylate poisoning caused by percutaneous absorption of salicylic acid (10% ointment) in a 7-year old boy with ichthyosis vulgaris was reported. Application of teething gels containing salicylic acid induced

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Salicylic acid has more irritant effects on gastric mucosa than acetylsalicylic acid and thus has been withdrawn from oral administration for many years. Acetylsalicylic acid may also cause gastric irritation. Perforated peptic ulcer also occurs extremely rarely. Hepatic: Hepatotoxicity may occur both after the therapeutic use of salicylate or following its over-dosage. Liver biopsy revealed acute hepatocellular necrosis with periportal inflammation and fatty changes in hepatocytes. Hepatic encephalopathy (Reye's Syndrome) has been reported in children taking aspirin for treatment of viral infections such as influenza. Urinary: Renal: Oliguria sometimes occurs, which is mostly due to dehydration. Renal failure may rarely occur in individuals without volume depletion, pre-existing renal and or systemic diseases. Endocrine and reproductive systems: High doses of salicylate cause release of adrenaline from the adrenal medulla; this is thought to be partly responsible for the observed hypoglycaemia due to glycogenolysis that sometimes occurs. Large doses of salicylate stimulate corticosteroids secretion by the adrenal cortex. Dermatological: Toxic epidermal necrosis in 13 patients associated with the use of salicylate have been reported. Eye, ear, nose, throat: local effects: Eye: Transient myopia occurred in a patient following ingestion of acetylsalicylic acid. Bilateral subconjunctival hemorrhage has been reported. Ear: Tinnitus and hearing loss caused by salicylate in overdose are due to increased labyrinthine pressure. It may also be due to an effect on the hair cells of the cochlea. There is a relationship between the hearing loss and the plasma salicylate concentration. Hematological: Salicylates prolong the bleeding time due to inhibition of collagen glucosyltransferase present in membranes of platelets. As a result, the adherence of platelets to connective tissue or collagen fibres is diminished. Salicylate overdose reduces the concentration of vitamin K-dependent coagulation factors, particularly prothrombin. Immunological: Salicylates have the capacity to suppress a variety of antigen-antibody reactions such as: the inhibition of antibody production, of antigen-antibody aggregation and of antigen induced release of histamine. Salicylates also induce a non specific stabilization of capillary permeability

during immunological insults. The concentration of salicylate causing this effect is high, and their relationship to the antirheumatic efficacy of salicylates is yet to be determined. Metabolic: Acid-base disturbances: Respiratory alkalosis is more often observed in adults than in children. Metabolic acidosis develops sooner in children than in adults. However, in severe salicylate poisoning in adults, metabolic acidosis may also occur. The acidosis is not therefore due to the presence of salicylic acid itself. The principle cause is competitive inhibition of NAD⁺-dependent dehydrogenases including lactate and oxoglutarate dehydrogenase and the other oxidative enzymes such as succinate dehydrogenase. Salicylate enhances entry and oxidation of fatty acids in liver cells, leading to increased ketogenesis. Competitive inhibition of amino acyl-tRNA synthetases in pairs and amino acid incorporation results in amino-acidemia. Dehydration and vasomotor depression results in poor renal perfusion and accumulation of sulfuric and phosphoric acids. Fluid and electrolyte disturbances: Increased renal secretion of sodium, potassium and water accompanies loss of bicarbonate in the urine. Fluid loss also results from vomiting, sweating and hyperventilation. Dehydration is commonly associated with hypernatremia. (1) Oxidative Phosphorylation: The uncoupling of oxidative phosphorylation by salicylate results in the inhibition of a number of ATP-dependent reactions and an increase in O₂ uptake and CO₂ production. (2) Nitrogen compound metabolism: Toxic doses of salicylate cause a significant nitrogen imbalance, characterized by amino aciduria, though this is due in part to stimulation of active tubular absorption because of reduced ATP formation. Fat metabolism: Salicylates enhance oxidation of fatty acids in muscle, liver and other tissues together with a decrease of concentrations of plasma, free fatty acids, phospholipids and cholesterol. Allergic reactions: Some people particularly asthmatics, exhibit marked sensitivity to salicylate, resulting in various reactions including urticaria and other skin eruptions, angioneuritis, oedema, rhinitis and severe and even fatal paroxysmal bronchospasm and dyspnea, hypotension, shock and syncope. Despite the fact that the symptoms (such as the ones mentioned above) resemble anaphylaxis, this reaction does not appear to be immunological in nature. It may be a shunt towards the lipoxygenase pathway leading to an increased production of leukotrienes and other inflammatory mediators. Although, this hypothesis is unproved and it does not explain why only a minority of patients with asthma or other predisposing conditions display the reaction. Even so, results in a small number of patients suggest that blockade of 5-lipoxygenase with the drug zileuton may prevent symptoms and signs of aspirin intolerance. Other clinical effects: The relationship between the use of salicylate and Reye's syndrome in children and adolescents (mostly 5 to 15 years) has been demonstrated by epidemiological studies. Special risks: Salicylate intoxication may occur through placental transfer and breast milk.

Symptoms related to the physical, chemical and toxicological characteristics

- IDENTIFICATION: Salicylic acid is an analgesic and antipyretic medication. Salicylic acid in the form of esters was found in several plants, notably in wintergreen leaves and the bark of sweet birch. It was made synthetically by heating sodium phenolate with carbon dioxide under pressure and microbial oxidation of naphthalene. Salicylic acid is colorless or white crystals. Colourless acicular crystals or a white crystalline powder. The synthetic form is white but if prepared from natural methyl salicylate, it may have a slightly yellow or pink tint. Salicylic acid is a white crystalline powder with a sweetish acid taste. If prepared from natural methyl salicylate, it may have a faint mint like odor. It is available in forms of ointments, cream, gel, transdermal patches, liquids and plaster. Salicylic acid is soluble in water, boiling water, alcohol, ether and chloroform. Salicylic acid has keratinolytic properties and is applied topically in the treatment of hyperkeratotic and scaling conditions such as dandruff, ichthyosis and psoriasis. Initially a concentration of 2% is used increasing to about 6% if necessary. It is often used in conjunction with many other agents, such as benzoic acid, coal tar, resorcinol and sulfur. Salicylic acid is also used in the form of paint and in the form of collodion basis (10 to 17%) or as a plaster (20 to 50%) to destroy warts and corns. It also possesses fungicidal properties and is used topically in the treatment of fungal skin infections such as tinea. HUMAN EXPOSURE: Main risks and target organs: The toxic effects of salicylic acid and salicylates are complex. Main risks with oral therapeutic doses are mostly gastrointestinal irritation. Hepatic encephalopathy (Reye's Syndrome) has been reported in children who had taken aspirin for treatment of viral infections such as influenza. Toxic doses of salicylate stimulate the respiratory centre leading to respiratory alkalosis. In severe intoxication, metabolic acidosis,

water and electrolyte loss occur as the principle secondary consequences. Central nervous system toxicity includes, tinnitus, hearing loss and in very severe cases particularly in children convulsions and coma. Target organs are central nervous system, lungs, kidneys and liver. Summary of clinical effects: Following oral ingestion of salicylic acid and or any other salicylate, nausea, vomiting, epigastric discomfort, tinnitus, loss of hearing, sweating, flushing (vasodilatation) tachypnea and hyperpnea are commonly observed. Local gastrointestinal (GI) irritation of SA is more marked than ASA (acetylsalicylic acid). In severe intoxication irritability, tremor, blurred vision, mental confusion, delirium, stupor, coma, fever, cerebral edema and cardiorespiratory arrest may occur. Central nervous system toxicity and gastrointestinal haemorrhage are more common after chronic (therapeutic) intoxication. A marked alteration of acid base balance from respiratory alkalosis to metabolic acidosis may be observed. In severe salicylate intoxication in adults, non cardiogenic pulmonary edema, nonfocal neurological abnormalities, unexplained ketosis and a prolonged prothrombin time can occur. Skin eruption and subconjunctival hemorrhage may be seen but marked thrombocytopenia is rare. Methyl salicylate poisoning has the odor of the drug which can be detected on the breath and in the urine and vomit. Central nervous system stimulation, intense hyperpnea and hyperpyrexia are prominent features. Diagnosis: Symptoms and signs of oral ingestion of salicylic acid overdose usually commence by nausea, vomiting and epigastric discomfort. However, in mild salicylism particularly with therapeutic intoxication, tinnitus, loss of hearing, dizziness, sweating, and flushing are more common. Severe salicylate poisoning is associated with marked respiratory and nervous system toxicity. Hyperventilation and respiratory alkalosis are more common in adults, whereas hypoventilation and metabolic acidosis are more commonly observed in children. A rapid screening test for the presence of salicylate in the urine may indicate the use of the drug. Estimation of salicylate concentration in plasma/serum can confirm the diagnosis and reveals the severity of intoxication. Due to the severe gastric irritation which salicylic acid causes, it is no longer used orally. However, when used topically it may cause an allergic contact rash in some people. If applied to large areas of skin, it may be absorbed into the blood stream and induce salicylism. Routes of entry: Oral: Salicylic acid causes gastric irritation and thus, there is no oral pharmaceutical available. However, Chinese medicated oil which contains 67% methyl salicylate has been taken orally. Dermal: Salicylic acid is readily absorbed from the skin and may induce toxicity (salicylism). Kinetics: Absorption by route of exposure: Salicylic acid is readily absorbed from the skin and may cause toxicity, particularly in children and the newborn. Herbal products such as the chinese medicated oil which contains methyl salicylate is also absorbed through gastrointestinal mucosa following ingestion. Distribution by route of exposure: About 50 to 80% of salicylate in the blood is bound to plasma proteins, while the rest remains in the active ionized state; protein binding is concentration dependent. Saturation of binding sites lead to more free salicylate and increased toxicity. The apparent volume of distribution is 0.1 to 0.2 L/kg. Acidosis increases the volume of distribution because of the enhancement of tissue penetration of salicylate. Biological half-life by route of exposure: The plasma salicylate half-life following therapeutic doses is 2 to 4.5 hours, but in over-dosage, increases to 18 to 36 hours. When the metabolic pathway is saturated (conjugation with glycine), zero order kinetics apply and thus the elimination half-life cannot be derived correctly. Metabolism: At low dosage, approximately 80% of salicylic acid is metabolized in the liver. Conjugation with glycine, forms salicyluric acid and when conjugated with glucuronic acid, acyl and phenolic glucuronide are formed. Small amounts of salicylic acid are also hydroxylated to gentisic acid. With large doses, the kinetics switch from first order to zero order (Michaelis-Menten) kinetics. Elimination and excretion: Salicylates are excreted mainly by the kidney as salicylic acid, salicyluric acid, salicylic glucuronides and gentisic acid. The proportion excreted of each metabolite, depends upon urinary pH. With urinary alkalinisation, salicylic acid excretion is enhanced. Mode of action: Toxicodynamics: Marked hyperventilation occurs as a result of direct stimulation of the respiratory centre. Indirect stimulation of respiration is caused by an increased production of CO₂ as a result of salicylate-induced uncoupling of oxidative phosphorylation. Respiratory alkalosis develops as a result of the direct and indirect stimulation of the respiratory centre. In an attempt to compensate, bicarbonate accompanied by sodium, potassium and water, is excreted in the urine. Dehydration and hypokalemia result, but more importantly, the loss of bicarbonate diminishes the buffering capacity of the body and allows the development

of a metabolic acidosis. The pyretic effect of toxic doses of salicylate is a direct result of the uncoupling of oxidative phosphorylation. High doses of salicylate have additional toxic effects on the central nervous system consisting of stimulation(including convulsions) followed by depression, confusion, dizziness, asterixis, delirium, psychosis, stupor and coma. Very high doses have depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse secondary to vasomotor depression. The loss of buffering capacity and the effects of salicylate on carbohydrate, lipid and protein metabolism lead to the development of a metabolic acidosis or, more commonly in practice, a mixed acid base disturbance. Both hypo-and hyperglycemia may occur in salicylate poisoning. The former most probably due to an increased tissue demand for glucose oxidation due to the uncoupling of oxidative phosphorylation. Neuroglycopenia can occur in the presence of normal blood glucose concentrations. If hepatic glycogen stores are adequate, catecholamines production stimulates glycogenolysis leading to hyperglycemia which can persist for several days. Salicylate intoxication is often accompanied by hypothermia due to a warfarin like action of salicylate on the vitamin K1 epoxide cycle, which rarely causes clinical problems. Pharmacodynamics: Salicylic acid alleviates pain, lowers an elevated body temperature and inflammation by inhibiting the synthesis of prostaglandins that occur in inflamed tissues. Salicylate inhibits the conversion of arachidonic acid to the unstable endoperoxide intermediate PG G₂, which is catalyzed by the enzyme cyclo oxygenase. Platelets are especially susceptible to this action as they are incapable of regenerating the enzyme, presumably they have little or no capacity for protein biosynthesis. Cyclooxygenase(COX) is present in two main isoforms. COX-1 is the isoform of the enzyme and is present under normal physiological conditions. COX-2 is the inducible isoform of the enzyme and is induced in settings of inflammation (production of eicosanoids and kinins). Inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcer. Adults: Since salicylic acid is available only in topical preparations, human data on toxicity have not been reported. However, the chinese medicated oil, which contains 67% methyl salicylate induced severe salicylate poisoning. Salicylic acid concentrations above 800 mg/L after 6 hours post exposure is severely toxic and may be lethal. Children: Salicylate intoxication is often more serious in small children (1-4 years) than in older children, due to an early development of a metabolic acidosis rather than a respiratory alkalosis. Teratogenicity: There is no evidence that moderate therapeutic doses of salicylates cause fetal damage in human beings; however, babies born to women who ingest salicylates for long periods may have a significantly reduced mass at birth. In addition, there is an increase in prenatal mortality, anemia, antepartum and postpartum haemorrhage, prolonged gestation and complicated deliveries. These effects occur when salicylates are administered during the third trimester, and thus its use during this period of pregnancy should be avoided. Interactions: Salicylic acid is highly protein-bound and may increase the unbound or free drug concentrations of other drugs such as hypoglycemics, anticoagulants and methotrexate(an antimetabolite chemotherapeutic drug), reaching toxic levels of these agents. The uricosuric activity of phenylbutazone, probenecid and sulphinpyrazone is strongly antagonized by salicylate and maybe completely diminished by small doses due to decreased tubular reabsorption of uric acid. In a report of two cases of severe salicylate poisoning, asystole occurred shortly after the intravenous administration of diazepam. Main adverse effects: Salicylic acid is a gastric irritant and because of the serious damage it may cause to the stomach lining, it has not been used orally. Topical use of salicylic acid may induce allergic contact dermatitis. Salicylic acid may cause excessive drying and irritation in some people. Some individuals, especially asthmatics exhibit sensitivity to salicylates. Urticaria, angioneurotic oedema, rhinitis, severe and even fatal paroxysmal, bronchospasm and dyspnea may occur. Acute poisoning: Ingestion: Initial symptoms of salicylate poisoning may be nausea and vomiting, epigastric pain and occasionally haematemesis. Hyperventilation, sweating, flushing, fever, irritability, tinnitus and loss of hearing are the common clinical features of mild to moderate salicylate intoxication. In severe intoxication, hypoventilation, stupor, hallucination, convulsions, papilledema and coma particularly in children may occur. Metabolic acidosis, non-cardiogenic pulmonary edema, hepatotoxicity and cardiac dysrhythmias may also occur. Skin exposure: Severe poisoning has been reported as a result of the use of salicylic acid ointment for dermatological problems and in the treatment of skin burns. Chronic poisoning: Ingestion: Chronic salicylate

poisoning occurred as a result of excessive therapeutic administration over a period of 12 hours or more were reported. Metabolic pathways of salicylic acid become saturated and thus plasma concentration increases, producing toxicity. Small children are at particular risk of overdose especially when fever, sweating and tachycardia of salicylate intoxication are attributed to the underlying illness and are used as indications for increasing the dose. Children may become intoxicated through breast milk. The presenting signs of chronic salicylate poisoning can include metabolic acidosis, hypoglycemia, lethargy, coma and fits. Skin exposure: Chronic usage of salicylic acid and or methyl salicylate in skin and rheumatic diseases may cause intoxication through percutaneous absorption. Life threatening salicylate poisoning caused by percutaneous absorption of salicylic acid (10% ointment) in a 7-year old boy with ichthyosis vulgaris was reported. Application of teething gels containing salicylic acid induced intoxication. Course, prognosis, cause of death: If a large quantity of a salicylate has been taken, nausea, vomiting, tinnitus, deafness, sweating, vasodilatation and hyperventilation may develop. Acid-base disturbances, electrolyte imbalance, non cardiogenic pulmonary edema, hypoventilation and hallucination, stupor, irritability, coma and convulsions particularly in children and older patients can proceed death. Loss of consciousness in adults is very rare and when occurs indicates poor prognosis. A review of 51 fatal cases of acute salicylate poisoning in Ontario during 1983 and 1984, discovered that salicylate was the most common cause of death, due to the ingestion of single drugs. Autopsy results showed that 50% of the patients had pulmonary abnormalities, 28% had lesions of the gastrointestinal tract, 18% had nervous system abnormalities and 25.6% had no pathological changes. Mortality from chronic salicylate intoxication is considerably higher (25%) than from acute overdose (1 to 2%). Death is often due to sudden cardiac arrest or occasionally due to multiple complications following severe brain damage. Systemic description of clinical effects: Cardiovascular: Sudden cardiovascular collapse is a recognized complication of salicylate poisoning. Two patients with severe salicylate intoxication developed asystole shortly after intravenous diazepam administration. Transient myocardial dysfunction (global left ventricular shortening fraction of 23%) with pulmonary edema was found in a 13-month-old boy with salicylate poisoning. Respiratory: Non-cardiogenic pulmonary edema may occur in salicylate intoxicated patients who are over 30 years of age. Cigarette smoking, chronic salicylate ingestion, metabolic acidosis and the presence of neurological symptoms and signs on admission are strong risk factors for the subsequent development of pulmonary edema. The exact mechanism is unknown. Three possible explanations are: (1) A direct toxic effect on pulmonary microvasculature; (2) Interaction with endogenous mediators such as prostaglandins; and (3) A central nervous system mediated effect. Neurological: Central Nervous System (CNS): In moderate to severe salicylate intoxication, CNS stimulation (irritability and convulsions) followed by depression, confusion, dizziness, delirium, psychosis, asterixis, stupor and coma occur usually when metabolic acidosis is the dominant acid-base abnormality. These features are thought to be due to reduced ionisation of salicylic acid and a shift of salicylate from the plasma into the brain. Very high doses of salicylate have a depressive effect on the medulla and may cause central respiratory paralysis as well as sudden circulatory collapse, secondary to vasomotor depression. Gastrointestinal: Ingestion of salicylate may result in epigastric discomfort, nausea and vomiting. Salicylic acid has more irritant effects on gastric mucosa than acetylsalicylic acid and thus has been withdrawn from oral administration for many years. Acetylsalicylic acid may also cause gastric irritation. Perforated peptic ulcer also occurs extremely rarely. Hepatic: Hepatotoxicity may occur both after the therapeutic use of salicylate or following its over-dosage. Liver biopsy revealed acute hepatocellular necrosis with periportal inflammation and fatty changes in hepatocytes. Hepatic encephalopathy (Reye's Syndrome) has been reported in children taking aspirin for treatment of viral infections such as influenza. Urinary: Renal: Oliguria sometimes occurs, which is mostly due to dehydration. Renal failure may rarely occur in individuals without volume depletion, pre-existing renal and or systemic diseases. Endocrine and reproductive systems: High doses of salicylate cause release of adrenaline from the adrenal medulla; this is thought to be partly responsible for the observed hypoglycaemia due to glycogenolysis that sometimes occurs. Large doses of salicylate stimulate corticosteroids secretion by the adrenal cortex. Dermatological: Toxic epidermal necrosis in 13 patients associated with the use of salicylate have been reported. Eye, ear, nose, throat: local effects: Eye: Transient myopia occurred in

a patient following ingestion of acetylsalicylic acid. Bilateral subconjunctival hemorrhage has been reported. Ear: Tinnitus and hearing loss caused by salicylate in overdose are due to increased labyrinthine pressure. It may also be due to an effect on the hair cells of the cochlea. There is a relationship between the hearing loss and the plasma salicylate concentration. Hematological: Salicylates prolong the bleeding time due to inhibition of collagen glucosyltransferase present in membranes of platelets. As a result, the adherence of platelets to connective tissue or collagen fibres is diminished. Salicylate overdose reduces the concentration of vitamin K-dependent coagulation factors, particularly prothrombin. Immunological: Salicylates have the capacity to suppress a variety of antigen-antibody reactions such as: the inhibition of antibody production, of antigen-antibody aggregation and of antigen induced release of histamine. Salicylates also induce a non specific stabilization of capillary permeability during immunological insults. The concentration of salicylate causing this effect is high, and their relationship to the antirheumatic efficacy of salicylates is yet to be determined. Metabolic: Acid-base disturbances: Respiratory alkalosis is more often observed in adults than in children. Metabolic acidosis develops sooner in children than in adults. However, in severe salicylate poisoning in adults, metabolic acidosis may also occur. The acidosis is not therefore due to the presence of salicylic acid itself. The principle cause is competitive inhibition of NAD⁺-dependent dehydrogenases including lactate and oxoglutarate dehydrogenase and the other oxidative enzymes such as succinate dehydrogenase. Salicylate enhances entry and oxidation of fatty acids in liver cells, leading to increased ketogenesis. Competitive inhibition of amino acyl-tRNA synthetases in pairs and amino acid incorporation results in amino-acidemia. Dehydration and vasomotor depression results in poor renal perfusion and accumulation of sulfuric and phosphoric acids. Fluid and electrolyte disturbances: Increased renal secretion of sodium, potassium and water accompanies loss of bicarbonate in the urine. Fluid loss also results from vomiting, sweating and hyperventilation. Dehydration is commonly associated with hypernatremia. (1) Oxidative Phosphorylation: The uncoupling of oxidative phosphorylation by salicylate results in the inhibition of a number of ATP-dependent reactions and an increase in O₂ uptake and CO₂ production. (2) Nitrogen compound metabolism: Toxic doses of salicylate cause a significant nitrogen imbalance, characterized by amino aciduria, though this is due in part to stimulation of active tubular absorption because of reduced ATP formation. Fat metabolism: Salicylates enhance oxidation of fatty acids in muscle, liver and other tissues together with a decrease of concentrations of plasma, free fatty acids, phospholipids and cholesterol. Allergic reactions: Some people particularly asthmatics, exhibit marked sensitivity to salicylate, resulting in various reactions including urticaria and other skin eruptions, angioneuritis, oedema, rhinitis and severe and even fatal paroxysmal bronchospasm and dyspnea, hypotension, shock and syncope. Despite the fact that the symptoms (such as the ones mentioned above) resemble anaphylaxis, this reaction does not appear to be immunological in nature. It may be a shunt towards the lipoxygenase pathway leading to an increased production of leukotrienes and other inflammatory mediators. Although, this hypothesis is unproved and it does not explain why only a minority of patients with asthma or other predisposing conditions display the reaction. Even so, results in a small number of patients suggest that blockade of 5-lipoxygenase with the drug zileuton may prevent symptoms and signs of aspirin intolerance. Other clinical effects: The relationship between the use of salicylate and Reye's syndrome in children and adolescents (mostly 5 to 15 years) has been demonstrated by epidemiological studies. Special risks: Salicylate intoxication may occur through placental transfer and breast milk.

SECTION 12: Ecological information

Not available

SECTION 13: Disposal considerations

Not available

SECTION 14: Transport information

Not available

SECTION 15: Regulatory information

Not available

SECTION 16: Other information

Not available

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