



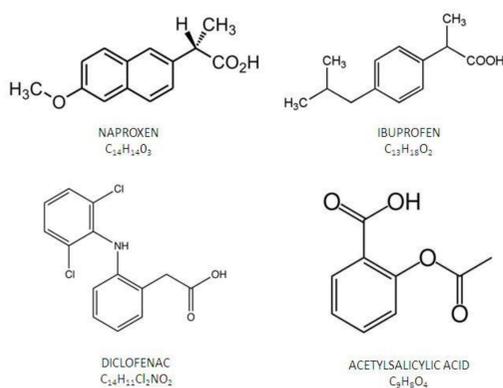
## ABSTRACT

Non Steroidal Anti-Inflammatory Drugs (NSAIDs) are increasingly identified in the environment from various sources. This project reviews the literature on low-level effects of NSAIDs to evaluate the potential environmental health impacts of trace levels of NSAIDs in aquatic systems. Our purpose is to identify potential short- and long-term exposure effects in humans and other organisms and to assess the potential for interactions with other chemicals in the environment that exert health effects through common mechanisms of action.

## INTRODUCTION

- NSAIDs are medications used for the treatment of pain and inflammation.
- Most are found easily and purchased over the counter.
- Frequently, they are purchased in bulk due to their easy and inexpensive availability. These medications' shelf lives often expire before they are consumed, and their improper disposal may lead to environmental exposure.

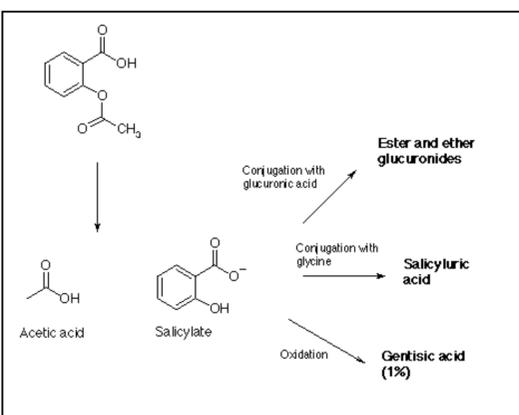
## FOUR COMMON NSAIDs



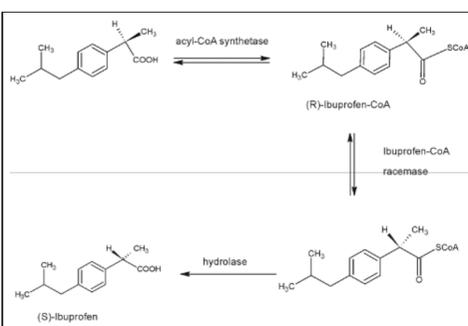
## ADVERSE EFFECTS IN HUMANS

- Diclofenac is the most toxic NSAID.
- Both Naproxen and Aspirin may cause internal bleeding problems, as well as hypotension.
- NSAIDs account for many cases of ulcers, or intestinal perforation in chronic users for pain and inflammation. (4)
- Aspirin use in Children has been linked to Reye's disease. (1)
- People exposed to unknown levels of NSAIDs, while already taking NSAIDs for pain or inflammation, or blood-thinning medication, may interact or synergize and cause internal bleeding, decrease platelet aggregation, or other serious side-effects (3).
- Allergic reactions may occur in patients without previous known exposure or hypersensitivity to NSAIDs, or in individuals with a history of angioedema, urticaria, asthma, and nasal polyps.
- Few sensitive people with the inability to metabolize even small amounts of aspirin may experience allergic-type reactions such as hives, swelling, and headache.
- The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene.

## BIOTRANSFORMATION



Aspirin (6)



Ibuprofen (6)

## DEGREE OF CONTAMINATION FOUND IN VARIOUS ENVIRONMENTS

Compound	Sample	Country	Analytical Procedure	[C] Reported ng/L
Acetylsalicylic Acid (Aspirin)	STP Effluent	Japan	SPE-GC-MS	38 – 111
Diclofenac (Rx)	STP Effluent	Spain	SPE-GC-MS	140 - 2200
Diclofenac (Rx)	Surface Water	United Kingdom	HPLC-MS/MS	<20 - 91
Ibuprofen (Advil)	Ground Water	USA	SPE-LC-MS	3110
Ibuprofen (Advil)	Hoje River Water	Sweden	SPE-GC-MS	10 - 220
Naproxen (Aleve)	STP Effluent	Canada	SPE-GC-MS/MS	271.4 – 7962.3
Naproxen (Aleve)	Paraiba do Sul River Water	Brazil	SPE-GC-MS	<10 - 50

(8)

## AQUATIC TOXICOLOGICAL ENDPOINTS AND POTENTIAL EFFECTS:

NSAIDs function by inhibiting one or both forms of cyclooxygenase (COX) enzyme, COX-1 and COX-2. These enzymes are involved in the synthesis of prostaglandins from arachidonic acid. (8) A COX enzyme similar to human COX-2 has been found in fish thereby making them potential targets for aquatic contamination. (8) All NSAIDs listed in this study are considered to have the same mode of action in humans. (7)

### Acetylsalicylic Acid (ASA):

Tests performed on algal showed an EC50 of (91.6-97.3 mg/L) resulting in growth inhibition. The *Daphnia* test group has an EC50 of 44.6-73.9 mg/L resulting in immobilization. (7)

### Diclofenac:

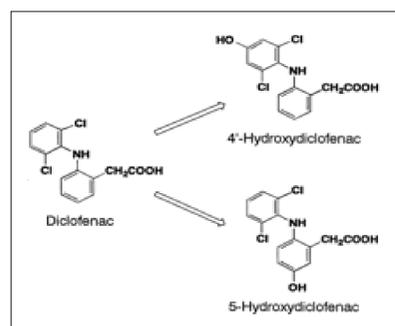
Chronic toxicity trials were performed in Rainbow Trout (*Oncorhynchus mykiss*) revealing cytological changes in the liver, kidneys and gills after 28 days of exposure to 1 µg/L of diclofenac. When concentrations raised to 5µg/L, renal lesions were evident as well as bioaccumulation in the liver, kidneys, gills, and muscle. Found in rivers, ground water, hospital effluents, and drinking water with concentrations in the order of ng/L.(8)

### Ibuprofen:

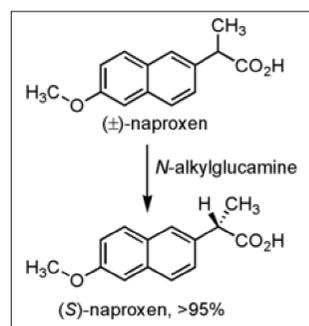
The female Japanese medaka fish (*Oryzias latipes*) was exposed to different concentrations over six weeks resulted in an increase of liver weight, increase in egg production and a decrease in the number of weekly spawning events. The water flea (*Daphnia magna*) was exposed to 0 – 80 mg/L. Reproduction was affected at all concentration, and completely inhibited at highest pharmaceutical levels. An activity decrease of the freshwater amphipod (*Gammarus pulex*) was noticed when exposed to 1 and 10 ng/L. Found in rivers, surface water, STP (influent and effluent) and drinking water. Two metabolites (carboxyl-ibuprofen and hydroxyl-ibuprofen) were also found in surface water and STP.(8)

### Naproxen:

Acute toxic effects were performed on rotifers (*brachionus calyciflorus*), the water flea (*Ceriodaphnia dubia*) and the fairy shrimp (*Thamnocephalus platyurus*). The LC50 and EC50 values are within the 1 – 100 mg/L range, photolysis products being even more toxic. Found in STP effluent, surface water, and drinking water.(8)



Diclofenac



Naproxen

## BIOTOXICITY IN THE AQUATIC ENVIRONMENT

- ASA has an EC50 for *D. subspicatus* (Algae) of 106.7 mg/L resulting in growth inhibition. The EC50 for *D. magna* (Crustacean) of 88.1 mg/L results in immobilization. (8)
- Diclofenac has an EC50 for *D. magna* (Crustacean) of 68mg/L resulting in immobilization. (8) The LOEC (28days) for *Oncorhynchus mykiss* (fish) is 1 µg/L resulting in cytological alterations. (8)
- Ibuprofen has an EC50 (7d) for *L. minor* (duckweed) of 22mg/L resulting in growth inhibition. The LC50 (96h) for *Hydra attenuata* (Cnidarian) is 22.36mg/L.(8)
- Naproxen has an LC50 (24h) for *B. calyciflorus* (Rotifers) is 62.48 mg/L. The EC50 (48h) for *D. magna* at 174mg/L is immobilization
- Photoderivatives of Naproxen have been shown to be 7 – 17 times more toxic than naproxen. (2)

## ADDITIVE AFFECT IN ALGAL GROWTH INHIBITION

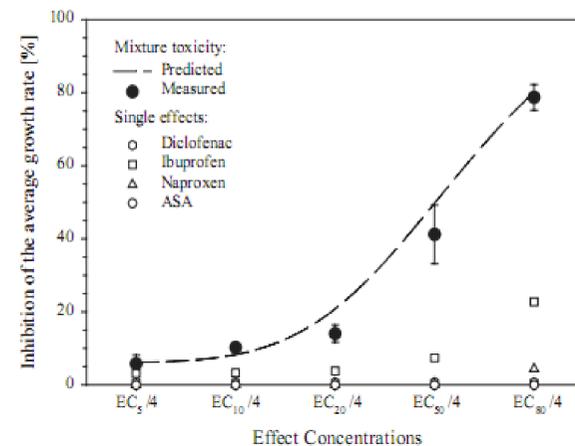


Fig. 1. Measured mixture toxicity of the NSAIDs tested as obtained in the algal growth inhibition test in comparison to the individual toxicities of the single compounds and the mixture toxicity predicted by the concept of concentration addition. (7)

## ADDITIVE AFFECT IN DAPHNIA IMMOBILIZATION

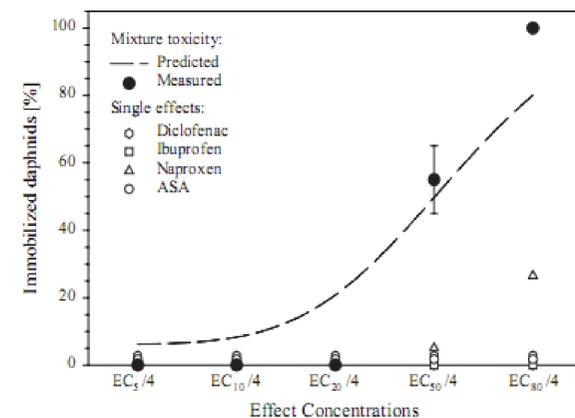


Fig. 2. Measured mixture toxicity of the NSAIDs tested as obtained in the acute *Daphnia* test in comparison to the individual toxicities of the single compounds and the mixture toxicity predicted by the concept of concentration addition. (7)

## A GREEN CHEMISTRY PERSPECTIVE

- NSAIDs environmental impact can be lessened by public education concerning proper disposal.
- California Sate Board of Pharmacy recommends that medication be properly disposed of by following these five steps:
  1. Keep medicine in its original child-resistant container.
  2. Place some water into the solid medication, such as pills or capsules. Add a nontoxic absorbent such as saw dust, kitty litter, charcoal, or powdered spices.
  3. Close and seal the container lids tightly with tape.
  4. Place medicine containers in durable packaging that does not show what's inside.
  5. Place in trash close to garbage pickup time.
- Reformulating NSAIDs to reduce their persistence in the environment can decrease the ecological impact.

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