Triclosan and Antibiotics resistance

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GreenFacts

Level 2 - Details on Triclosan and Antibiotics resistance

The answers to these questions are a faithful summary of the scientific opinion
produced in 2010 by Scientific Committee on Consumer Safety (SCCS):
"Opinion on triclosan (antimicrobial resistance)"

The full publication is available at: https://copublications.greenfacts.org/en/triclosan/
and at: http://ec.europa.eu/health/opinions/en/triclosan/

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1. What is the biocide triclosan?

1.1 What are biocides?

Biocides are products that kill, inactivate or control the growth of harmful microorganisms, including bacteria, fungi, protozoa and viruses. Biocides are used as disinfectants, preservatives and antiseptics.

One of the most widely used biocides is triclosan, which has many applications in consumer products, including cosmetics. Triclosan is effective against a wide range of microorganisms but it does not kill bacterial spores and there are types of bacteria that are unaffected by it.

1.2 What is triclosan?

Triclosan is a very well known biocide which has been in use for over 40 years. The main application of triclosan in the EU is in cosmetics, where the maximum allowed concentration is currently 0.3%.

Commercial products contain triclosan mixed with several other ingredients but the exact formulation is often unknown because companies do not want others to copy them. The effectiveness of triclosan depends on the formulation of the product itself and on the conditions in which it is used. Perhaps the most important factor is the amount of triclosan present in the product. At high concentrations, triclosan kills its target quickly, although it is not equally effective on all microorganisms. The efficacy of triclosan decreases rapidly with dilution but nevertheless, even at lower concentrations triclosan is still successful at controlling the growth of microorganisms.

2. What are the main uses of triclosan?

Triclosan is effective against many different bacteria as well as some fungi and protozoa it is widely used as an antiseptic, preservative and disinfectant in healthcare and in many consumer products including cosmetics, household cleaning products, plastic materials, toys and paints. It is also included in surface of medical devices, plastic materials, textiles and kitchen utensils where it acts as a bactericide for extended periods of time.

Triclosan is used in detergents and soaps
Credit: Sanja Gjenero

In the EU, about 450 tons of triclosan were used in 2006. About 85% of the total volume of triclosan was used in personal care products, compared to 5% for textiles and 10% for plastics and food contact materials. Since then, triclosan has been banned from use in food-contact materials.

2.1 How is triclosan used in cosmetics?

Triclosan is incorporated in cosmetics mainly as a preservative, to stop bacteria from growing on the product and spoiling it. It is also used as a biocide in many other personal care products such as deodorants, soaps and shower gels. Another biocidal application of triclosan is in toothpastes and other dental products to control plaque and improve the health of the gums.

A limit of 0.3% concentration of triclosan in toothpastes, hand soaps, body soaps/shower gels and deodorant sticks is considered safe, but people who use many different cosmetics containing triclosan, could end up being exposed to excessive and unsafe amounts. Using triclosan in products that are intended to be left on the consumer and not rinsed off such as body lotions or mouthwashes is not safe.

2.2 How is triclosan used in health care and medical devices?

Triclosan is very effective at killing microorganisms so it is widely used in healthcare. For instance, many of the handwashes in hospitals and the detergents that medical personnel use to scrub up before surgery, contain triclosan. Patients who have MRSA (Methicillin-resistant *Staphylococcus aureus)* are also washed with triclosan-containing products before an operation.

Triclosan is used in a number of medical devices. For example, it is coated on the surface of catheters and surgical sutures from where it is slowly released over a period of time. The effectiveness of triclosan in surgical sutures is unclear but it is well known that triclosan stops urinary catheters being invaded and blocked by bacteria and so prevent urinary tract infections.

2.3 How is triclosan used in other consumer products?

Triclosan is used in a wide range of products intended for home use such as liquid soaps, detergents, chopping boards, children’s toys, carpets.

Triclosan and other biocides are increasingly added to clothing articles. The fabrics are treated with chemicals that trap the biocide inside so that they have antibacterial properties over a long period of time.

The benefits of using anti-microbial soap are still unclear, some studies suggest that soaps containing less than 1% triclosan (where the EU limit is 0.3%) seem to provide no benefit over soaps containing none, while some have seen a reduction in the amount of bacteria on the hands even at 0.46% Triclosan. It is also unclear if the antibacterial action of the soap has any positive health effect by preventing disease.

2.4 Is triclosan used in food production?

Triclosan has been added to the surface of cutting boards, food storage containers and other kitchen utensils to stop microorganisms growing on them. However, since March 2010, triclosan cannot be used in the EU in food contact materials or as an additive in plastics that come into contact with food.

Triclosan is not used as a disinfectant in food and feed production and it is not approved as a food preservative in Europe. Triclosan is used in biocidal products for veterinary hygiene but it is banned as a preservative in animal food.

Triclosan has been identified as a contaminant in drinking water in some parts of the world.

3. What happens to triclosan in the environment?

3.1 How does triclosan reach the environment?

Because of it widespread use triclosan finds its way to waste water treatment plants. Depending on the technical capabilities of the plant, between 58% and 99% of the triclosan is removed before the treated water is released, but the rest will end up in surface waters.

When triclosan is removed it is partly broken down, but approximately half of the incoming mass of triclosan remains in the sewage sludge. Some of this triclosan will eventually end up in the soil, because the triclosan-laden biosolids are often spread over agricultural as fertilizer.

Triclosan has been widely detected in the water coming in and out of waste water treatment plants, in lakes, rivers and sea water in various countries in Europe, in the USA, in Canada, in Australia, in Japan and in Hong Kong.

3.2 To what extent does triclosan break down or persist in the environment?

Triclosan is chemically very stable but it brakes down rapidly in the environment when exposed to light and is also degraded by ozone. Some of the break-down products are more toxic than triclosan itself, but bacteria also attack and break these up further.

Triclosan does not react with water over a reasonably large pH range and it is stable in the presence of strong acids and bases. However, triclosan dissolved in water and exposed to light, degrades and forms radicals. Triclosan also degrades in chlorinated water.

When triclosan is dissolved in water in the presence of oxygen, it is easily broken down by several bacteria although very little is known on how this biodegradation takes place. In the absence of oxygen and light, triclosan is quite stable.

Because triclosan is not very soluble in water, it attaches itself to solid particles so it tends to accumulate in sediments. The presence of triclosan reduces significantly the ability of bacteria to deal with the solid sludge in wastewater treatment plants.

3.3 Are microbial populations in the environment affected by triclosan?

High levels of triclosan have been measured in some sediments, biosolids and activated sludge in wastewater treatment plants. In general, these levels would not be high enough to kill microorganisms but they would be sufficient to control their growth.

Triclosan does not seem to affect the activity of enzymes in the soil or respiration, but it can disturb the nitrogen cycle in some soils.

Bacteria often join in very large numbers to form colonies called biofilms and these are widespread throughout the environment. When such a biofilm from a domestic kitchen sink was exposed repeatedly to sub-lethal doses of triclosan, only a few types of bacteria were left but these did not show any increased resistance to antimicrobials. This lack of effect could be due to the particular types of bacteria in that specific biofilm and it is possible that other bacterial species could respond differently. Alternatively, the coordinated effort of all the bacteria in the biofilm could have been sufficient to degrade the triclosan.

Complex mixtures of bacteria are found in many environments, for instance inside the human mouth. In general, exposing these to repeated doses of triclosan does not seem to make them resistant but the results vary with the species considered. For instance, E. coli does become considerably less sensitive to triclosan when treated with it.

4. When are bacteria said to be “resistant”?

Although antimicrobial products are used in concentrations that are usually sufficient to inhibit or kill the targeted bacteria, some strains of bacteria are able to survive and even grow at these concentrations; they are said to be “resistant”.

Bacteria are considered resistant to antibiotics or biocides in any of the following situations:

- when a strain is not killed or inhibited by the antimicrobial concentration typically used in practice,
- when a strain is not killed or inhibited by a concentration at which the majority of strains of that micro-organism are affected
- when bacterial cells are not killed or inhibited by a concentration acting upon the majority of cells in that culture.

In some cases, resistance mechanisms against biocides can contribute to resistance to antibiotics.

Bacteria are called “**insusceptible**” when they have natural (innate) properties, such as a specific envelope structure, that impairs biocide penetration. Bacteria develop “ **tolerance** ” if they become less affected by a biocide concentration that is active on susceptible strains, so that higher concentrations of the biocide are needed to stop them multiplying.

Bacteria can transfer diverse bits of genetic material (plasmids, transposons, etc.) to other bacteria containing several associated genes. When genetic information coding for different antimicrobial resistance mechanisms is transferred to a new host it is referred to as “**co-resistance**”.

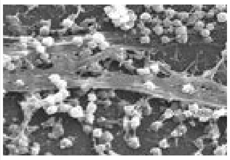
“**Cross-resistant**” bacteria are those that have developed survival methods that are effective against different types of antimicrobial molecules having the same mechanism(s) of action.

The term **Multi-Drug Resistance** (MDR) is used when a bacterial strain is resistant to several different antimicrobial classes.

5. Can bacteria become resistant to Triclosan?

5.1 What are the mechanisms of resistance to triclosan?

The effects of triclosan depend largely on the concentration used.


Bacteria that grow as a biofilm are able to survive hostile conditions.Credit: Janice Carr

At high concentrations, triclosan works by interfering with the outer membrane that protects bacteria, making it permeable so that triclosan can penetrate it and kill the microorganism. At lower concentrations, triclosan attacks several targets. For instance, it slows down drastically several important biochemical reactions inside the bacteria.

Some bacteria have an innate resistance to triclosan, possibly because their outer membrane does not let it through. Bacteria can also become resistant to biocides using a variety of methods that lower the concentration of biocide inside the bacteria. For instance, some bacteria have mutated so that triclosan does not disrupt their vital biochemical reactions, or they have found ways of bypassing the steps in these reactions that are affected by triclosan. Other bacteria have developed systems that "pump out" any substances that are harmful to them, such as triclosan. In principle, some of these defence mechanisms can be passed not only from one generation of bacteria to the next, but also from one bacterium to another.

Different mechanisms may also work in conjunction and together, have a greater effect than each one has separately. For instance, some highly resistant bacteria have both: a modified outer membrane that does not let triclosan through easily, and ways of expelling any of the biocide that manages to get inside the cell.

Biofilms require a special mention. Bacteria are rarely found as single individuals. Instead, huge numbers join together and attach themselves to surfaces forming a biofilm. These bacterial biofilms have a wide repertoire of defence mechanisms and are much more resistant to antimicrobials than are isolated bacteria. There is very little research in this field but there is some evidence that biocides could be ineffective against biofilms made of resistant bacteria. On a positive note, using triclosan followed by an antibiotic could be effective against bacterial biofilms. This would be extremely beneficial given the serious problems that biofilms pose in hospitals and other medical centres.

5.2 Could exposure to triclosan lead to cross-resistance to antibiotics?

When bacteria are exposed to triclosan, some strains become resistant to it by mutating or by activating resistance genes. Some of these genes are also involved in cross-resistance and multi-resistance to different types of antibiotics and biocides so there is a concern that exposing bacteria to low concentrations of triclosan could lead to the emergence of highly resistant bacteria that would be very difficult or virtually impossible to eradicate. However, a study from 2004 found that treating bacteria with low concentrations of triclosan does not generally lead to drug-resistance, and any resistance cannot be transferred from one bacterial species to another.

Several laboratory studies have found that bacteria which are resistant to a biocide are also resistant to other types of antimicrobials. However, to date there is no evidence of a similar link in real situations outside the laboratory. The results vary with the concentration of biocide used and also with the species of microorganism investigated. Some bacteria that are treated with relatively low concentrations of triclosan become less susceptible to antibiotics. However, other types of bacteria are unaffected and, in the case of E. coli, triclosan-resistant bacteria were more easily treated with an antibiotic than the original or unexposed strain.

5.3 Has bacterial resistance to triclosan been observed in the environment?

Triclosan is the most studied of all biocides but most of the research has been done on laboratory samples and at concentrations too low to be of relevance to real working situations. Despite these caveats, we can draw some useful conclusions.

A study from 2006 on bacteria collected from human saliva and a second one from 2004 on bacteria found in teeth concluded that repeated exposures to triclosan did not systematically produce high level triclosan resistance in all bacteria. A relatively small number of strains did become harder to treat to triclosan but many others didn't. What is more, the increased resistance was limited to triclosan so even triclosan-resistant strains could still be killed by other biocides and by antibiotics.

A study from 2003 tested samples of bacteria collected in consumers' homes and found that households that used antibacterial products had fewer harmful bacteria than those who didn't. In both cases, the researchers did not find any evidence of cross resistance, and strains of bacteria that were resistant to antibiotics were still susceptible to antibacterial products. Users of antibacterial handwash did not harbour any more resistant strains of bacteria in their hands compared to non-users.

Triclosan is sometimes added to toothpaste to control plaque and improve the health of gums. These products are generally effective and there is no evidence that using triclosan-containing toothpaste leads to increased resistance or to cross-resistance.

With respect to microorganisms in the environment, whether or not a strain of bacteria becomes resistant to triclosan depends largely on the concentration of the substance that reaches it and this is by no means simple to measure. Triclosan attaches itself to solid particles and may bioaccumulate, posing a concern for aquatic organisms; but on the other hand, is degraded by ozone, chlorine, sunlight and by micro-organisms. Some of the concentrations of triclosan measured in the wastewater, sediments and sludge from wastewater treatment plants are high enough to affect microorganisms but we do not know how much of this triclosan is actually taken up by bacteria. In addition to triclosan, there are other biocides and antibiotics present in the environment and it is difficult to assess the effect of triclosan alone, or to understand how these different antimicrobials work when combined.

5.4 How can bacterial resistance be determined?

In most cases, resistance has been determined by measuring the minimum concentration of biocide that will stop bacterial growth (MIC). Whether or not a strain of bacteria is found to be resistant by this measure is largely irrelevant because the concentrations of triclosan used in practice are considerable larger than these MIC values, and are sufficient to kill all the bacteria treated, including those deemed to be resistant. For practical purposes, a better indicator of resistance is the minimum concentration that will kill the bacteria treated (MBC), which is closer to the real, in-use values.

Commercial products usually contain many ingredients in addition to triclosan, but laboratory studies usually dissolve triclosan in a single solvent. Therefore, it is difficult to make general conclusions since the effects of the biocide depend on the specific product involved and little is known about how different chemicals might act when combined.

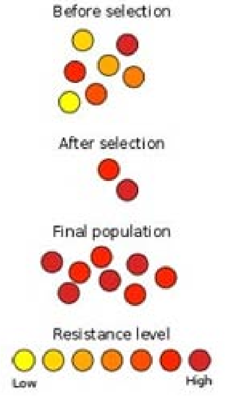
There are studies which expose bacteria to low concentrations of a biocide and measure how bacterial growth changes with time. This is useful to determine changes in the characteristics of the bacteria that survive the biocide, but it does not tell whether or not bacteria will become resistant to the biocide and cross-resistant to unrelated compounds.

The methods used to determine antibiotic resistance are many and varied and this has lead to contradicting results. There are no standardised protocols that measure whether or not a biocide can lead to antibiotic-resistant bacteria, either because the bacteria become resistant or because the non-resistant bacteria are wiped out so that only the resistant or insusceptible strains survive.

It would be useful to develop tools to define the minimum concentration of a biocide that will select or trigger the emergence of a mechanism that will make bacteria antibiotic resistant. It would also be useful to link the specific genetic profile of bacteria with the resistance mechanism that they are likely to develop. Using modern genetic methods it may even be possible to develop routine tests that would identify bacteria with resistance mechanisms.

6. Conclusions of the SCCS

6.1 Does triclosan pose a risk, and what are the current gaps in knowledge?



Resistant bacteria can survive biocide concentrations that would kill others.

The Scientific Committee on Consumer Safety (SCCS) concludes that at present there are important scientific and technical gaps in knowledge.

Scientific gaps:

1. Environmental studies to measure any resistance and cross-resistance to antibiotics following the use of triclosan.
2. There are some studies that measure whether exposure to relatively low concentrations of triclosan leads to antibiotic resistance. This research should be extended to a much wider range of bacteria.
3. There is evidence from laboratory samples that triclosan could have a role in antibiotic resistance. To determine whether or not these results have any relevance for public health, full epidemiological studies are needed.
4. Bacteria have the capacity to transfer genetic information from one another, and this can in theory lead to the propagation of resistance or virulence. It is not known at present if this process is affected by the presence of Triclosan.

Technical gaps:

1. We need to have standard methods of measuring resistance and cross-resistance.
2. To assess the amount of triclosan that bacteria are exposed to, we need information on the amount of triclosan that is manufactured and used.
3. Triclosan is widespread in the environment but we need to know the actual values much more accurately. To determine whether or not resistance will develop in the environment, we also need to know in more detail which microorganisms come into contact with triclosan, how much of it they take up and whether or not their genetic make up is such that resistance genes could be activated and perhaps transferred to other bacteria.
4. We need methods of measuring the minimum concentration of triclosan that can lead to antibiotic or biocide resistance.
5. Laboratories need to use biofilms rather than single bacterial cells, to assess the efficacy of biocides and there need to be European standards of such tests for healthcare applications.

There are several reasons why the use and release of triclosan into the environment could pose a risk:

- From a genetic point of view, exposing bacteria for short periods of time to concentrations of triclosan that are not high enough to kill them, makes bacteria secrete substances involved in resistance or activates resistance genes in bacteria. Some of these genes are also involved in resistance to different drug families, can move from one bacterium to another and, in principle could be activated in bacteria already present in soils.

- Triclosan, like any other biocide, contributes to the selection of less susceptible bacteria, because it eliminates competition since it wipes out those bacteria that are more susceptible to it. However, the impact of such a selection is unclear.
- Biofilms are widespread in the environment and show increased resistance. They have a tough exterior, a wide range of defence mechanisms and the potential to exchange resistance genes between different species of bacteria that live together as part of a colony.

Triclosan is the most studied biocide with respect to bacterial resistance. However, there is still not enough information to do a full risk analysis. In particular, we need to know the amount of triclosan that bacteria are exposed to in the environment, and how much of this they actually take up. We cannot tell either how much each different type of product contributes to the pool of triclosan found in the environment. Other chemicals that can also affect microorganisms are found together with triclosan so it is difficult to tease out the effects of each biocide separately.

There are no epidemiological data linking exposure to triclosan in cosmetics or other products, and outbreaks of resistant bacteria that are harmful for humans or animals.

When used appropriately, biocides, including triclosan, have an important role to play in disinfection, antisepsis and preservation. Information on the expression/triggering of bacterial resistance mechanisms should be considered to (re-)assess the uses of triclosan in order to preserve its efficacy.

6.2 Is it still safe to use triclosan as a preservative in cosmetic products?

To date, there is no evidence that using triclosan leads to an increase in antibiotic resistance. However it is too early to say that triclosan exposure never leads to microbial resistance.

One cannot ignore the hazards identified in laboratory studies so it is important that industry continues investing in research to understand better the role of triclosan on bacterial resistance. The research available was state-of-the-art at the time it was done but modern tools are much more powerful than these so there should be additional studies, particularly on bacteria taken from hospitals or the environment, rather than on isolated samples grown in the laboratory.

Partner for this publication