PRODUCT MONOGRAPH

SAFEWAY COATED DAILY LOW-DOSE ASA

(Acetylsalicylic acid enteric coated delayed-release tablets, USP)

81 mg

Analgesic, anti-inflammatory, antipyretic and

platelet aggregation inhibitor

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THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Analgesic, anti-inflammatory, anti-pyretic and platelet aggregation inhibitor.

ACTION AND CLINICAL PHARMACOLOGY

Acetylsalicylic acid (ASA) interferes with the production of Prostaglandins in various organs and tissues through acetylation of the enzyme cyclo-oxygenase. Prostaglandins are themselves powerful irritants and produce headaches and pain on injection in man. Prostaglandins also appear to sensitize pain receptors to other noxious substances such as histamine and bradykinin. By preventing the synthesis and release of Prostaglandins in inflammation, Acetylsalicylic acid delayed release tablets may avert the sensitization of pain receptors.

The antipyretic activity of ASA is due to its ability to interfere with the production of prostaglandin E_1 in the brain. Prostaglandin E_1 is one of the most powerful pyretic agents known.

The inhibition of platelet aggregation by ASA is due to its ability to interfere with the production of thromboxane A_2 within the platelet. Thromboxane A_2 is largely responsible for the aggregating properties of platelets.

INDICATIONS AND CLINICAL USE

Acetylsalicylic acid (ASA) is indicated for the relief of pain, fever and inflammation of a variety of conditions such as influenza, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, fractures, myositis, neuralgia, synovitis, arthritis, bursitis, burns, injuries, following surgical and dental procedures.

Safeway Coated Daily Low-Dose ASA is also indicated for the following uses, based on its platelet aggregation inhibitory properties:

-For reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction;

-For reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction;

-For prophylaxis of venous thromboembolism after total hip replacement;

-For reduction of adhesive properties of platelets in patients following carotid endarterectomy to prevent recurrence of TIA and in hemodialysis patients with a silicone rubber arteriovenous cannula.

CONTRAINDICATIONS

Salicylate sensitivity, active peptic ulcer.

WARNINGS

ASA is one of the most frequent causes of accidental poisonings in toddlers and infants. Tablets should be kept well out of the reach of children.

A possible association between Reye's syndrome and the use of salicylates has been suggested but not established. Reye's syndrome has also occurred in many patients not exposed to salicylates. However, caution is advised when prescribing salicylate-containing medications for children and teenagers with influenza or chickenpox.

PRECAUTIONS

Salicylates should be administered cautiously to patients with asthma and other allergic conditions, a history of gastrointestinal ulcerations; bleeding tendencies; significant anemia or hypoprothrombinemia.

Patients taking ASA daily are at an increased risk of developing gastrointestinal bleeding following the ingestion of alcohol.

Caution is necessary when salicylates and anticoagulants are prescribed concurrently, as salicylates can depress the concentration of prothrombin in the plasma.

Diabetics receiving concurrent salicylate and hypoglycemic therapy should be monitored closely; reduction of the sulfonylurea hypoglycemic drug dosage may be necessary; insulin requirements may change.

High doses (3g daily) of ASA during pregnancy may lengthen the gestation and parturition time.

Salicylates can produce changes in thyroid function tests.

Sodium excretion produced by spironolactone may be decreased by salicylate administration.

Salicylates in large doses are uricosuric agents; smaller amounts may depress uric acid clearance and thus decrease the uricosuric effects of other drugs.

Salicylates retard the renal elimination of methotrexate.

Concomitant use of ASA and valproic acid may cause increased valproic acid levels and may lead to an increased risk of bleeding. Valproic acid may cause hypoprothrombinemia and inhibit platelet aggregation.

ADVERSE REACTIONS

Gastrointestinal: (the frequency and severity of these adverse effects are dose-related): nausea, vomiting, diarrhea, gastrointestinal bleeding and/or ulceration, dyspepsia, heartburn.

Ear: tinnitus, vertigo, hearing loss.

Hematologic: leukopenia, thrombocytopenia, purpura, anemia.

Dermatologic and hypersensitivity: urticaria, angioedema, pruritus, skin eruptions, asthma, anaphylaxis.

Miscellaneous: mental confusion, drowsiness, sweating, thirst.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: In mild overdosage these may include rapid and deep breathing, nausea, vomiting,

vertigo, tinnitus, flushing, sweating, thirst, arid tachycardia. In more severe cases, acid-base disturbances including respiratory alkalosis and metabolic acidosis can occur. Severe cases may show fever, hemorrhage, excitement, confusion, convulsions or coma and respiratory failure.

Treatment: Treatment is largely symptomatic and supportive. Induce emesis or perform gastric lavage, then administer activated charcoal. If hyperthermia is present, sponge the patient with tepid water or use a cooling blanket. Maintain appropriate fluid therapy based on the patient's fluid, acid-base and electrolyte status. Minor blood gases, blood glucose, serum creatinine and urea, urinary output and pH. Draw blood for determination of serum salicylate level. Sodium bicarbonate I.V. should be used cautiously to correct metabolic acidosis and to enhance renal elimination of salicylate. Care should be taken to avoid sodium overload or alkalosis. Hypokalemia may require administration of I.V. potassium chloride. If present, hypoglycemia may be managed with dextrose solutions. Seizures may be treated with I.V. diazepam. Alkalinization of the urine to enhance urinary excretion of salicylates may be useful in severe intoxication but should be performed very cautiously in selected patients. Vitamin K may be administered to patients with hemorrhagic complications or prolonged PT. Peritoneal or hemodialysis may be required if serum salicylate concentrations are greater than 6.5mmol/L 6 hours after ingestion, in complex acid-base disturbance unresponsive to conventional therapy, if the patient is in renal failure, or if the patient is deteriorating clinically despite appropriate care.

DOSAGE AND ADMINISTRATION

Analgesic and antipyretic:

Adults: 325 mg to 650 mg orally every 4 hours.

Children under 12: 10 to 15 mg/kg every 6 hours, not to exceed a total daily dose of 2.4 g.

Anti-inflammatory:

A*dults:* 975 mg 4 to 6 times a day, up to 9750 mg daily, may be required for optimal anti-inflammatory effect. A blood level between 15 and 30 mg per 100 mL is in the desirable therapeutic

range.

Children: 60 to 125 mg/kg daily in 4 to 6 divided doses.

Platelet aggregation inhibitor:

- For reducing the risk of morbidity and death in patients with unstable angina and in those with previous myocardial infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician. **Safeway Coated Daily Low-Dose ASA (Acetylsalicylic acid enteric coated delayed release tablets) is specifically indicated for these uses.**

- For reducing the risk of transient ischemic attacks (TIA) and for secondary prevention of atherothrombotic cerebral infarction: 80 - 325 mg daily according to the individual needs of the patient, as determined by the physician. **Safeway Coated Daily Low-Dose ASA is specifically indicated for these uses.**

- For prophylaxis of venous thromboembolism after total hip replacement: 650 mg twice a day (1,300 mg daily), started 1 day before surgery and continued for 14 days.

- For other platelet aggregation inhibitory uses: 325 - 1300 mg daily, according to individual needs and generally accepted standards of care for each indication.

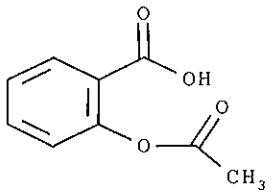
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Acetylsalicylic acid

Chemical Names: 2-(Acetyloxy) benzoic acid;
Salicylic acid acetate.

Structure:



Molecular Formula: $C_9H_8O_4$

Molecular Weight: 180.16

Description: White granules, commonly tabular or needle-like, or white crystalline powder. Odorless or having a faint odor.

Solubility: Slightly soluble in water; freely soluble in alcohol; soluble in chloroform and ether; sparingly soluble in absolute ether.

pK value (25°C): 3.49

Melting Point: 135°C (rapid heating)

COMPOSITION

Safeway Coated Daily Low-Dose ASA:

Each tablet contains 81 mg acetylsalicylic acid as active ingredient.

Non-medicinal ingredients: Hydrogenated soya bean oil, hydroxypropyl methylcellulose, lactose, polyethylene glycol, pregelatinized starch, stearic acid.

AVAILABILITY OF DOSAGE FORM

Safeway Coated Daily Low-Dose ASA:

Each round, white film-coated tablet contains 81mg acetylsalicylic acid. In packages of 30, 120 and 180 tablets.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°-30°C).

PATIENT INFORMATION TO BE DISTRIBUTED ONLY BY PHYSICIANS/PHARMACISTS

SAFEWAY Coated Daily Low-Dose ASA 81 mg

This section provides you with information about **Safeway Coated Daily Low-Dose ASA 81 mg** acetylsalicylic acid (enteric coated) tablets and how to take this medication. ***Please read carefully before you take this medication.***

Your physician has recommended **Safeway Coated Daily Low-Dose ASA 81 mg** for supervised adult long-term preventative therapy.

Follow your physician's instructions concerning the use of **Safeway Coated Daily Low-Dose ASA 81 mg** as well as any lifestyle changes, e.g. diet and/or exercise, that he/she may have recommended. Always contact your physician if you experience any difficulties while taking this product.

Safeway Coated Daily Low-Dose ASA 81 mg contains acetylsalicylic acid, commonly referred to as ASA, as its active ingredient. Plain (uncoated) ASA, particularly when taken regularly, may cause stomach upset in some people. The special enteric coating of **Safeway Coated Daily Low-Dose ASA 81 mg** tablets allows them to pass intact through the stomach and on into the intestine before they dissolve which may reduce the risk of stomach upset.

Your physician has specifically recommended **Safeway Coated Daily Low-Dose ASA 81 mg** because it contains a special, low-dose, enteric-coated, formulation of ASA. Other medications such as acetaminophen or ibuprofen that are meant to relieve pain do not have the same preventative action as **Safeway Coated Daily Low-Dose ASA 81 mg** which has been specifically formulated for your condition.

DIRECTIONS FOR USE

It is very important that you take this medication as directed by your physician. If you have not seen a physician, do not take this medication until you have done so.

Dosage:

1 to 4 tablets daily, depending on your physician's instructions. Your doctor may tell you to take **Safeway Coated Daily Low-Dose ASA 81 mg** with other medications. He/she may also advise you to make certain lifestyle changes, (e.g. diet, exercise, smoking cessation), to safeguard your health. You should take this medication at the same time every day to help you to remember to take it. For maximum effectiveness, it is very important to take **Safeway Coated Daily Low-Dose ASA 81 mg** every day, as directed by your physician. Do not take more tablets than your physician recommends.

Safeway Coated Daily Low-Dose ASA 81 mg tablets must be swallowed whole for the medication to work properly.

Safeway Coated Daily Low-Dose ASA 81 mg tablets have a special enteric coating designed to help prevent stomach upset. To benefit from this protection, the tablets should not be crushed or broken.

ANSWERS TO COMMONLY ASKED QUESTIONS

WHY WAS SAFEWAY COATED DAILY LOW-DOSE ASA RECOMMENDED BY MY DOCTOR?

It can be used to prevent a second stroke or heart attack. If you have experienced either a stroke or a heart attack you may be at risk for a second one. There are certain risk factors that can place you at an increased risk:

-Overweight
-Smoking
-Inactive (sedentary) lifestyle
-Stress
-High blood cholesterol
-High blood pressure

These can be discussed with your physician in order to complement the effectiveness of Safeway Coated Daily Low-Dose ASA 81 mg.

Your doctor may recommend changes in diet, exercise and lifestyle for your benefit in avoiding a second heart attack or stroke.

If you experience any difficulties with your treatment always discuss with your doctor or pharmacist.

WHAT IF I FORGET TO TAKE MY MEDICATION?

If you forget to take your medication at the usual time, take it when you remember. Do not take extra medication to compensate for a missed dosage unless instructed by your physician.

WILL I EXPERIENCE ANY SIDE EFFECTS WITH THIS MEDICINE?

Like any medication, ASA may occasionally produce unwanted side effects. You should call your physician if you experience any of the following: nausea, vomiting, bleeding or stomach irritation, dizziness, weakness, fainting spells, any loss of hearing, including ringing or buzzing in the ears or pain; skin rashes, hives or itching and breathing difficulties.

WHAT ELSE SHOULD I KNOW BEFORE TAKING THIS MEDICINE?

Your doctor will have asked you many questions about your health, lifestyle, and medications before recommending **Safeway Coated Daily Low-Dose ASA 81 mg.** This is why it is very important that you tell your doctor all such information. If you have forgotten to tell your doctor about any of the following, call your doctor or pharmacist before you take this medicine.

- Allergy to salicylates
- Asthma
- Stomach problems
- Peptic ulcer
- Severe liver disease
- Severe anemia
- History of blood clotting defects or receiving blood thinners
- Are pregnant or breast-feeding
- Will be having surgery in five to seven days
- Are taking other medications containing salicylates or acetaminophen
- Are taking anti-inflammatory drugs, anticonvulsants, anti-diabetics or gout medication
- Are taking or planning to take this product while consuming alcohol

CAUTION

This product is not recommended for children or teenagers. This package contains enough drug to seriously harm a child. Keep out of children's reach. Do not administer to children and teenagers for chicken pox or flu symptoms before a doctor is consulted. Reye's Syndrome, which can occur in children or teenagers, is a rare but serious illness reported to be associated with ASA.

It is especially important not to use this medication during the last 3 months of pregnancy unless specifically directed to do so by your physician because it may cause problems in the unborn child or complications during delivery.

Call your doctor before taking this drug when nursing.

In case of accidental overdose call a doctor or hospital immediately, even if there are no symptoms.

Product Monograph is available to physicians and pharmacists upon request.

PHARMACOKINETICS

ASA is absorbed rapidly from the gastro-intestinal tract where the majority of absorption occurs in the jejunum and small bowel by virtue of its surface area Salicylate absorption occurs by passive diffusion, primarily of the non-dissociated, lipid-soluble molecule (salicylic and acetylsalicylic acids), across gastrointestinal membranes. Some ASA is hydrolyzed to salicylate in the gut wall. After absorption ASA is rapidly converted to salicylate but during the first 20 minutes following oral administration or 4-6 hours for enteric–coated ASA, ASA is the predominant form of the drug in the plasma. Many factors tend to affect salicylate tablet absorption: dissolution rate, food, pH, physical condition, concurrent drugs etc.

ASA is 80% to 90% bound to plasma proteins and is widely distributed; its volume of distribution is reported to be 170ml per kg body weight in adults. As plasma-drug concentrations increase, the binding sites on the proteins become saturated and the volume of distribution increases. Both ASA and salicylate have pharmacological activity; only ASA has an anti-platelet effect.

Salicylate appears in breast milk and crosses the placenta. Salicylate is removed by haemodialysis.

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include the salicyluric acid (the glycine conjugate), the ether or salicylphenolic glucuronide, the ester or salicylic acyl glucuronide, gentisic acid, and gentisuric acid. The formation of the major metabolites, salicyluric acid and salicylphenolic glucuronide is easily saturated and follows Michaelis-Menten kinetics; the other metabolic routes are first order processes. As a result, steady-state plasma-salicylate concentrations increase disproportionately with dose. Following a 325-mg ASA dose, elimination is a first order process and the plasma-salicylate half-life is about 2 to 3 hours; at high ASA doses, the half-life increases to 15 to 30 hours. The serum half-life of salicylates is dose-dependent; thus the larger the dose employed, the longer it will take to reach steady state.

Salicylate is also excreted by the kidney unchanged in the urine; Studies in man indicate that salicylate is excreted in the urine as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic (10%) and acyl (5%) glucuronides, and gentisic acid (<1%). The amount excreted by this

route increases with increasing dose and also depends on urinary pH. Thus, in alkaline urine, more than 30% of the ingested drug may be eliminated as free salicylate due to promoted excretion, whereas in acidic urine this may be as low as 2% due to facilitated reabsorption by renal tubules (12).

PHARMACOLOGY

Analgesia:

The analgesic effect of ASA has been recognized and utilized clinically for more than half a century. The degree of analgesia attained with ASA is moderate but it has proved highly suitable in the management of pathological pain of mild to moderate severity. As regards site of action, both peripheral and CNS factors appear to contribute significantly to the pain relief afforded by ASA (12). As for mechanism of action, the accumulated evidence of recent years indicates that ASA acts by interfering with the synthesis and release of prostaglandins, thereby averting the sensitization of pain receptors to mechanical stimulation or to other mediators (12).

Antipyresis:

Interference with the synthesis and release of prostaglandins is also involved in ASA's antipyretic activity (12, 32). ASA effects a significant reduction in elevated body temperature, but has little effect on normal body temperature. This latter is maintained by a delicate balance between heat production and heat loss, with the hypothalamus regulating the set point at which body temperature is maintained. Fever is induced by synthesis and release of prostaglandins in this temperature-regulating area and ASA acts by interfering with this process. Heat production is not inhibited but dissipation of heat is augmented by increased peripheral blood flow and by sweating.

Anti-inflammatory effect:

Components of the anti-inflammatory action of the salicylates are increased capillary resistance, thus reducing capillary leakage in response to local toxins, interference with the production of tissue-destructive lysosomal enzymes and inhibition of the synthesis of prostaglandin E compounds which have been shown to be potent mediators of the inflammatory process (32). Besides interfering with

the synthesis of prostaglandins ASA also acts by interfering with lymphocyte activation and lymphokine production. Lymphokines are produced by activated thymus lymphocytes, which are abundant in the inflammatory tissues of patients suffering from rheumatoid arthritis. They cause increased vascular permeability and white blood cell chemotaxis, activate macrophages and stimulate lymphocyte DNA synthesis. They also induce release of tissue-destructive lysosomal enzymes as well as prostaglandins. The prostaglandins themselves, beside causing many manifestations of inflammation lymphokine production. An indepth review of the effects of ASA on the lymphocyte-macrophage axis in inflammation has recently been published (10).

Effects on platelets: relation to hemostasis and thrombosis.

Platelets play an important role in normal hemostasis and clinical pathologic and experimental evidence indicates that their aggregation may play an equally important role in the evolution of a variety of disease states including cerebrovascular disease, ischemic heart disease and myocardial infarction (25). Safeway Coated Daily Low-Dose ASA inhibits platelet aggregation by irreversibly acetylating platelet cyclo-oxygenase, thereby blocking the production of prostaglandin endoperoxides PGG_2 and PGH_2 which are precursors of the major platelet-aggregating material, thromboxane A_2, which is also a powerful vasoconstrictor (10, 22). However, Safeway Coated Daily Low-Dose ASA does not prevent the adherence of platelets to damaged vessel walls or the release of granule contents from these adherent platelets (22). As the anuclear platelets are unable to synthesize new enzyme molecules to replace those that have been inactivated, inhibition of platelet aggregation by Safeway Coated Daily Low-Dose ASA thus persist for the life of the platelets.

Acetylation of platelet cyclooxygenase by oral ASA is dose dependent and cumulative with repeated administration (23). Measurements of serum thromboxane B" and its urinary excreted metabolites reflect platelet cyclooxygenase inhibition by ASA. Single oral doses of 6-100mg resulted in dose-dependent inhibition of platelet TXB_2 production ranging from 12 to 95% after 24hr. (23). Daily administration of doses ranging from 40 to 325mg ECA have been studied in healthy subjects in a multidose-regimen of 7 days (17). But 80mg ASA daily was the lowest dose ECA resulting in greater than 90% inhibition of platelet cyclooxygenase (17). Doses in excess of 80mg/d resulted in substantial inhibition of endogenous prostacyclin biosyntheses (11). Several animal models have

demonstrated the protective effect of ASA against experimentally induced thrombus formation or atherosclerosis (7, 8, 20, 24).

ASA inhibits the arachidonate pathway blocking the formation of the aggregating agent, thromboxane A_2, by platelets and also blocking the synthesis of prostaglandin I_2 (PGI_2) by vessel wall (22). Prostacyclin (PGI_2) is produced by vascular endothelial cells and is a potent inhibitor of platelet function. It is one of the most powerfully acting platelet deaggregators and vasodilators. In normal conditions platelet aggregation on the intimal endothelial surfaces is prevented, and existing small aggregates are deaggregated by prostacyclin. ASA does not prevent platelet adherence to damaged vessel walls or release of granule contents from these adherent platelets. The inhibition effect on prostacyclin production is shorter lasting because vascular endothelial cells are able to regenerate cyclooxygenase in a relatively short time (10). It would then seem that vascular endothelial cell cyclooxygenase is less sensitive to ASA inhibition than platelets. Thus keeping the vasculature patent, ASA-interference with the haemostatic processes would depend on the ratio of thromboxane to prostacyclin. It has been claimed that ASA prolongs bleeding time only when given in small doses and its effects on bleeding time are reduced when large doses are given (22). Several ASA studies have shown a beneficial effect in preventing thromboembolic complications associated with surgery. The bleeding times for all ASA treated groups were longer than baseline. No paradoxical shortening of the bleeding time was noticed at a 3.6g dose (2). However it is probable that under some conditions, high doses of ASA may be thrombogenic in many parts of the vascular tree.

ASA has been clinically tested and supported in secondary prevention of thrombotic events more specifically in patients with myocardial infarction, stroke or transient ischemia and unstable angina (16, 29, 33).

A number of clinical trials (5, 6, 16, 18, 19, 26, 28-30, 33) involving patients with documented myocardial infarction unstable angina, stroke or transient cerebral ischemia supported the use of ASA in the secondary prevention of cardiovascular disease. In two respective large studies the medium term and long term effects of a daily dose of 75mg on the risk of myocardial infarction and

death were similar to the effects in patients treated with 324 and 1300mg. Overall, large trials suggest that ASA initiated weeks to years post-infarction can reduce the risk of fatal and nonfatal cardiovascular events by 25% (1).

Lower doses of ASA as compared with higher doses (30-1200mg/day) indicated a significant decrease in gastrointestinal adverse effects (14, 15, 27, 31). When ingestion of high doses of ASA are administered inhibition of cyclooxygenase activity in extra-platelet sites i.e. the gastric mucosa and the kidney can lead to significant adverse effects (9).

Recent studies (1) have worked on the efficacy of ASA for the primary prevention of myocardial infarction and stroke. Two randomized trials, one in the United States and one in the United Kingdom have evaluated prophylactic ASA use among apparently healthy male physicians. These two-primary-prevention studies demonstrate a significant ($P<0.0001$) reduction in nonfatal myocardial infarction of about one third. Neither study indicated mortality. Indeed some increase in non-fatal disabling strokes is observed (13). Controversies exist on comparing these specific populations with different ASA regimens to the general public. There is no established dosage regimen for ASA use in primary prevention, thus the prescription of ASA should remain "a matter of judgement in which the physician considers the cardiovascular risk profile of the patient and balances the known hazards of ASA against the clearly established reduction in the incidence of a first myocardial infarction" (13).

TOXICOLOGY

The clinical and pathological signs of poisoning from toxic and lethal oral doses of ASA have been extensively described for man (12), much less extensively for other species.

The acute toxicity of ASA in animals has been studied and reviewed in detail by Boyd (3, 4). The signs of poisoning in rats from doses in the lethal range are due to varying degrees of gastroenteritis, hepatitis, nephritis, pulmonary edema, encephalopathy, shock and minor toxic effects on other organs and tissues. Death is due to convulsions or cardiovascular shock. The major difference between species appears to be the ability to vomit toxic doses seen in man, cats and dogs, but not in mice, rats and rabbits. Otherwise, the pathological reaction to toxic doses of ASA is similar in all species in which such studies have been reported. The acute oral LD_{50} values have been reported as being over 1.0 g/kg in man, cat and dog, 0.92 g/kg in female and 1.48 g/kg in male albino rats, 1.19 g/kg in guinea pig, 1.1 g/kg in mouse and 1.8 g/kg in rabbit (3, 4).

Chronic toxicity studies were reported in mice (34) and rats (3). When ASA was administered at 2 to 20 times the maximum tolerated clinical dose to mice for up to one year, a dose-related deleterious effect was observed on mean survival time, number of young born and number of young raised to wearing age, no evidence of carcinogenic effect was found (34).

The chronic oral LD_{50} in male albino rats has been reported as 0.24g/kg/day when given for 100 days (3). At these daily doses ASA produced no anorexia and no loss of body weight. It did produce polydipsia, aciduria, diuresis, drowsiness, hyperreflexia, piloeraction, rapid and deep respiration, tachycardia, and during the second month, soft stools, epistaxis, sialorrhea, dacryorrhea and death in hypothermic coma. Autopsy disclosed the presence of a hypertrophied stomach, renal congestion, mild hepatitis and pneumonitis (3). While teratogenic effects were noted in animals at near lethal doses, there is no evidence to indicate that ASA is teratogenic in man (12).

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