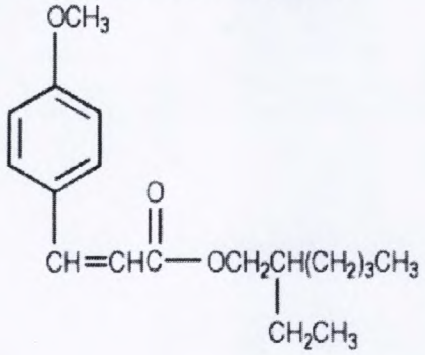
Octinoxate



Chemical Identity

Chemical Abstract Service (CAS) Registry Number: 5466-77-3

Molecular Weight (MW) – 290.40 (A molecular weight below 500 Daltons allows for easy absorption of the chemical through animal and human membranes – e.g.; cells, skin, placenta ... etc).

United Nations Global Harmonized System (GHS) – Hazard Statements: H413 – May cause long lasting harmful effects to aquatic life [Hazardous to the aquatic environment, long-term hazard]

Technical Name(s): 2-Ethylhexyl Methoxycinnamate; 2-Ethylhexyl 4-Methoxycinnamate;

p-Methoxycinnamic Acid, 2-Ethylhexyl Ester; 3-(4-Methoxyphenyl)-2-Propenoic Acid, 2-Ethylhexyl Ester; Octyl Methoxycinnamate; 2-Propenoic Acid, 3-(4-Methoxyphenyl)-, 2-Ethylhexyl Ester.

Trade Name/Supplier: AEC Ethylhexyl Methoxycinnamate (A & E Connock Perfumery & Cosmetics) Ltd.); Custoscreen OMC (Custom Ingredients, Inc.); Escalol 557 (Ashland Inc.); Heliosol 3 (Laboratoires Prod'Hyg); Jeescreen OMC (Jeen International Corporation); Neo Heliopan AV (Symrise); Nomcort TAB (The Nisshin OilliO Group, Ltd.); OriStar OMC (Orient Stars LLC); Parsol MCX (DSM Nutritional Products, Inc.); Uvinul MC 80 (BASF Corporation); Uvinul MC 80 N (BASF Corporation).

FDA Voluntary Cosmetic Registration Program (VCRP): Use as of 01/2015 = 4,783 products.

Use Level: Up to 7.5% in Sunscreens in the United States; Up to 10% in other countries.

Reported Product Categories:

Aftershave Lotions; Baby Shampoos; Basecoats and Undercoats; Bath Capsules; Bath Oils, Tablets, and Salts; Bath Preparations, Misc.; Bath Soaps and Detergents; Blushers (All types); Body and Hand Preparations (Excluding Shaving Preparations); Bubble Baths; Cleansing Products (Cold Creams, Cleansing Lotions, Liquids

and Pads); Colognes and Toilet Waters; Cuticle Softeners; Deodorants (Underarm); Eye Lotions; Eye Makeup Preparations, Misc.; Eye Shadows; Eyebrow Pencils; Eyeliners; Face Powders; Face and Neck Preparations (Excluding Shaving Preparations); Foundations; Fragrance Preparations, Misc.; Hair Coloring Preparations, Misc.; Hair Conditioners; Hair Dyes and Colors (All Types Requiring Caution Statements and Patch Tests); Hair Preparations (Non-coloring), Misc.; Hair Rinses (Coloring); Hair Shampoos (Coloring); Hair Sprays (Aerosol Fixatives); Hair Wave Sets; Indoor Tanning Preparations; Lipsticks; Makeup Bases; Makeup Fixatives; Makeup Preparations (Not eye), Misc.; Manicuring Preparations, Misc.; Moisturizing Preparations; Nail Creams and Lotions; Nail Polish and Enamel Removers; Nail Polish and Enamels; Night Skin Care Preparations; Paste Masks (Mud Packs); Perfumes; Personal Cleanliness Products, Misc.; Powders (Dusting and Talcum, Excluding Aftershave Talcs); Rouges; Shampoos (Non-coloring); Shaving Preparations, Misc.; Skin Care Preparations, Misc.; Skin Fresheners; Suntan Gels, Creams, and Liquids; Suntan Preparations, Misc.; Tonics, Dressings, and Other Hair Grooming Aids.

Octinoxate: Human and Environmental Contamination

Octinoxate is a ubiquitous environmental contaminant – it is found in streams, rivers, lakes and in marine environments from the Arctic Circle (Barrow, Alaska) to the beaches and coral reefs along the equator [1-7, 82]. It is considered an environmental hazard in many locations [6-9, 86, 87], and is one of 10 chemicals listed on the European watch list of substances that may pose a significant risk to the aquatic environment [10]. Octinoxate can be found in both municipal treated and desalinated drinking water [11-13, 24]. Sewage sludge can be heavily contaminated by Octinoxate and other Personal Care Product Chemical, further expanding the types of sources contaminating the environment (e.g., biosolids)[14]. Swimmers directly contaminate water sources, but point and non-point sewage and treated waste-water effluent discharges maybe the largest source of contamination [14-16]. The United Nations Global Harmonized System (GHS) is used in the United States (US) by OSHA, EPA, DOT and CPSC as well as European and Asian countries, and identifies Octinoxate as an environmental hazard and carries the following warning label "H413 – May cause long lasting harmful effects to aquatic life" (see diamond logo at top of page)[17]. As sunscreen usage increases worldwide (projected global sales of $11 billion by 2020), so can the levels of environmental contamination that impact human and aquatic life. As of 2015, the U.S. Food & Drug Administration Voluntary Cosmetic Registration Program identifies 4,753 sunscreen and cosmetic formulas that contain Octinoxate [18].

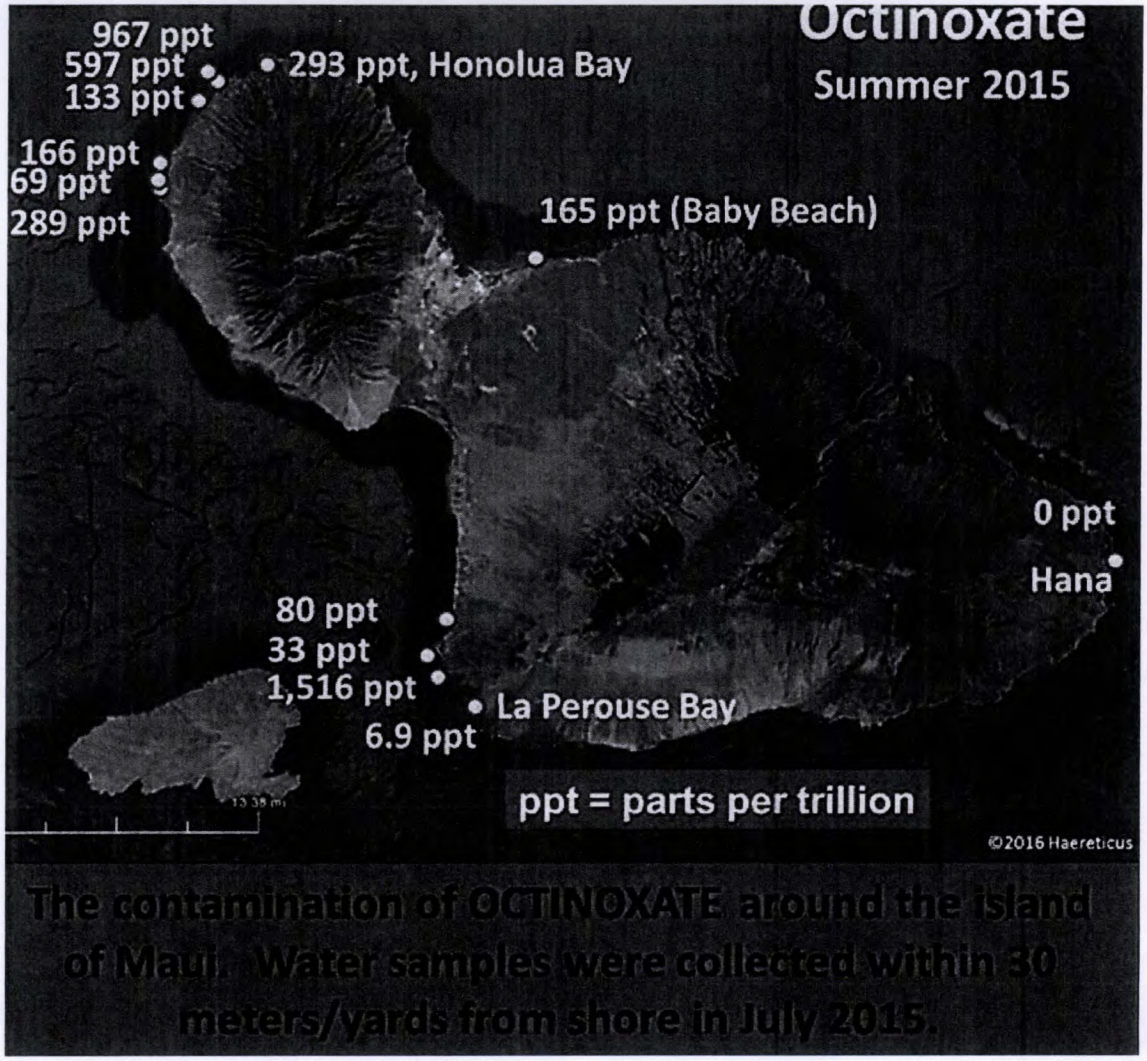
Octinoxate is absorbed directly through the skin, via the application of sunscreens and other personal care products. Depending on the topical vehicle used, relatively little chemical (less than 1% to 6%) is absorbed into the skin and excreted in the urine, leaving 94% – 99% on the skin that can be washed off into various water sources [19-23]. Octinoxate is a fat-soluble chemical, which means that some of it that absorbed by the body will be metabolized and excreted in urine, but much of it will be stored either in fat tissue or lipid-rich tissue such as the placenta [26, 27].

In aquatic and marine environments, water depth, light intensity and the amount of dissolved organic carbon content in the location determine the fate of Octinoxate [28]. Additionally, photo-degradation in the presence of titanium dioxide leads to the formation of more toxic by-products [34]. The increased toxicity is partially accounted for by the formation of 4-methoxybenzaldehyde, which is toxic to algae and aquatic invertebrates, such as *Daphnia*[29]. In sunscreen formulations, Octinoxate can react with Avobenzone reducing the overall sun protection factor of the product, leading to photo-instability and an increase risk of sunburn[30].

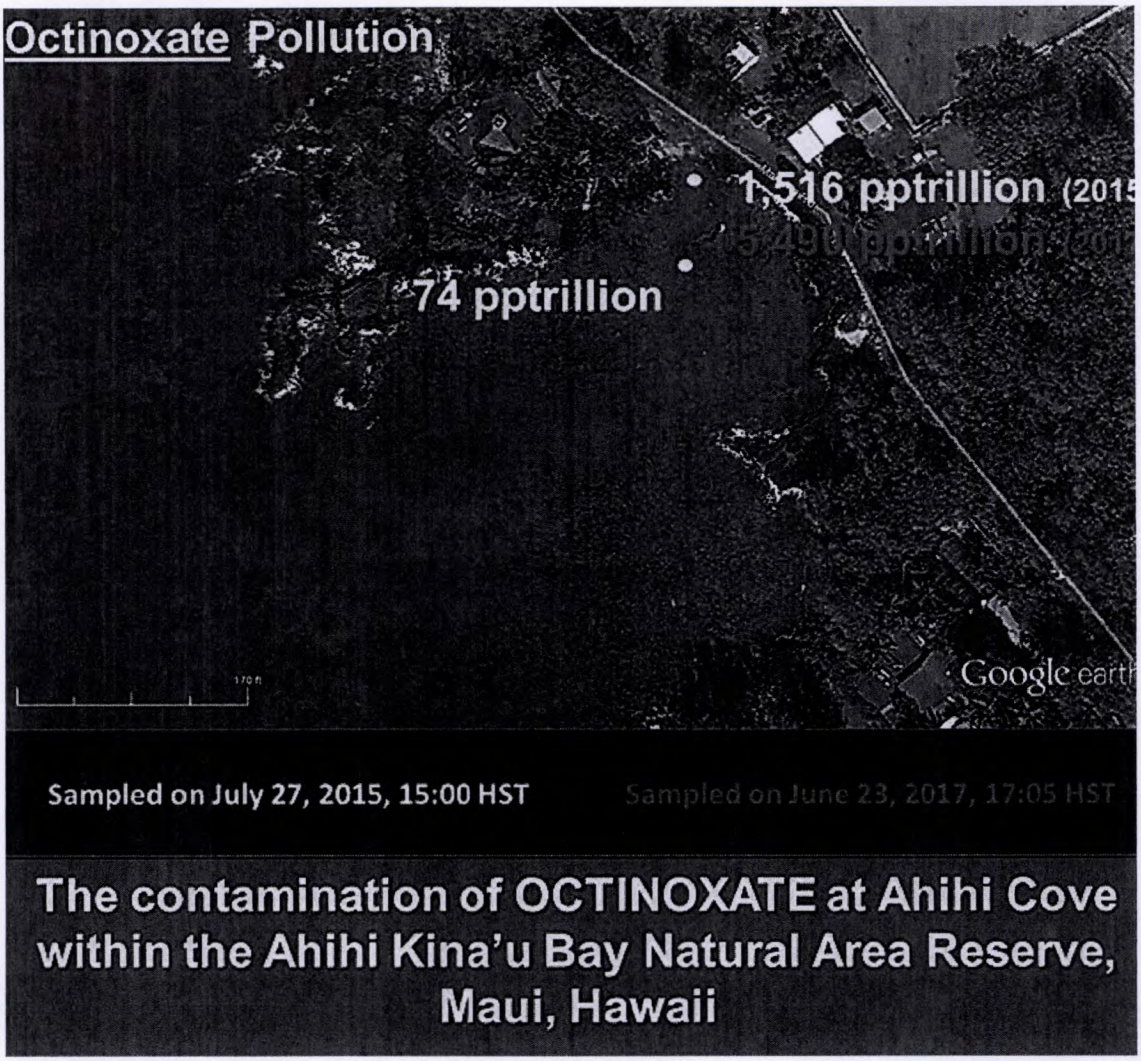
Octinoxate may also bioaccumulate and be *biomagnified* in organisms [28,87]. Biomagnification means Octinoxate may increase in concentration in the tissues of organisms as it travels up the food chain. A number of aquatic and marine species have been discovered to be contaminated, from carp, catfish, eel, white fish,

trout, barb, chub, perch and mussels to coral, mahi-mahi, dolphins, sea turtle eggs, and migratory bird eggs (24,28, 86)

In coral reef environments, Octinoxate can reach more than 10 parts per billion. Along the west coast of Maui in 2015, Hawaii, 11 coral reefs sites that were sampled had octinoxate concentrations from 6.9 parts per trillion to 1,516 parts per trillion.



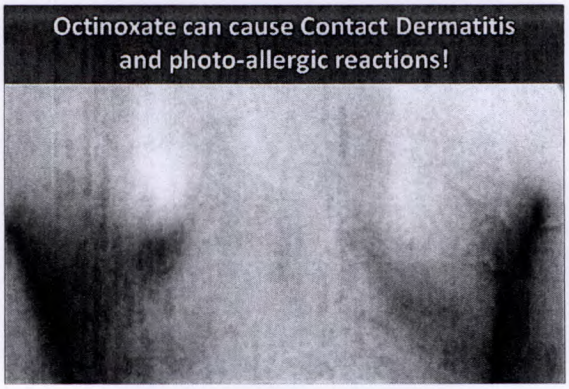
In the Ahihi Kina'u Bay marine protected areas, Octinoxate concentrations increased 3.6 times from 2015 to 2017.



Several scientific groups in different countries have done a formal environmental risk assessment of octinoxate to their marine ecosystems and have demonstrated that Octinoxate was a threat to the health of these ecosystems [6, 82, 86, 87].

Octinoxate Ecotoxicology

For humans and mammals, the most common pathological reaction to Octinoxate is contact dermatitis and photoallergic reactions [31-38].



Octinoxate on top of the skin or in the epidermal layer can be degraded by sunlight (called photodegradation), and those breakdown products can be especially toxic [39].

Once in the body, Octinoxate can cause toxicity to a number of different organ systems. Developing fetuses, babies, pre-adolescents, and even the pregnant mother are especially susceptible. In pregnant rats exposed to Octinoxate, there was a significant decrease in thyroid hormone levels (Thyroxine) [51]. Young male rats whose mothers were exposed to octinoxate had smaller testicals and lower semen quality, and a dose-dependent reduction in testosterone levels – meaning the more Octinoxate the mother was exposed to, the lower the level of testosterone in the offspring male. Young female rats from the same Octinoxate-exposed mothers exhibited reduced motor activity levels [51]. Like Oxybenzone, Octinoxate can impair both neurological and reproductive abilities [52-57, 73].

Another study that focused on two generations of rats exposed to Octinoxate also exhibited liver/blood disease, occurrence of ulcers in the stomach, and a higher risk to miscarriage [60]. Furthermore, the off-spring had reduced organ weights, increased difficulty gaining weight during breast feeding, and a significant delay in sexual maturation [60]. It is by reasonable argument that Octinoxate should be classified as a **reproductive endocrine disruptor** [58-59]. A number of studies demonstrate that Octinoxate is a multi-system or multi-axis endocrine disruptor – meaning it can disrupt more than one type of endocrine system. Octinoxate can adversely affect estrogen receptors, androgen receptors, progesterone receptors, and thyroid hormone receptors [40-43, 48, 75, 80]. This mimicking of estrogen by Octinoxate was also shown to be able to adversely impact the immune system [67].

There have been a number of strong scientific studies on the impact of Octinoxate to the mammalian Thyroid gland and its function [53, 61]. Octinoxate affects both adult and juvenile mammals.

Danish scientists publicized in 2016 the impact of 29 different UV filters on sperm function and viability. Octinoxate was one of the UV filters that had an adverse effect on sperm function [85].

Genotoxicity of a chemical is a critical factor for its regulation and use in consumer products. The trend in the scientific literature indicates that Octinoxate is a genotoxin – meaning it damages DNA and the genetic material, and can give rise to genetic mutations, further resulting in the potential manifestation of reduced reproductive viability, adverse embryonic development, and cancer. One study provided data, using the Ames Test, that Octinoxate was mutagenic, as well as in a Fruit Fly genetic test [76]. The authors, in their paper, stated that "A trace contaminant may be implicated because many samples were obtained from several sources and the results were batch-related." This begs the question of why this study was allowed to be published by the journal, or were such statements in the paper a result of pressure from outside forces on the Journal's editorial staff. Other studies on Octinoxate's genotoxicity using bacterial models demonstrated positive mutagenicity [66, 77, 78]. One relatively recent study showed that Octinoxate does prevent one type of DNA damage by UV radiation, but it does not prevent DNA damage caused by oxidative stress [68].

There have been some *in vitro* cell culture studies, showing the toxicity of Octinoxate to neuroblastoma cells, liver stem cells, and human white blood cells [69, 70]. Some of these cell types exhibited a DNA-damage gene response exhibited, further arguing that Octinoxate is genotoxic [70, 72].

By 1994, over a million pounds of Octinoxate is manufactured each year (10). If historical evidence indicates the propensity of Octinoxate to be genotoxic, better studies by independent laboratories characterizing its genotoxicity and threat to human and ecological receptors is a necessity.

A "sister" compound of Octinoxate, called Cinoxate, supports this call for further investigation. Cinoxate was found to cause an increase in chromosome aberrations (type of genotoxicity) in mammalian cells using an industry-accepted method [79].

Carcinogenicity arises out of the interaction between genetic damage and cellular/tissue environmental instability. A recent paper by Alamer and Darbre shows that Octinoxate, Oxybenzone, Benzophenone-1 (breakdown product of oxybenzone), homosalate, and 4-MB-Camphor increased the metastatic behavior of breast cancer cells [80].

Toxicity to Wildlife – Most of the research has focused on the toxicity of Octinoxate to fish. Exposure to non-lethal concentrations radically alters the activation of genes in fish, altering the expression of over 1130 different gene transcripts [47]. Many of the altered genes play a role in hormonal regulation, including enzymes and proteins regulating estrogen and testosterone, as well as DNA damage and lipid synthesis.

At least three other studies in fish demonstrate that Octinoxate is an endocrine disruptor and causing reproductive disease at relevant environmental concentrations [44, 48-50]. A team of Dutch scientists were one of the first to show that Octinoxate induced estrogenic disruption in fish (Zebrafish) [48]. Scientists from Japan showed that male fish (*Medaka*) exposed to Octinoxate caused a reproductive endocrine disruption by having these male fish produce egg proteins [49]. Scientists in Switzerland confirmed these results using a different species of fish (fathead minnows); and that Octinoxate impacted multiple hormonal systems [50].

A team of Korean scientists did some amazing work showing that exposure to Octinoxate during embryonic development results in organ and body axis deformities in Zebrafish [71]. Octinoxate exposure had a statistically significant effect to induce liver defects. In this same study, a mixture of Oxybenzone and Octinoxate induced synergistic deformities in embryonic development of Zebrafish.

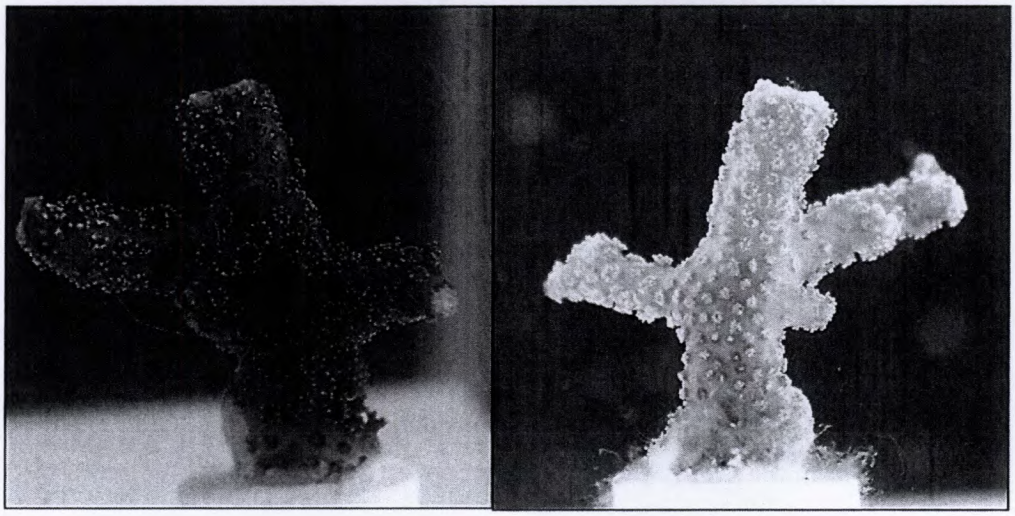
For invertebrates, such as a crustacean species of Daphnids, the same authors demonstrated that exposure of Octinoxate caused immobilization of *Daphnia*, as well as deformities [71, 45]. These results were consistent with an earlier study done by German Scientists on Octinoxate toxicity and Daphnia [83], which saw growth inhibition of Octinoxate at 240 parts per billion and as low as >40 parts per billion.

Studies on other invertebrates, such as the larvae of the aquatic midge, *Chironomus riparius*, indicated that Octinoxate induced the Stress Protein response in midges, as well as induced the overexpression of an insect hormone receptor (ecdysone receptor), indicating that it acts as an endocrine disruptor to insects [45].

One of the best scientific papers to examine the ecotoxicity of Octinoxate on the different trophic levels of a marine ecosystem was the work done by group of Spanish scientists [81]. In this study, the researchers looked at the toxicity of Octinoxate to an algae, a mussel, a sea urchin, and a shrimp (carnivore). They saw toxic effects of Octinoxate of these four organisms as low as 52 parts per billion and concluded that Octinoxate (and Oxybenzone) "could pose significant risks to marine aquatic ecosystem."

Future work from the Haereticus laboratory will be demonstrating the toxicity of Octinoxate to coral, including the inducing corals to undergo bleaching. Coral exposed to pollutants that causes them to bleach, makes these corals more susceptible when a climate event occurs, such as an El Nino-induced mass bleaching event.

Octinoxate Induces Coral Bleaching



Time 0

1 part per billion Octinoxate 14 days

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Are Your Products Safe?

We've come up with a list of chemicals and attributes in personal care products (e.g., sunscreen lotions and sprays) that are found in a number of different aquatic and marine ecosystems that can have a detrimental effect on their existence. We call this list of chemicals and physical-attributes the "HEL LIST." See the list here

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