# PERMITTED DAILY EXPOSURE FOR ASPIRIN

## 1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of Aspirin have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

## 2. INTRODUCTION:

Aspirin, or acetylsalicylic acid (ASA), is commonly used as a pain reliever for minor aches and pains and to reduce fever. It is also an anti-inflammatory drug and can be used as a blood thinner. It reduces the levels of prostaglandins (Chemicals that are released when there is inflammation and that cause pain and fever). Inhibition of prostaglandins also reduces the function of platelets and the ability of blood to clot. This is why Aspirin is used for preventing heart attacks and strokes.

## 3. IDENTITY OF THE ACTIVE SUBSTANCE:

Aspirin is a common non-steroidal anti-inflammatory drug (NSAID), after oral administration, aspirin is rapidly absorbed from the small intestine.

**IUPAC NAME:** 2-Acetoxybenzoic acid

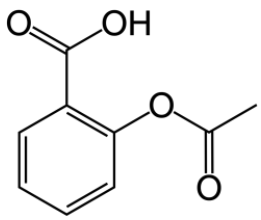
**Chemical Abstract Services (CAS) Registry Number:** 50-78-2

**Molecular Weight:** 180.158 g/mol

**Chemical Formula:** $C_9H_8O_4$

**Chemical Description:** White Crystalline powder

**Molecular Structure:**



**4. HAZARDS IDENTIFIED:**

| CATEGORIZATION: | | | |
|---|---|---|---|
| **TOXICITY** | **YES** | **NO** | **UNKNOWN** |
| **Genotoxicant** | - | √ | - |
| **Carcinogen** | - | √ | - |
| **Reproductive/Developmental Toxicant** | - | √ | - |
| **Highly Sensitizing potential** | - | √ | - |

| SUMMARY OF HAZARD IDENTIFICATION: | |
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| **Pharmacodynamics data** | Irreversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A2, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation; has antipyretic, analgesic and anti-inflammatory properties. |
| **Acute Toxicity** | The magnitude of the toxic effects in acute intoxication can be predicted if one can determine the amount of drug ingested. If a patient ingests less than 150 mg/kg of salicylate, the likelihood of any serious symptoms developing is negligible. In the range of 150 to 300 mg/kg, patients experience mild to moderate toxic reactions; these patients can be cared for easily on an outpatient emergency basis. At doses in excess of 300 mg/kg of salicylate, patients will show prolonged and more severe effects, even when appropriate emergency measures have been given. A dose of more than 500 mg/kg of salicylate is considered potentially lethal.<br>A toxic reaction occurs in cases of chronic administration when more than 100 mg/kg/24 hr has been given for two or more days. |
| **Repeated Dose Toxicity (Chronic Toxicity)** | In repeated dose study on Rabbits, maternal toxicity was exhibited in the 250 and 350 mg/kg per day groups by mortality and decreased food consumption and body weight gain. Fetal body weight was significantly reduced in the repeated dose study at 350 mg/kg per day. Hence it can be concluded that Aspirin is not teratogenic in rabbits, even when large doses are administered on singly days during specific windows of development. |
| **Carcinogenicity** | The carcinogenicity of ASA was assessed in rodents. Mice received 1 and 5% and rats received 0.25% and 2% ASA in drinking water. The results were negative for both mice and rats (Odashima, 1980). Epidemiological studies have shown an association between intake of ASA and reduced risk of colorectal cancer (Rothwell et al., 2010). |
| **In vivo/In vitro Genotoxicity Studies** | ASA was negative when tested for in vitro mutagenicity in the Ames test (Kawachi et al., 1980), and in vivo clastogenicity in the Drosophila sex-linked recessive lethal assay (King et al., 1979). |
| **Reproductive/Developmental Toxicity** | Administration of 200 mg/kg/day of ASA for the last six days of gestation were studied in rats. A prolongation of gestation and parturition time and foetal deaths was observed. The foetal deaths were believed to be attributed to the prolonged parturition time caused by the effects of ASA on prostaglandins synthesis (Tuchmann - Duplessis et al., 1975). This was consistent with the findings of another study, where daily administration of 261 mg/kg/day gave a significant increase in gestation length. In this study, administration of ASA also induced maternal toxicity as reduction of body weight and food consumption (Procter & Gamble, 1994e).<br>Several studies have explored the Teratogenic potential of ASA in animals. ASA was administered by oral or parental route at various times during gestation at different doses (ranging from 75 to 500 mg/kg/day) in rats, mice or monkeys. Foetal malformations (such as skeletal malformations and cleft lip), resorption and foetal |

| SUMMARY OF HAZARD IDENTIFICATION: | |
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| | death (Trasler, 1965;Wilson et al., 1977; Tanaka et al., 1973; Nakatsuka et al., 1979). |
| **Highly Sensitizing Potential** | Aspirin does not come under the category of Highly Sensitizing Potential chemicals. There are only limited data regarding skin irritation after topical application of ASA. The topical application of ASA at a dosage of 2 g/kg to rabbit did not cause any skin irritation or sensitivity (SCCNFP, 2001). |
| **IDENTIFICATION OF CRITICAL EFFECTS:** | |
| **Sensitive Indicator of an adverse effect seen in non-clinical toxicity data** | Use of Aspirin during pregnancy has been associated with increased risk of cryptorchidism. (Kristensen et al; 2011).<br>The use of aspirin in children has been restricted by the medicines regulatory authorities in Europe. The reason for limiting the use of Aspirin in children is because of a possible association between aspirin & Reye syndrome, which is a grave reaction of children to certain viral infections, such as chicken pox. |
| **Clinical therapeutic and adverse effects** | Aspirin should be taken with food. Doses range from 50 mg to 6000 mg daily depending on the use.<br>• Usual doses for mild to moderate pain are 350 or 650 mg every 4 hours or 500 mg every 6 hours.<br>• Doses for rheumatoid arthritis include 500 mg every 4-6 hours; 650 mg every 4 hours; 1000 mg every 4-6 hours; 1950 mg twice daily.<br>• Heart attacks are prevented with 75, 81, 162 or 325 mg daily.<br>• 160 to 325 mg of non-enteric coated aspirin should be chewed immediately when experiencing symptoms of a heart attack.<br>• The dose for preventing another stroke is 75 to 100 mg daily.<br><br>**Adverse effects:**<br><br>• Aspirin should be avoided by patients with peptic ulcer disease or poor kidney function, since this medication can aggravate both conditions.<br>• Aspirin may exacerbate asthma.<br>• Aspirin can raise the blood uric acid level and is avoided in patients with hyperuricemia and gout.<br>• Children and teenagers should avoid aspirin for symptoms of the flu or chickenpox because of the associated risk of Reye's Syndrome, a serious disease of the liver and nervous system that can lead to coma and death.<br>• Aspirin can increase the effect of medicines used to treat diabetes mellitus, resulting in abnormally low blood sugars if blood sugar levels are not monitored.<br>• NSAIDs should be discontinued prior to elective surgery because of a mild tendency to interfere with blood clotting. Aspirin, because of its prolonged effect on platelets, is best discontinued at least ten to fourteen days in advance of the procedure. |

| PURE & CURE HEALTHCARE PVT. LTD., HARIDWAR | DETERMINATION OF PERMISSIBLE DAILY EXPOSURE (PDE)<br>FOR<br>ASPIRIN<br>(ORAL DOSAGE) |
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| **NOAEL/LOAEL** | The NOAEL value is based on data obtained from clinical trials.<br>The therapeutic plasma concentration of ASA for the analgesic and antipyretic effect is estimated to be in the range of 10 to 30 mg/dL (0.7 to 2.2 mmol/L) (Hill, 1973). A blood plasma concentration of 10 mg/dL ASA equals a total amount of 10 mg/kg bw in the body.<br>Doses in the range of 75-325 mg/day are used for cardiovascular prevention (Campbell et al., 2007; Fox et al., 2006). Daily low doses of ASA have been shown to cause gastric mucosal bleeding (Prichard et al., 1989; Yeomans et al., 2009).<br>Thus, as 75 mg/day has been shown to cause gastric mucosal bleeding in humans, we used this value to calculate NOAEL.<br>LOAEL = 75 mg/day/60 kg (default value) = 1.25 mg/kg bw/day<br>NOAEL = LOAEL/3 = 1.25 mg/kg bw/3 = 0.42 mg/kg bw/day |

| APPLICATION OF ADJUSTMENT FACTORS: | | |
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| **F1:** Extrapolation between species | **2.5** | For extrapolation from rabbits to humans |
| **F2:** Inter Individual Variability | **10** | Used for differences between individuals in the human population |
| **F3:** Duration of Toxicity | **1** | For 13 days study in rabbits in repeat dose toxicity |
| **F4:** Severe Toxicity (1-10) | **1** | No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed |
| **F5:** NOAEL or LOAEL (10 if LOAEL) | **5** | NOAEL value is selected |
| **PK Correction** | For PDE calculation no pharmacokinetic correction was carried out | |

| CALCULATION | |
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| **PDE Calculation** | NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)<br>F1 x F2 x F3 x F4 x F5<br><br>= 0.42 (NOAEL) x 50<br>2.5 x 10 x 1 x 1 x 5<br><br>= 0.168 mg/day |

**5. REFERENCES:**


- https://en.wikipedia.org/wiki/Aspirin.
- https://www.mattilsynet.no/kosmetikk/stoffer_i_kosmetikk/risk_profile_acetylsalicylic_acid_30.11319/binary/Risk%20Profile%20Acetylsalicylic%20acid%2030.
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