





451 Florida Street
Baton Rouge, Louisiana 70801-1765

Telephone: 225-388-8011
Facsimile: 225-388-7686

Health and Environment Department
Toxicology and Regulatory Affairs
Facsimile: 225-388-7046

Health Risks from Lead in Ibuprofen Products

Introduction:

A great deal of information on the health effects of lead is available from decades of medical observation of affected humans and scientific research in animals using various forms of lead and routes of administration. There is a high degree of certainty as to the health effects of lead, and relationships between lead exposure and the health effects have been established. Concern for these health effects led regulatory agencies to ban or restrict lead in gasoline and paints in the early 1970's. Regulatory agencies continue to be concerned because adverse effects have been associated with ever decreasing levels of lead exposure. Some scientists question that there can ever be an allowable amount of lead exposure since no risk-free blood level for lead has been established. (ATSDR, 1999; US EPA IRIS).

Toxicity of Lead:

Lead is known to affect adversely a number of different biochemical and physiological processes, cell types, tissues, and organ systems. The primary targets for the toxic effects include the red blood cell forming tissues as well as the cells themselves, the central and peripheral nervous system and the kidneys. In addition, lead may affect the neurobehavioral development of newborns, infants, and children exposed to lead either in utero or postnatally. Other processes adversely affected at low exposure levels include heme biosynthesis and vitamin D metabolism. High levels of adult human exposure have also been related to reproductive dysfunction (ATSDR, 1999). Lead has sufficient evidence of carcinogenicity in at least ten rat bioassays and one mouse assay to demonstrate increases in renal tumors to lead to classification by regulatory agencies as a probable human carcinogen (EPA B2 carcinogen, IARC Group 2 B). Shorter term studies have shown lead affects gene expression. (US EPA IRIS; WHO, 1995).

Effect Levels for Lead:

Blood levels of 5 – 20 ug/dL blood have demonstrated a correlation between blood lead level and performance on cognitive tests in children. Blood levels as low as 10 ug/dl are considered effect levels; the US Department of Health and Human Services has determined that primary prevention activities should begin at that blood lead level in children (CDC, 1991). There is no evidence that the placenta is a barrier to lead; therefore 10 ug/dL is considered an effect level for pregnant women also.

Adult blood levels of 30 ug/dL have been repeatedly associated with peripheral nerve dysfunction, red blood cell protoporphyrin elevation and elevated blood pressure levels. (US EPA, 1986; World Health Organization, 1995). Higher blood levels (50-100 ug Pb/dL) are associated with central nervous system effects, chronic renal failure, reproductive dysfunction in males and females, and anemia. (ATSDR, 1999).

Extrapolation of the blood levels associated with effects to the oral intake that would produce those blood levels is complicated by uncertainties unique to lead. Absorption, release and excretion of lead in humans is influenced by age, gender, health status, nutritional status, existing body burden of lead and the duration of the exposure. Several regulatory agencies which normally develop "safe harbor" levels of chemical exposure have declined to establish such numbers for lead because the uncertainties indicate that standard procedures would not truly estimate risk. (IRIS; ATSDR, 1999).

Risk of Effects from Oral Routes of Lead Exposure

Lead exposure is an actual, rather than a potential, problem. Human exposure to lead above baseline levels is common (ATSDR, 1999). Baseline refers to naturally occurring level of lead in soil or dust that is not due to the influence of humans. Any source of lead contributes to the current exposure level. Sources can include stationary emission sources, occupational exposures, pica, contact with interior lead paint dust, smoking, and wine consumption, as well as the diet.

Total diet studies have found lead intake contributed from all major food groups. Prior to 1989, lead soldered food cans were a source of lead in food. Total lead intake from the diet for the average adult in 1980-1982 was about 56 ug/day. More current data from 1990-1991 after reduction of lead solder in cans, and the phase out of leaded gasoline estimates that total dietary lead ranges from 1.8 to 4.2 ug/day. (ATSDR, 1999, citing FDA Total Diet Food Studies).

A provisional tolerable total dietary intake of lead was established by FDA in 1990 of 6 ug/day for children, and 75 ug/day for adults (Carrington, 1996). These values were established when dietary intake levels were higher than the less than 5 ug/day best current estimate, and using safety factors no longer considered protective. Several scientists believe that more rigorous safety factors should be applied, which would lower the 6 ug/day TTDI for children to 1 ug/day. (Ross, 2000; Carrington, 1996).

Contributions to oral lead exposure from sources other than food are regulated by several agencies. The State of California under Proposition 65 declared lead a chemical of concern for effects on reproduction and established a maximum allowable dose level for these endpoints of 0.5 ug/day (MADL = NOEL/1000). For the cancer potential of lead, California calculated a no significant risk level of 15 ug/day. California considers "no significant risk" to mean no risk for cancer above background levels above 1 in 100,000 (1×10^{-5}).

EPA, under the Safe Drinking Water Act, set a Maximum Contaminant Level Goal for lead of 0 mg Pb/liter drinking water based on its carcinogenicity potential. (US EPA, 1991). The maximum contaminant level (MCL) for lead is set at 0.015 mg/liter of drinking water. Based on the assumption that an adult would ingest 2 liters of drinking water per day, an adult could receive 30 ug/day from water containing lead at the MCL concentration.

A US EPA modeling program for Superfund sites, contains default levels for lead contributed from food or drinking water. The food contribution would be 5 ug/day, and the default from water contribution (2 liters per day) would be 8 ug/day for an adult. (ATSDR, 1999).

Lead in Over the Counter Health Products

With increasing popularity of over the counter health products due to increasing publicity and benefit claims, ensuring the quality of products available to the public is a high priority. The risk of exposure to lead from over the counter products such as calcium supplements has been well recognized for over 40 years (US FDA, 1981). A more recent study of available brands of calcium supplements showed 14 of 25 products tested would cause lead ingestion rates greater than the provisional total tolerable daily intake for lead (Ross, 2000).

Contamination of OTC ibuprofen with lead could be as great a concern as lead in calcium supplements. Since many insurance companies will not pay for the OTC form of drugs, patients may switch brands based on cost alone and expose themselves to higher risk of contaminant exposure (Ross, 2000). Patients taking OTC ibuprofen instead of prescription ibuprofen for rheumatoid arthritis because of cost savings would have at least 3 times the amount of lead consumption as from the recommended OTC dosage for minor pain or fever. Duration of exposure would be chronic compared to the 10 day maximum recommendation by the FDA for OTC ibuprofen.

Depending on the country of origin and based on the limited samples obtained globally, ibuprofen tablets were found to contain lead in a range from non-detect to over 6 ppm. The following table contains highest estimated lead doses that could result from consumption of lead containing ibuprofen tablets. Doses were calculated for consumption of 1.2 grams of ibuprofen (the U.S. OTC dosage) or 3.2 grams (the U.S. prescription dose for rheumatoid arthritis). For comparison, the multiple of a comparison reference dose is indicated.

Health Risks from Lead in Ibuprofen Products

Sample (ibuprofen per tablet, lead analyzed per tablet)	Lead, adult daily intake from prescribed dose for rheumatoid arthritis (x reference dose)	Lead, adult daily intake from OTC dose for fever (x reference dose)	Reference dose (ug/day)	Reference dose source
400 mg IB tablet (4.33 ug Pb)	34.64 ug	12.99 ug	0.5 ug	California Prop 65 MADL (reproductive endpoints)
	(69.3 x)	(26.0 x)		
	(2.3 x)	(.9 x)	15 ug	California Prop 65 NSRL (cancer endpoints)
	(1.2 x)	(.4 x)	30 ug	US Safe Drinking Water MCL (assume 2 liters drunk per day per adult)
	(34.6 x)	(13.0 x)	1 ug	Proposed tolerable total dietary intake using more rigorous safety factors (Carrington, 1996)
	(6.9 x)	(2.6 x)	5 ug	Default food lead contribution, US EPA 1991 model for assessing exposures from Superfund sites
200 mg tablet (1.13 ug Pb)	(4.3 x)	(1.6 x)	8 ug	Default lead from drinking water contribution, US EPA model for Superfund sites (assume 2 liters drunk per day)
	18.03 ug	6.76 ug	0.5 ug	California Prop 65 MADL (reproductive endpoints)
	(36.1 x)	(13.5 x)		
	(1.2 x)	(.5 x)	15 ug	California Prop 65 NSRL (cancer endpoints)
	(.6 x)	(.2 x)	30 ug	US Safe Drinking Water MCL (2 liters drunk per day per adult)
	(18.0 x)	(6.8 x)	1 ug	Proposed tolerable total dietary intake using more rigorous safety factors (Ross, 2000, Carrington, 1996)
	(3.6 x)	(1.4 x)	5 ug	Default food lead contribution, US EPA 1991 model for superfund sites
	(2.25 x)	(.9 x)	8 ug	Default lead from drinking water contribution, US EPA model for superfund sites

MADL: Maximum allowable dose level for reproductive endpoints (NOEL/1000)

NSRL: No significant risk level for cancer endpoints (risk of excess cancer over background no greater than 1×10^{-5})

MCL: Maximum Contaminant Level for drinking water (for carcinogens, the Maximum Contaminant Level Goal is 0)

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