Factsheets on uses and hazards of chemical ingredients of Sanitized® preparations

(with particular reference to criteria for "substances of very high concern" under REACH)

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Contents

Summary

This series of short factsheets is intended to provide background information on the properties of four key antimicrobial chemicals reported to be used in preparations and articles marketed under the Sanitized® label:-

- 2,4,4'-Trichloro-2-hydroxydiphenyl ether or **Triclosan** (CAS number 3380-34-5)
- 1,2-Benzisothiazolin-3-one or **BIT** (CAS number 2634-33-5)
- 2-n-Octyl-4-isothazolin-3-one or **Kathon 893** (CAS number 26530-20-1)
- 3-Iodo-2-propynyl-butylcarbamate or **IPBC** (CAS number 55406-53-6)

The main focus of these factsheets, other than providing background information on uses, toxicity and environmental fate, is to determine the likelihood that each chemical would be identified as a "chemical of very high concern" under REACH (by comparison with criteria in Annex XII of the current proposal). They are not, therefore, intended to provide exhaustive reviews of the literature.

For triclosan, the literature is extensive, but focuses heavily on consequences of use on microbial resistance to other agents. While this is a substantial concern, it is not central to the purpose of these factsheets. For the other three compounds, relatively little information is available. Moreover, the majority of what is available focuses on contact dermatitis and other allergic responses. This literature is reviewed briefly in each case, though again it may have relatively little bearing on the ultimate status if these chemicals under REACH.

In short, the available information in openly published literature has allowed for only a limited evaluation in each case. Additional information undoubtedly resides with industry and authorities but is difficult, if not impossible, to access. The available information can be summarised as follows:-

- All four chemicals have known and well established irritant properties, with some evidence in each case of ability to cause skin sensitisation (*i.e.* increased severity of reaction with repeated exposures) and allergic responses such as contact dermatitis.
- None of the four chemicals appear to be identified as CMR chemicals under Community law. However, in most cases very little information is available on which to make an assessment of CMR properties
- Three of the four chemicals (triclosan, BIT and Kathon 893) are classified as "very toxic to aquatic organisms" according to Directive 67/548. The fourth chemical (IPBC) does not appear to be classified within Europe; nevertheless, available evidence suggests that it shows a similar, if not even higher, toxicity to aquatic organisms
- Triclosan, for which the greatest amount of information is available, appears to be a good candidate for identification as a PBT chemical. It seems certain that the B and T criteria, at least, are met. In terms of P, slow rates of degradation in northern latitudes and long-term persistence in aquatic sediments give a strong indication that this criterion will also be met, though no simple quantitative comparison is possible
- In the case of BIT, Kathon 893 and IPBC, it seems reasonable to suggest that these would also meet the T criterion on the basis of aquatic toxicity. However, insufficient information is available on which to evaluate persistence and propensity to bioaccumulate.
- The possibility that one or more of the additional hazards presented by these chemicals (*e.g.* bacterial resistance, olfactory inhibition) will be sufficient to meet requirements for "equivalent concern" under REACH remains to be evaluated

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Factsheet on 2,4,4'-Trichloro-2-hydroxydiphenyl ether (Triclosan)

Name

2,4,4'-Trichloro-2-hydroxydiphenyl ether or Triclosan. Synonyms include Irgasan DP 300 and Irgasan ch 3635. Fibres and polymers that have been impregnated with triclosan have names such as Ultra-Fresh, Amicor, Microban, Monolith, Bactonix and Sanitized (see Adolfsson-Erici *et al.* 2002).

CAS number

3380-34-5

Uses

Triclosan is a commonly used antibacterial agent for products including detergents, soaps, cosmetics, deodorants, toothpastes and mouth-washes (see Adolfsson-Erici *et al.* 2002, Babich and Babich 1997). Triclosan is incorporated in some polymers and fibres to give these materials antibacterial properties. For example, it is used in mattress pads, food cutting boards, shoes and sportswear (see Tixier *et al.* 2002).

In Sweden, the use of phenolic antibacterial substances like triclosan in hospitals was abandoned several years ago since they were considered unnecessary for practical use (see Adolfsson-Erici *et al.* 2002).

Environmental Fate

Triclosan is a relatively stable, lipophilic compound (Lindström *et al* 2002). It has been detected in wastewater/sewage treatment plants, the aquatic environment and humans.

Lindström *et al.* (2002) detected triclosan in the influents and effluents of wastewater treatment plants. Influent concentrations are typically in the range of 1-10 μgL^{-1} (McAvoy *et al* 2002, Bester 2003 & Lindström *et al* 2002) with higher levels being found in the US to Europe. It has been shown that triclosan concentrations in WWTP effluent may be up to 95% less than those in influent (McAvoy *et al* 2002, Bester 2003). Typical effluent levels range from 0.1-2 μgL^{-1}. However, although activated-sludge treatment can remove approximately 95% of the Triclosan from the aqueous phase, by no means all of this removal results from biodegradation. Up to 30 % of the triclosan leaves the plant weakly bound to sludge (Bester 2003): *Koc* for adsorption to activated sludge is 47 000 (Singer *et al* 2002). It is likely that the balance either undergoes biodegradation or forms tightly bound residues with the sludge. Precise budgets are likely to vary significantly from plant to plant.

Biological degradation by activated sludge occurs readily under aerobic conditions, but not under anaerobic (McAvoy *et al* 2002). Federle *et al* (2002) have shown that a high degree of mineralization in activated sludge can occur. Their experiments showed that more than 94% of triclosan in activated sludge was removed by biodegradation. 4.5% was removed by sorption to the waste sludge. However, experimental concentrations and conditions employed in this study did not match those encountered during normal operations of treatment plants .

Other forms of waste water treatment are less effective; for example removal from the aqueous phase by trickling-feeder treatment varied from 58%-86% (McAvoy *et al* 2002).

Formation of methyl triclosan occurs in WWTPs. This conclusion is drawn from evidence that higher concentrations are found in effluent that in influent (Lindström *et al* 2002) despite a high propensity for elimination to sludge. McAvoy *et al* (2002) report levels of methyl triclosan in sludge of up to 25% those of triclosan (up to 1 μg/g), even when influent levels were too low to quantify using the most sensitive methods available.

Despite degradation and sedimentation in waste water treatment plants, Triclosan has been shown to enter the aquatic environment in significant quantities via effluent from such plants. For example, triclosan was detected in several rivers and lakes in Sweden at concentrations of up to 14 ng/L (Lindström *et al.* 2002). In a study of streams across the USA, triclosan was found in 57.6% of the 139 streams tested at a median concentration of 140 ng/L (Kolpin *et al.* 2002). Lindström *et al.* (2002) also showed that another chemical, methyl triclosan, is formed from triclosan during processing at wastewater treatment plants. This chemical was detected in rivers and lakes in Sweden. Although it was detected at consistently lower concentrations (up to 0.8 ng/L) than triclosan itself, methyl triclosan appears to be more resistant to degradation and, therefore, more persistent than triclosan. It also has a greater propensity to accumulate in living tissues (see below).

Results from a study by Lindström *et al.* (2002) suggested that triclosan is rapidly degraded in sunlight by photolysis in the surface waters of lakes. The importance of phototransformation as an elimination process for triclosan from surface waters has been further supported by Tixier *et al* (2002). This latter paper elegantly demonstrates triclosan elimination from the epilimnion (surface layer) of a Swiss lake. The rate of transformation is dependent upon the form of triclosan present, which in turn is dependent upon pH. At water pH >8 (above triclosan pK_a), the anionic (de-protonated) form dominates. This undergoes phototransformation far more readily; 2,8-dichlorodibenzodioxin (2,8-DCDD) has been shown to be one of the products of this process.

At the pH range typically found in surface waters, however, it is unlikely that yields of 2,8-DCDD greater than 4% of the original triclosan concentration will occur (Latch *et al* 2003, Mezcua. *et al* 2004). Other products may include de-chlorinated congeners or rearranged products (Latch *et al.* 2003), some of which have been tentatively identified (Ferrer *et al* 2004). It is has been postulated that the photo-excited triclosan would couple with dissolved organic molecules such as those present in the natural humic substance fulvic acid. This may represent a major degradation pathway.

Methyl triclosan does not readily undergo photolysis and so, as noted above, is more persistent (Lindström *et al.* 2002). Levels in rivers are typically below 2ng/l. However, the distribution and fate of methyl triclosan in sediment remains, as yet, poorly researched.

Indeed, while the fate of triclosan and its biodegradation products in sediments have been studied to some extent, available literature is very limited and far from conclusive. Due to positive K_{ow} values for both substances, adherence to sediment particles is clearly important. Singer *et al* (2002) report triclosan concentrations in sediment dating back to 1960 (Figure 1) and yielding a time sequence of changing concentrations with depth. This study not only confirms the persistence of triclosan in freshwater sediments but also illustrates the impact of changes in anthropogenic activity. Levels are seen initially to rise with increased usage in the

period 1960-75. The introduction of biological WWT thereafter reduced the inputs to sediment in the late 70s/early 80s, though this trend was subsequently reversed, probably reflecting increases in overall volumes of use of triclosan.

Triclosan has been detected in the bile of wild fish that were living downstream of 3 wastewater treatment plants in Sweden (Adolfsson-Erici *et al.* 2002). It was also found in caged experimental fish placed in the same environment. A study of 4 lakes in Switzerland that had an input from wastewater treatment plants detected methyl triclosan in fish up to 35 ng/g wet weight or 365 ng/g on a lipid basis (Balmer *et al.* 2004). No methyl triclosan was detected in fish from a remote lake in Sweden and a small lake in Switzerland which had no input from wastewater treatment plants. The study noted that results were consistent with previous research in Japan that had reported methyl triclosan in fish (1-38 ng/g wet weight) in the Tama River. The study estimated a bioconcentration factor of methyl triclosan in fish was in the order of 1-2.6 x 10^5 (lipid basis). This is in the range of other persistent organic pollutants.

In humans, a study in Sweden detected triclosan in blood plasma (Hovander *et al.* 2002). High levels of triclosan (60, 130 and 300 μg/kg lipid weight) were detected in 3 out of 5 samples of human breast milk in another Swedish study (Adolfsson-Erici *et al.* 2002).

Toxicity

Triclosan has been shown to be a skin irritant in rabbits (see Moss *et al.* 2000). Triclosan is also a contact allergen (Schnuch *et al.* 1998, see Saino and Kanerva 1995). Studies on the toxicity of triclosan showed that it affected liver enzymes in the rat liver and that this could contribute to its toxicity (Hanioka *et al.* 1996, Hanioka *et al.* 1997). Triclosan was not found to be mutagenic in both *in vitro* and *in vivo* tests (Russell and Montgomery 1980, Gocke *et al.* 1981).

Triclosan has been shown to be toxic to rainbow trout and to the aquatic invertebrate *Daphina magna* (see Adolfsson-Erici *et al.* 2002). Other studies suggest that triclosan is highly toxic to the early life stages of fish (medaka), and that some metabolites may be weakly estrogenic (Ishibashi *et al.* 2004), although no adverse effects on reproductive success and offspring have been detected.

The major concern of triclosan contamination in environmental surface waters is its toxicity to certain algae species such as *Scenedesmus subspicatus* (see Tixier *et al.* 2002). The no-observed effect concentration of this species is 500 ng/L, which leads to a predicted no-effect concentration of about 50 ng/L.

Some studies indicate a possible bacterial resistance to triclosan, although clinical studies with long-term exposure to products containing triclosan, such as deoderants or toothpastes, have not indicated development of bacterial resistance on skin or mucous membrane (see Tixier *et al.* 2002). However, one study has demonstrated multi drug resistance (MDR) conveyed by triclosan to *Pseudomonas aeruginosa* (Chuanchuen *et al.* 2001). MDR *Pseudomonas aeruginosa* is a bacterial strain of foremost clinical importance because it is a cause of death in many hospital-acquired infections due to its intrinsic resistance to many antibiotics. It has been well established that over use of antibiotics is the main cause for the development of antibiotic resistance. The results of this study raised the notion that widespread and unregulated use of triclosan may promote the selection of MDR bacteria and thus compound antibiotic resistance.

Triclosan is readily converted to various polychlorinated dibenzo-*p*-dioxins by heat and UV irradiation (see Hanioka *et al.* 1996). A study which tested both a commercially available

sample of Irgasan DP 300 and a sample direct from the manufacturer, found that both contained di- and trichlorinated dibenzodioxins and -furans in the ppb range (Beck *et al.* 1989). The samples did not contain any of the more toxic 2,3,7,8-substituted isomers or the mono-chlorinated and higher chlorinated PCDDs and PCDFs. The study noted that the congeners found in triclosan are of relatively low toxicity because they are metabolised very rapidly and do not accumulate in humans and animals.

Triclosan has been shown to rapidly react with chlorinated water to produce chloroform (trichloromethane) (Rule *et al* 2005). Chloroform and other halomethanes occur in drinking water as a result of chlorination. These substances are associated with adverse health effects, chloroform is classified as possibly carcinogenic to humans (group 2B) by the International Agency for Research on Cancer (IARC). Current EU legislation sets a maximum concentration of 100 ug/l for trihalomethanes in drinking water (Council Directive 98/83/EC). Therefore, whilst the presence of triclosan in cleaning and personal care products at relatively high concentrations (0.1- 1%) is not the excusive source of chloroform in the home it will certainly increase overall exposure: possibly resulting in trihalomethane levels higher than those permitted by legislation.

Further research includes evidence for contact allergy, particularly after occupational exposure, reviews of applications of triclosan and their safety in hospitals and formation of dioxins during combustion of triclosan impregnated materials. These aspects have not been reviewed in detail for the purpose of this summary.

Relation to PBT and CMR criteria under REACH

The NOEC for algae is stated to be 500 ng/L (or 0.0005 mg/L). The criterion for toxicity under Annex XII of REACH is a long-term NOEC for freshwater organisms less than 0.01mg/L. Therefore, triclosan appears to qualify as “toxic” for the purposes of REACH.

With a log K_{ow} of 4.8 (Lopez-Avila & Hites 1980), triclosan may be expected to bioconcentrate. Empirical studies in zebra fish (see Orvos *et al* 2002) suggest total accumulation factors for different tissues in the range 2000 to 5,200, with greatest accumulation in the intestines. The estimated bioconcentration factor based on these data is approximately 2500. Comparison against the criterion for bioaccumulation under Annex XII of REACH (BCF >2000) indicates that triclosan qualifies as “bioaccumulative” for the purposes of REACH.

Estimates of persistence of triclosan in the aquatic environment vary. In the surface layer of waterways and lakes, half-life is heavily dependent upon incident solar flux (sunlight) and water pH (Tixier *et al* 2002). Figure 2 demonstrates the effect of latitude and season on degradation rate, indicating that, in northern latitudes at least, half lives for photo-transformation in surface waters may exceed the REACH Annex XII criterion of 40 days for a large part of the year. Few other quantitative data are available.

Reiss *et al* (2002) report half lives for aerobic biodegradation in soil of between 17.4 – 35.2 days. This is well below the relevant criterion given under Annex XII of REACH (120 days). Nevertheless, persistence in sediments, particularly anaerobic sediments is undoubtedly much greater, as indicated by its presence in lake sediments from several decades ago (Singer *et al.* 2002). Unfortunately no conclusive data currently exist on which to base an estimate of sediment half-life. However, it seems reasonable to suggest that, in the sediment compartment at least, triclosan is likely to qualify as “persistent” for the purposes of REACH.

Triclosan is not identified as a CMR substance under Community legislation.

Risk Phrases applicable under Directive 67/548:

R36/38 (Irritating to eyes and skin)
R50/53 (Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment).

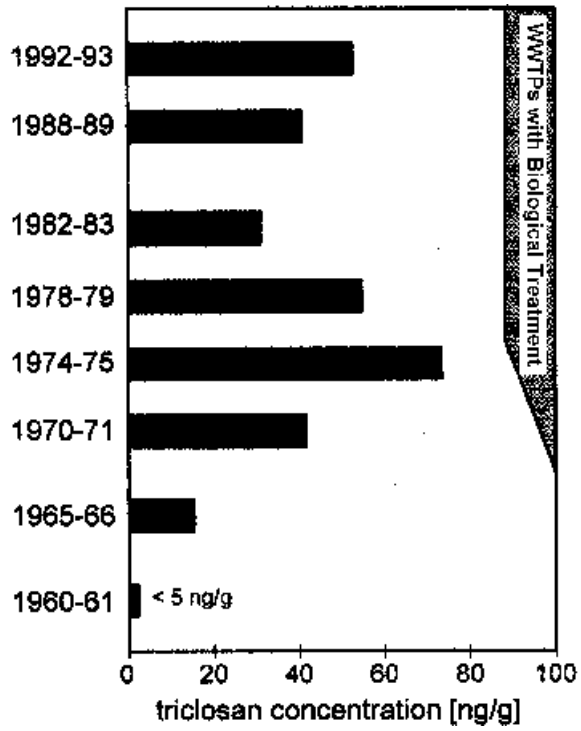

Figure 1 Variation in triclosan concentrations in Swiss lake sediment with time. (Singer *et al* 2002)

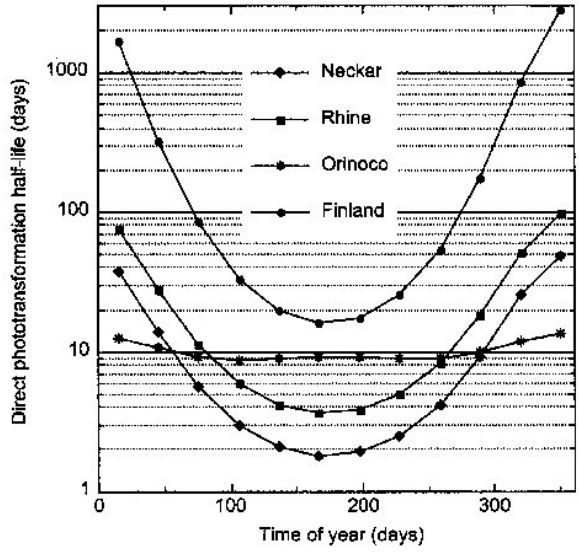

Figure 2 Phototransformation of triclosan as a function of season. (Tixier *et al* 2002)

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Factsheet on 1,2-Benzisothiazolin-3-one (BIT)

Name

1,2-Benzisothiazolin-3-one or BIT. Synonyms include benzisothiazolin or Proxel GXL.

CAS number

2634-33-5

Uses

BIT has long been known to have a strong antimicrobial activity even at relatively low concentrations (Muhn and Sasseville 2003). It is reportedly widely used as biocide and as a preservative to prevent the growth of microorganisms in a diverse range of products (see Chew and Maibach 1997). Known uses of BIT registered in Denmark include use as an additive in cleaning agents, polishes, paints, preservatives, fabric softeners, pigments, surfactants, binders, platicizers, construction materials, curing agents, anti-adhesive agents, adhesives/glues and pesticides (Nielsen 1994). Other uses include use as an additive in certain metal working fluids (Chew and Maibach 1997) and for slime control in paper mills (Burden *et al.* 1994).

Nielsen (1994) identified a total of 156 products that contained BIT, of which 139 had information on the concentration of BIT. 54% of these 139 products contained BIT at a concentration of equal to or greater than 0.01% (100 ppm).

Toxicity

BIT is a known skin sensitizer and irritant (Chew and Maibach 1997). Allergic contact dermatitis has been reported in a diversity of occupational settings, including in manufacture of water-based paints and glues (Ezzelarab *et al.* 1994), in metal working operations (Alomar 1981) and in manufacture of air fresheners (Dias *et al.* 1992). Ayadi and Martin (1999) reported a case of pulpitis (swelling) of the fingers in an individual who was exposed to BIT while handling glue in a shoe factory. The authors noted that tests seemed to indicate a combination of irritant and allergic contact dermatitis due to BIT.

Useful reviews of reported skin reactions to BIT are provided by Chew and Maibach (1997) and Muhn and Sasseville (2003). Several of these studies have also confirmed that BIT has more general irritant properties. However, Chew and Maibach (1997) questioned the clinical validity of some early studies as it was difficult to confirm whether BIT was a true allergen using the particular method of skin patch tests commonly employed. They suggested that further experimental studies would help increase the knowledge of BIT reactions and also suggested practical ways of improving skin patch testing for future studies. Further studies which followed these suggested changes include that conducted by Cooper and Shaw (1999), which nevertheless confirmed that allergic contact dermatitis on the hands of an worker employed to assemble water softening devices was due to exposure to BIT.

A study on an individual laboratory worker who presented with patchy eczema on the hands reported hypersensitivity to BIT and to another chemical (2-methyl-4,5-trimethylene-4-isothiazolin-3-one, or MTI) (Burden *et al.* 1994). The study concluded that multiple sensitization by both chemicals was possible, but that cross-reactions between these chemicals may also have occurred. Nevertheless, in a subsequent study involving 928 individuals, which reported allergic reactions to BIT in 1.3% of participants, simultaneous reactions to mixtures of

3 related chemicals were very rare (Geier and Schnuch 1996). Results indicated that, where such reactions did occur, it was more probably due to multiple sensitization to the chemicals than cross-reactivity.

In a study on the acute toxicity of BIT to laboratory rats, the oral LD_{50} was 1020 mg/kg (see Søderlund 1992). Søderlund (1992) noted that BIT had not at that time been tested for reproductive toxicity or teratogenicity in animals, and that no complete carcinogenicity study had been performed (although results from a preliminary study were negative). From available published literature, it appears that such studies still remain to be conducted.

Environmental fate

Little is known about the environmental fate and effects of BIT. There is some evidence that BIT undergoes photodegradation in the environment, (Lugg 2001). Using commercial preparations containing BIT, this research showed complete removal of biocidal activity following 3 months exposure to sunlight, while activity remained in samples placed in the dark. However, the simple experimental design employed in this study does not allow estimation of degradation rates.

Relation to PBT and CMR criteria under REACH

No appropriate data were located to allow comparison against PBT criteria or CMR criteria.

BIT is not identified as a CMR substance under Community legislation.

Risk Phrases applicable under Directive 67/548:

R22 (Harmful if swallowed)
R38 (Irritating to the skin)
R41 (Risk of serious damage to eyes)
R43 (May cause sensitisation by skin contact)
R50 (Very toxic to aquatic organisms).

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Factsheet on 2-n-octyl-4-isothiazolin-3-one (Kathon 893)

Name

2-n-octyl-4-isothazolin-3-one. Synonyms include Kathon 893, Skane M-8, RH 893, OIT and octhilinone.

CAS number

26530-20-1

Uses

Kathon 893 is one of many compounds captured under the Kathon tradename. It is reportedly used as a biocide in fibres, rubbers and polymer films (Horn *et al.* 2003). Its presence has also been reported as a formaldehyde substitute in wallpaper adhesives and as an additive in some household paints sold in Japan (Nakashima *et al.* 2000).

Toxicity

Although there are relatively few studies available for this compound, those which are available confirm that Kathon 893 can cause contact dermatitis and sensitisation in some individuals. Oleaga *et al.* (1992) reported two cases of contact dermatitis following exposure to this biocide, one in a worker exposed occupationally in a rubber factory and another in a woman exposed to the chemical as a result of its use as a preservative in shoe leather. More recently, Young *et al.* (2004) reported dermatitis in a student exposed to the chemical in a laboratory setting, with strong evidence for greatly increased sensitivity over time following repeated exposure to the vapours.

As part of a broader path test study of allergic responses to isothiazolinone derivatives, Geier and Schnuch (1996) reported 0.6% positive reactions from a total of 928 individuals. Alexander (2002) provides a recent review of other such studies, yielding similar results.

Other than allergic and sensitising reactions, very little information concerning the toxicity of Kathon 893 could be found in the open literature. In the only available study concerning environmental toxicity, Sasikumar *et al.* (1995) reported acute toxicity of solutions of Kathon 893 to both brine shrimp (*Artemia salina*) and barnacle nauplii (*Balanus amphitrite amphitrite*). The barnacle nauplii appeared to be particularly sensitive to this compound, yielding a 24 hour LC50 of only 2 ug/l (2 ppb).

Environmental fate

Little is known about the environmental fate of Kathon 893. In standard test chamber studies, Horn *et al.* (2003) reported its loss to the atmosphere from commercially available polymer foils, commonly used as membranes under roof tiles, which contain the chemical as a biocide. Clearly, therefore, it can be lost from products in which it is incorporated.

Relation to PBT and CMR criteria under REACH

No NOEC values could be identified from the limited literature available. However, given the reported LC50 of only 2 ug/l (2 ppb) for mortality of barnacle nauplii (Sasikumar *et al.* 1995), it seems likely that the NOEC for aquatic toxicity will fall below the long-term NOEC limit established under Annex XII of REACH (10 ug/l, 10 ppb). It seems reasonable to expect that Kathon 893 would qualify as “toxic” for the purposes of REACH.

Insufficient data were available to evaluate the persistence and bioaccumulative potential for Kathon 893.

Kathon 893 is not identified as a CMR substance under Community legislation.

Risk Phrases applicable under Directive 67/548:

R22 (Harmful if swallowed)
R41(Risk of serious damage to eyes)
R24 (Toxic in contact with skin)
R34 (Causes burns)
R43 (May cause sensitisation by skin contact)
R50/53 (Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment).

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Factsheet on 3-Iodo-2-propynylbutylcarbamate (IPBC)

Name

3-iodo-2-propynyl-butylcarbamate or IPBC. Synonyms include iodopropynyl butylcarbamate, Permatox IBP and Troysan. Polyphase P-100 is an antisapstain wood preservative that contains 97% IBPC. A cosmetics preservative called Glycasil ™ contains 10% IPBC and 90% sodium bicarbonate.

CAS number

55406-53-6

Uses

IPBC is a highly efficient bactericide, fungicide and acaricide (kills mites). It is used as a preservative for wood and paints (Bryld *et al.* 1997). For example, in the forest products industry it is used in an antisapstain product to prevent the growth of moulds and fungi that stain milled lumber (Farrell *et al.* 1998). An estimated 36 tonnes of IPBC was used for this purpose in British Columbia alone in 1996 (Juergensen *et al.* 2000). As of 1995, industry sources suggested that IPBC was globally the most commonly used industrial antifungal agent (Nakashima *et al.* 2000).

IPBC is also marketed for use in building materials and household products. In addition, it is used as a preservative in cosmetics and has been reported to be used in shampoos, lotions, powders, make-up creams and baby products (Bryld *et al.* 1997, Nakashima *et al.* 2000, Jensen *et al.* 2003).

In wood preservatives and in paints, the concentration of IPBC varies from 0.02 to 2.0%. In 1997, the cosmetics directive of the EU permitted the use of IPBC in cosmetic products to a maximum concentration of 0.1% (Bryld *et al.* 1997).

Toxicity

IPBC is known to be an irritant and is a suspected contact allergen. Exposure *via* dusts and aerosols appears to be particularly irritating, causing laboured breathing and long-term lung damage in rats (Lanigan 1998). Irritation is a common reaction in animals, though skin sensitization/allergic reactions occur less frequently.

Bryld *et al.* (1997) conducted a study in which 311 patients presenting with contact dermatitis were patch tested for IPBC to evaluate the sensitizing potential of this chemical. Of three positive results, one individual was subsequently confirmed to have an allergic reaction to IPBC. This sensitization was thought to have resulted from exposure to high concentrations of IPBC in the workplace, a paint factory. The authors recommended that further investigation of the skin irritancy and contact allergy potential of IPBC be carried out.

More recently, Jensen *et al.* (2003) have reported another case of contact dermatitis in an paint factory worker exposed to airborne vapours of IPBC. In a study of 23 workers in the Dutch metalworking industry, 5 individuals showed positive reactions to IPBC (Majoie and van Ginkel 2000).

In a large study involving more than 4800 patients, Schnuch *et al.* (2002) reported 0.3% showed allergic reactions to a relatively low dose of IPBC within 3 days of application to the skin. A

higher number showed equivocal allergic or simple irritant responses, with effects only appearing in some individuals as much as 3 days after testing.

It has been recommended at EU level that products containing more than 0.01% IPBC should be labelled "irritant" unless otherwise demonstrated (Bryld *et al.* 1997). An exception exists for cosmetics where a concentration of up to 10 times greater, that is 0.1% in a product, is permitted by the EU. However, Jensen *et al.* (2003) stress that, whereas IPBC is currently considered to be one of the safer preservatives licensed for use in cosmetics, previous experience with other chemical additives indicates that population sensitivity can increase substantially over time as use becomes more widespread. Indeed, a case of facial dermatitis resulting from use of a face cream containing IPBC has recently been reported (Pazzaglia and Tosti 1999).

There is currently no evidence that IPBC is genotoxic, carcinogenic or toxic to reproduction, although studies are limited and some effects on the stomach and salivary gland in rats have been reported following chronic exposure (Lanigan 1998).

In terms of environmental effects, IPBC appears to display high toxicity to aquatic organisms even at relatively low (ug/l or ppb) doses. Farrell *et al.* (1998) conducted a study on the aquatic toxicity of Polyphase P-100, an antisaptain product containing 97% IPBC which is heavily used in the timber industry in the US and Canada. The study showed that certain fish and invertebrates were killed at concentrations below the regulatory limit set for this chemical in storm water runoff from lumber mill sites in British Colombia (120 ppb). Moreover, concentrations of IPBC substantially higher than the regulatory limit (up to 370 ppb) were detected in some storm water runoff samples from saw mills in British Colombia.

Very recent research has indicated that IPBC, among other similar agents, can interfere with olfactory (chemical) reception in the Pacific coho salmon (*Oncorhynchus kisutch*) at extremely low concentrations (Jarrard *et al.* 2004). EC50 for reduction in olfactory sensitivity in exposed fish was only 0.47 ug/l (ppb) and recovery after removal of exposure was slow. These effects, which occur at concentrations more than a hundred times lower than doses causing lethal effects (95 ppb for coho smolts, Farrell *et al.* 1998), nevertheless could be of enormous significance given the importance of olfactory reception to the lifecycle of salmon. IPBC exposure also led to significant increases in acetylcholine esterase (AchE) activity in the salmon brain.

Environmental fate

Other than the studies noted above, relatively little is known about the environmental fate and effects of IPBC. Horn *et al.* (2003) reported its loss to the atmosphere from wood and masonry products treated with commercially available IPBC formulations, indicating that it can be lost to the surrounding environment from products in which it is incorporated.

Juergensen *et al.* (2000) predict that, given its moderate water solubility, IPBC is unlikely to accumulate to high levels in sediments or suspended solids, although there appears to be no direct evidence for this. These authors also note that IPBC is not expected to bioaccumulate and that rapid hydrolysis is expected to occur in surfaces waters, though again no studies could be identified to confirm this.

Relation to PBT and CMR criteria under REACH

Adverse effects on fish (fathead minnows) and invertebrates (*Daphnia magna*) are reported to occur down to the 20-70 ug/l (ppb) range (Juergensen *et al.* 2000) but it is difficult to compare these results against criteria established under Annex XII of REACH. This is also the case for reports of 96 hour LC50 for coho salmon smolts of 95 ppb as the NOEC is merely reported as <70 ppb (Farrell *et al.* 1998). However, a 48 hour NOEC of <10ppb is given by Farrell *et al.* (1998) for *Dapnia magna*, which does suggest that IPBC would qualify as "toxic" under the criteria set out in Annex XII of REACH.

No appropriate data were located for comparison against criteria for persistence or bioaccumulative potential established under Annex XII of REACH.

Risk Phrases applicable under Directive 67/548

IPBC does not appear to be listed under this Directive

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