The natural versus chemical products debate is becoming polarized in favour of natural and organic at any cost for many in the West, but this leads to an unnecessary blight on the word ‘chemical.’ What is natural may not be safe and what is chemical may well be derived from a natural product and no risk at all.

We know that we are directly affected by what we eat, drink and breathe, but what we put on our skin has, until recently, been seen to affect us in the same way. (If we did take this seriously, perhaps we would give up eating chocolate from countries where women are plagued with skin disease from handling pesticide-covered cocoa beans.)

We find out whether the hype around parabens is justifiable, with the help of scientist, Cuross Bakhtiar, director of Harley Street Cosmetics...

**Parabens**, which are commonly found in skin creams and other beauty products, glues and some foods, have been around since the 1930s. They’re currently the most widely-used preservatives in cosmetic, pharmaceutical and industrial products, but recent news reports linking parabens to breast cancer in women and lab studies that have shown the hormonal effects of the chemical, has lead the Cosmetic Ingredient Review Expert Panel to reevaluate they’re safety.

**WHAT ARE PARABENS?**

“Methyl and ethyl parabens are the most frequently used parabens and, with the exception of water, the most commonly used ingredients in cosmetic preparations,” says Bakhtiar. Parabens are popular because they are inexpensive, colourless, odourless, non-toxic, with a wide spectrum of antimicrobial activity – they’ve been used as preservatives for over 80 years.

In 1995, the US Environmental Protection Agency granted GRAS (Generally Recognised As Safe) status to parabens and current European Union cosmetic regulations permit a total concentration of 0.8% for methyl-, ethyl-, propyl- and butylparaben in cosmetic products – that’s just enough to stop your anti-wrinkle cream going off.

The Japanese and Australian medical health boards, which are the hardest to please, have also accepted parabens as. But could the Cosmetic Ingredient Review Expert Panel review could change all that?

**EXPOSING THE MYTH**

“In the USA, the average total paraben exposure per person is estimated to be approximately 76mg per day (1.3mg/kg/d for a person weighing 70kg),” says Bakhtiar. “Cosmetics and personal products provide the bulk of exposure at 50mg per day, whereas drugs (medicines) supply 25mg per day and food accounts for approximately 1mg per day. The concentration of parabens in foods is usually less than 1%.

“In the past, concentrations of parabens in topical over-the-counter products were as high as 5% in the US. Currently, however, the concentrations of parabens in cosmetics are generally less than 0.3%, but may range up to a total concentration of 1%,” he continues. “Each paraben ester has a different solubility and spectrum of antimicrobial activity. As the alkyl chain length increases, water solubility decreases and oil solubility increases. The greater the paraben’s lipid solubility, the greater the penetration through the skin – so penetration increases with ester chain length.

“The potential for absorption of parabens through the skin is influenced by this relative distribution of the oil/water phases of formulation and this is further altered by the addition of various surfactants. In oil-based formulations, methylparaben therefore requires a higher concentration to maintain effectiveness, which is why we might take in more through cosmetics than other products. But although parabens are frequently found in cosmetics, they are considered relatively weak sensitisers in these formulations.”

What is now more controversial is scientific evidence that has shown that parabens accumulate in the body and that their effects can build up over time. Given they were present in larger quantities in the past, most of us may well have them in our body.

**ALLERGIC REACTIONS**

Parabens are, for the most part, non-irritating and non-sensitising. They can, however, cause skin irritation and contact dermatitis in the allergy-prone amongst us – a small percentage of the general population.

“Of course, as the cocktail of environmental hazards increases, it may well be that the number of sensitised...
individuals increase,” says Bakhtiar. “But even paraben-sensitive individuals are mostly able to tolerate paraben-containing cosmetics when applied to normal intact skin. They are also for the most part non-irritating from patch-test studies done using human skin, whereas the same cannot be said for other preservatives.

"Parabens also have a broad spectrum of activity against yeasts, moulds, and bacteria," says Bakhtiar. “Their antimicrobial activity increases with alkyl chain length so they are often combined and enhanced to do so."

THE CANCER CONNECTION
"Trials have shown that butylparaben, but not other parabens, have weak estrogenic activity, acting as xenoestrogens," says Bakhtiar. “Butylparaben is around 100,000 times weaker than estradiol, but at a dose level 25,000 times higher than is used to preserve products.” Since estrogens are known to drive the growth of tumors, this study has elicited some concern about the use of butylparaben and, to a lesser extent, other parabens in cosmetics and antiperspirants. But there is no evidence that any cosmetics containing parabens pose a health risk, because of the low doses involved and the fact that parabens are still generally thought unlikely to penetrate the tissue or to accumulate, although the jury is still out on this.

“One scientific study reports that parabens were found in samples of breast tumours,” revealed Bakhtiar. “But the validity of theses conclusions drawn by Dr Darbre, who has been researching in this field for twenty years, have been hotly debated. Darbre’s study has primarily fuelled the belief that parabens in underarm deodorants or other cosmetics migrated into the breast tissue and contributed to tumour development. However, no causal link with cancer has ever been proven and so far there is no scientific evidence to support any link with any form of cancer.”

A recent review of the data concluded it was biologically implausible that parabens could increase the risk of any estrogen-mediated disruption, including effects on the male reproductive tract or breast cancer and that the worst-case daily exposure to parabens would present substantially less risk relative to exposure to naturally occurring endocrine active chemicals (EACs) in the diet, such as daidzein. The American Cancer Society has concluded that there is no good scientific evidence to support a claim that use of cosmetics such as antiperspirants increases an individual’s risk of developing breast cancer – a feeling that’s also shared by the UK Medical Control Agency (MHRA) and the European Scientific Committee.

A PARABEN-FREE LIFE
Despite the conflicting evidence, some manufacturers in the UK are shifting away from using parabens in products. “Further studies are necessary in order to determine the safety of parabens, as well as other preservatives, currently used in the marketplace,” says Bakhtiar. “The cosmetic industry believes that most cosmetic ingredients are perfectly safe due to their long-term use and safety record, but cosmetic campaigns that raise awareness about the safety concerns of potentially risky ingredients to avoid can only help us to question this unproven line of thinking. “The development of new preservatives (both man-made and natural) has given the cosmetic scientist and consumer a choice, which is undoubtedly a step in the right direction.” In the meantime, your health is in your hands.

THE LIFESCAPE VERDICT
CRUELTY FREE 0/5
ORGANIC 0/5
FAIR TRADE 0/5
HEALTH HAZARD 1/5
WORRY FACTOR 2/5
PROVEN CANCER RISK 0/5

These days it's not science that drives cosmetic reformulation – customers vote with their feet, with the help of the cosmetic industry and consumer groups. The hype around parabens however, when compared to many other far more questionable chemicals, doesn't seem to be that well warranted. To date there is no scientific proof that exposure causes cancer. There is no proof that ingesting it is less hazardous than smearing it on the body, but given the amount of toothpaste we eat, there is reason to err on the side of caution. Many people will still want to avoid parabens, given they are extensively used on animals for research purposes. Scare stories can often distract from hard facts, but they help us to be cautious. Parabens aren't the worst of the bunch, but if you can find products with more natural ingredients, opt for them instead.

PARABENS EXPLAINED Parabens are the most commonly used preservatives in cosmetic, pharmaceutical and industrial products and foods such as frozen dairy products, processed vegetables and jams. Natural cosmetics are increasingly labelled ‘paraben-free’ to be seen as better for our health. Are cosmetics companies cashing in on our fears, or are they simply more aware of the dangers?

YOUR PARABEN HIT LIST Parabens are esters of para-hydroxybenzoic acid, which is where they get their name. Common parabens include methylparaben (E number E218), ethylparaben (E214), propylparaben (E216) and butylparaben. Less common parabens include isobutylparaben, isopropylparaben, benzyperaben and their sodium salts. Some parabens are naturally occurring and found in plant sources such as methylparaben, from the fruit of the blueberry shrub and acts as an antimicrobial agent.

“THERE IS NO SCIENTIFIC EVIDENCE TO SUPPORT A LINK BETWEEN PARABEN EXPOSURE AND ANY FORM OF CANCER”
During the last decade there has been an increase in consumer awareness with regard to chemicals used in everyday life. To this effect the pressure from consumers, pressure groups, media institutions and governments around the world has increased significantly on the safety of certain groups of raw materials used in personal care and cosmetic formulations. Fragrances, dyes, preservatives, surfactants and even naturally derived materials such as those of the tea tree have come under scrutiny or so-called attack. The evolving technology and techniques now employed in evaluating the toxicity of existing materials means that the safety of many raw materials is being scrutinised, reassessed and in some cases banned from use by regulatory and safety authorities.

This article looks at the importance of preservatives in the cosmetics and personal care industry and also the historical/future trends of preservatives in cosmetic applications and how these are being influenced by various publications and media headlines.

**Definition**
Preservatives are a group of chemicals used to prevent the growth and proliferation of microorganisms in cosmetic and personal care products which would otherwise cause spoilage or contamination of the finished product.

**Background**
The use of preservatives is nothing new to every industry globally and most consumers would be amazed at the level of preservative use in common domestic and industrial materials such as coatings, concrete, cooling water, detergents, food, fuel, glues, leather, paper, textiles, wood, electronics, plastics, tiles, and even NASA Space Suits. In fact, without the use of preservatives in all these materials, proliferation of microorganisms would lead to spoilage and safety concerns.

There are two main reasons for preserving cosmetic and personal care products and the reasons are the same for nearly every industry/application: namely health hazards and product spoilage.

**Health hazards**
Most cosmetic and personal care products present an ideal environment for microorganisms to grow and multiply quite easily. All the vital components such as temperature, nutrients, pH, and water are present in cosmetic products which make contamination highly likely if preservatives were not used.

In most countries around the world, the use of preservatives in cosmetic and personal care formulations is not compulsory. However there is a duty of care and responsibility by the supplier/manufacturer to ensure that consumer products such as cosmetics and other personal care products do not cause harm to the end user if used under normal conditions.

Some microorganisms are pathogenic (harmful to humans) and if allowed to contaminate and proliferate in cosmetics and personal care products might cause severe harm to the end user. Another safety concern with regard to contamination is that the toxins released by these microorganisms can also be harmful to humans. This cannot be underestimated since, in most cases, it is the toxins which actually pose the threat to health. Cosmetics are commonly contaminated by four types of microorganisms: gram negative, gram positive, yeast and fungi.

Organisms such as *Pseudomonas aeruginosa, B. Cepacia, Staphylococcus*...
<table>
<thead>
<tr>
<th>Preservative active</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Paraben Esters.**  | • Low toxicity.  
                     • Used in food and pharmaceuticals.  
                     • Stable and effective over a wide pH range.  
                     • Approved worldwide in personal care in all applications.  
                     • Used to broaden the spectrum of activity of formaldehyde donors.  | • Low water solubility (except sodium esters)  
                     • Slightly weak antibacterial activity.  
                     • Incompatible with some proteins and some non-ionic emulsifiers.  |
| (methyl, ethyl, propyl, isopropyl, butyl, isobutyl).  
Typical use concentrations 0.1%-0.3%. | | |
| **Organic acids.**  | • Used in food and pharmaceuticals.  
                     • Low toxicity.  
                     • Good against fungi. | • Very poor against bacteria.  
                     • Severe dissociation and loss of activity begins at very low pH (above 5.0).  
                     • Incompatible with proteins, cationics, nonionics.  |
| Sorbic acid.  
Benzoic acid.  
Dehydroacetic acid. | | |
| **Bronopol.**  | • Excellent bactericidal activity.  
                     • Excellent in moist cleansing wipes when used in combinations with parabens.  
                     • Not bounded by fabric. | • Poor fungicidal activity.  
                     • Associated with nitrosamine formation.  
                     • Detectable formaldehyde release.  
                     • Not globally approved.  |
| Typical use concentrations 0.01%-0.04%.  
Used in combination with parabens or other anti-fungal agents. | | |
| **DMDM Hydantoin.**  | • Cheap.  
                     • Water soluble.  
                     • Good broad spectrum activity.  
                     • Active between pH 4-10.  
                     • Not bounded by fabric. | • Formaldehyde donor – bad publicity due to formaldehyde being classified as a Class 3 Carcinogen.  
                     • Slightly weaker against fungi.  |
| Typical use concentrations 0.15%-0.4%.  
Used in combination with parabens. | | |
| **Imidazolidinyl Urea.**  | • Water soluble.  
                     • Low oil solubility.  
                     • Good antibacterial activity.  
                     • Active between pH 4-9.  
                     • Non-volatile.  
                     • Easier to handle than formaldehyde.  
                     • Low formaldehyde release (not activity-dependent). | • Poor antifungal activity.  
                     • Formaldehyde donor – bad publicity due to formaldehyde being classified as a Class 3 Carcinogen.  
                     • Relatively expensive.  
                     • Poor heat stability.  |
| Typical use concentrations 0.2%-0.5%.  
Used in combination with parabens or other anti-fungal agents. | | |
| **Iodopropynyl butylcarbamate (IPBC).**  | • Extremely powerful fungicidal activity.  
                     • Compatible with nonionics and proteins.  
                     • Good synergy demonstrated with phenoxyethanol. | • Virtually insoluble in water.  
                     • Very poor bactericidal activity.  
                     • Can cause discoloration.  
                     • Not globally approved.  
                     • Contains iodine labelling requirement for leave on products above 0.2%.  
                     • EU – being considered for a ban on children’s products.  |
| Typical use concentrations 0.01%-0.05%.  
Can be used in combination with good bactericides. | | |
| **Methylchloroisothiazolinone & Methylisothiazolinone.**  | • Broad spectrum activity.  
                     • Active at very low concentrations.  
                     • Compatible with nonionics. | • Skin sensitiser.  
                     • Restrictive concentration limit of 15 ppm.  
                     • Hazardous to handle as supplied.  
                     • Poor stability above pH 8.  
                     • Rarely used in moist cleansing wipes especially in Europe and Asia due to sensitisation concerns.  |
| Typical use concentrations 7.5 ppm – 15 ppm. | | |
| **Phenoxyethanol.**  | • Good activity against Pseudomonas.  
                     • Low toxicity.  
                     • Compatible with nonionics and proteins.  
                     • Used as solvent in blends to boost overall activity of parabens. | • High concentrations required if used alone.  |
| Typical use concentrations 0.4%-1%.  
Used in combination with parabens and other actives. | | |
| **Benzyl alcohol.**  | • Good activity against gram +ve and moulds.  
                     • Low toxicity.  
                     • Compatible with nonionics and proteins.  
                     • Combinations with parabens improves efficacy. | • High concentrations required if used alone.  |
| Typical use concentrations 0.4%-1%.  
Used in combination with parabens and other actives. | | |
| **Methyldibromo glutaronitrile.**  | • Excellent preservative.  
                     • Excellent antibacterial activity.  
                     • Compatible with nonionics and proteins. | • Slightly weak against fungi.  
                     • Discoloration in presence of iron.  
                     • Unstable above pH 8.  
                     • Sensitisation and irritation issues.  
                     • EU – banned for use in leave on.  
                     • EU – possible ban for all products being considered.  |
| Typical use concentrations 0.02%-0.06%.  
Used in combination with phenoxyethanol. | | |
**Incidents of contamination**

The CDC (Centre for Disease Control) has had numerous reported incidences where cosmetic product contamination has been blamed for health hazards. For instance in 1989, a 47 year old woman reportedly scratched her left eye with mascara and this led to progressive pain, redness, light sensitivity and swelling. Three days later she had severely impaired vision and was examined by an ophthalmologic consultant. Sadly, following treatment, her vision on the left eye did not improve and analysis of the mascara showed high contamination by *P. aeruginosa*. In a very limited search I came across nine old cases where mascara had been contaminated with *P. aeruginosa* leading to eye problems.

Another organism commonly found in contaminated cosmetic products is *Staphylococcus aureus*. It is a bacterium frequently found living on the skin and in the nose of healthy individuals. In compromised patients it can cause illnesses ranging from minor skin infections (such as pimples, boils, cellulitis) and abscesses to life threatening diseases such as pneumonia, meningitis and septicaemia. Each year around 500,000 patients in American hospitals contract a staphylcoccal infection. In some cases *S. aureus* has become resistant to commonly used antibiotics.

It can be argued that in nearly 99% of these cases, the contamination is likely to come from poor hygiene and not cosmetic products, but nevertheless no supplier or manufacturer will be confident putting a product into the marketplace that could potentially be contaminated by *S. aureus*.

Although very few incidents like these occur today, care still needs to be taken when formulating to ensure that formulations are adequately preserved.

**Product spoilage**

The second reason for preserving cosmetic products is to avoid product spoilage. When microorganisms proliferate in, for instance, a cream, they break down the emulsion causing thinning, separation, pH changes, malodour, colour change, etc which means that the product not only looks and smells different but also may not function properly when used. Creams usually contaminated with moulds go black/grey on the surface and although some of these moulds are not harmful, they can be off-putting to the customer.

Nearly 50% of all recalls and withdrawals are due to the fact that products have become contaminated by microorganisms. In most cases the offending product is spotted not by testing but by people in factories, shops, warehouses, etc who notice the difference in colour, smell or appearance and subsequent testing highlights contamination. In fact the first thing a quality department does when faced with a consumer/customer complaint is check the number of organisms (if any) present.

From the aforementioned limited cited examples it is clear that contamination of products must be avoided by all cosmetic manufacturers. This has led to preservatives being the second most common ingredient after water to be used in cosmetic products. Cosmetic manufacturers are faced with the dilemma of which preservatives to use to solve this problem because they have to consider safety, efficacy, regulatory, compatibility, and many more factors.

**Methods of microbiological control**

The first point to stress is that preservatives should not be added to cosmetic and personal care products to clean the product and kill off microorganisms already present. Preservatives should be added to prevent or limit the growth of microorganisms which might contaminate the product after manufacture either from air, water or even human contact. There is a common misconception among many manufacturers who use preservatives as a fail safe option due to poor plant hygiene and manufacturing systems. This strategy often fails miserably, resulting in many product recalls and contamination incidents due to the preservative system being overloaded and used up fighting contamination before the product has even left the manufacturing vessel.

Although this article will not focus on plant/manufacturing considerations, it is still worth mentioning that the use of preservatives should be in conjunction with good manufacturing practices (GMP) with a few guidelines below:

- Raw materials need to be screened to ensure contamination is at a minimum.
- Process water used in manufacturing must also be checked regularly and sterilised before use in products.
- Mixing vessels, pipes and other plant equipment such as pumps, valves, etc need to be sterilised and checked regularly to limit contamination.
- Methods of manufacture and techniques used also need to be carefully designed so as to minimise contamination of product.
- Training of staff and audits need to be carried out to ensure all controls, procedures and processes are fully complied with and relevant to what they are designed to achieve.

**TABLE 4: TRENDS IN PRESERVATIVES**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Methylparaben</td>
<td>5,693</td>
<td>7,306</td>
<td>7,731</td>
<td>6,893</td>
<td>7,161</td>
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<td>Propylparaben</td>
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<td>6,030</td>
<td>6,278</td>
<td>5,621</td>
<td>5,809</td>
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<td>483</td>
<td>1,072</td>
<td>1,991</td>
<td>1,274</td>
<td>2,326</td>
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<tr>
<td>Imidazolidinyl Urea</td>
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<td>2,499</td>
<td>2,498</td>
<td>2,025</td>
<td>2,038</td>
</tr>
<tr>
<td>Ethylparaben</td>
<td>31</td>
<td>581</td>
<td>1,240</td>
<td>1,451</td>
<td>1,725</td>
</tr>
<tr>
<td>Phenoxyethanol</td>
<td>17</td>
<td>253</td>
<td>1,143</td>
<td>1,480</td>
<td>1,670</td>
</tr>
<tr>
<td>DMDM Hydantoin</td>
<td>15</td>
<td>318</td>
<td>955</td>
<td>943</td>
<td>993</td>
</tr>
<tr>
<td>Isothiazolinones</td>
<td>0</td>
<td>512</td>
<td>808</td>
<td>595</td>
<td>699</td>
</tr>
<tr>
<td>Diazolidinyl Urea</td>
<td>0</td>
<td>130</td>
<td>690</td>
<td>701</td>
<td>725</td>
</tr>
<tr>
<td>Quaternium- 15</td>
<td>599</td>
<td>673</td>
<td>704</td>
<td>505</td>
<td>516</td>
</tr>
</tbody>
</table>

Source: D. Steinberg, Cosmetic & Toiletries FDA; frequency of use of preservatives in cosmetic formulations in the USA.
one preservative which will be effective against all organisms and all formulations?” While there are preservatives which are effective against most organisms (broad spectrum) and would even work in most formulations, effectiveness and application are not the only criteria to consider.

Formulators, chemists, and marketing, safety and regulatory managers in all companies around the world would probably recognise the list below as it contains some of the criteria preservative suppliers are required to meet when developing an ideal preservative (if such a thing exists).

- Broad spectrum – against all organisms.
- Safe at use concentrations (non-irritant, non-sensitising, non-mutagenic, etc).
- Cost-effective at use concentrations.
- Global approval, particularly EU, USA, South America, Asia/Japan.
- Stable and effective throughout product shelf life.
- Easy to use and handle.
- Effective at target pH of product.
- Raw material and formulation compatibility.
- Readily soluble in water.
- Heat stable.
- What the customer wants?

The variety of requirements per customer per formulation varies so much that it is safe to say that the ideal preservative will never exist because as soon as a preservative is developed, a new important criteria will be stipulated by customers which the preservative will not meet. In the late 19th to early 20th Centuries, formaldehyde was the ideal preservative.
but now in nearly all cosmetic products, in Europe at least, it is not even considered as a preservative option any more.

Having said that, there are some preservatives which have passed the test of time and I will look into these preservatives and consider why they are still being used in formulations today. Preservatives such as parabens, phenoxyethanol and even some formaldehyde donors such as imidazolidinyl urea and DMDMH are still being used extensively in the majority of personal care products.

Even though the above ideal preservative list seems extremely long and never ending, there are still three key criteria which all preservatives must meet before being considered as a preservative option by any customer:

- The first criterion to consider is the regulatory status. This is quite simple since if a preservative is not approved or banned, it cannot be used.
- The second important criterion to meet is safety. The safety of a preservative is directly related to its regulatory status since this is the most important factor government agencies and scientists consider when regulating preservatives.
- Finally, the third important point to meet is broad spectrum effectiveness against all organisms since it is pointless using a preservative that does not work.

Regulatory approval

Once again it must be stressed that if a preservative is not approved or banned, it cannot be used. It must also be noted that preservatives can also be approved but restricted so that they cannot be used in some applications such as baby products, eye, mucus membrane, leave on, etc. Also the concentration will be limited to a maximum level which needs to be considered even if the preservative is approved.

Various regions and countries have different ways of regulating cosmetic products and preservatives. In the EU for instance, The 7th Amendment contains a positive list of preservatives called Annex VI which means that all preservatives added to formulations for the sole purpose of preserving the product must come from that list. It is always advisable to check the regulatory status of a particular preservative for that region/country before making the decision about which preservative to use.

Table 1 shows the number of preservatives approved, and from this it can be seen that the choice of globally approved preservatives is as low as 16, or even less if more Asian countries are considered.
As you can see from Table 2 not all globally approved preservatives are allowed in every application. Parabens and phenoxyethanol have no restriction with regard to all applications.

**Safety**
The regulatory status of a preservative is a good indication of the safety profile of that preservative. In most cases you will notice that in cases where preservative use concentrations have been limited to an extremely low level, say ppm, this means that their safety in use needs to be controlled so that customers do not exceed safety margins. A good example is the use concentration of isothiazolinones compared to parabens or phenoxyethanol. This is because at higher concentrations they will cause sensitisation in some consumers hence they need to be restricted to even lower levels. The same applies to methyl dibromo glutaronitrile and IPBC where they are restricted in some applications and are not even globally approved in many countries. It is directly related to safety profile or lack of safety information.

This does not mean that these preservatives have no place in cosmetic formulations since they can still be used safely in many formulations. However with regard to widespread acceptance, they continue to struggle to gain global acceptance by many customers who would prefer to avoid it altogether.

**Broad spectrum effectiveness**
The effectiveness of a preservative is also very important. Ideally a preservative should be effective against all types of organisms such as gram negative, gram positive, yeast and fungi. If there are gaps in its activity, then other preservatives will have to be added to ensure the formulation/product is adequately preserved. An example of this is the use of parabens and phenoxyethanol in blends because although parabens have good broad spectrum activity, in difficult-to-preserve formulations they are sometimes weak against gram negative bacteria such as *Pseudomonas aeruginosa*. Phenoxyethanol on the other hand is very effective against gram negative bacteria and as such the two preservatives complement each other when blended.

Again the question is: “Why not use a very powerful preservative and blast everything within sight of the product?” This goes back to the safety concern since the use of very powerful highly efficient preservatives also comes at a price of poor safety profile. For instance formaldehyde, isothiazolinones and methyl dibromo glutaronitrile can do the job in most formulations but they are either not approved in all applications or may increase incidence of sensitisation and hence more customer complaints reported on cosmetic products.

Having looked at three of the most important factors, let us now look at the advantages and disadvantages of commonly used preservatives.

From Table 3 it can be seen that all nearly all preservatives have their limitations and no single active can be considered the “ideal preservative”. The only way to move closer to an ideal preservative scenario is to blend various actives with the hope of achieving the desired favourable end characteristics.

Looking at the trend during the last three decades it is clear to see that parabens, phenoxyethanol and imidazolidinyl urea have remained consistently in the top six throughout that period. This is quite surprising considering the number of newly claimed, more powerful preservatives that have been launched by suppliers during the last two decades. The explanation is quite simple – safety and regulatory approval is more important to customers than performance. Most new preservatives such as isothiazolinones, IPBC, and methyl dibromo glutaronitrile have poor toxicological properties compared to parabens and as such have had their use restricted by regulatory authorities around the world.

As a result of this restriction consumers and customers have been very cautious in using these new preservatives in many of their formulations. Nevertheless the author strongly believes these preservatives still have an important role to play within the industry. They are still being used in special cases where they are either cost-effective or where some of their effectiveness/properties make them better to use than parabens, imidazolidinyl urea and phenoxyethanol.

The question on everyone’s lips is: “Will this trend change or will parabens still dominate the preservative market, particularly in light of recent publicity with regards to certain claimed adverse heath effects?” Before attempting to answer that complex question, it is important look at why parabens have been the number one used preservative globally for over 50 years (Table 4 indicates how trends can change).

There are three key reasons why parabens have been the number one preservative during the last 50 years and it is no coincidence that these properties coincide with the three factors mentioned previously. These are:

- They are globally approved in all applications – even sensitive ones such as eye, baby, leave on, mucus membrane, etc.
- They have an excellent safety profile mainly compiled by independent institutions around the world.
- Finally, they have good broad spectrum capabilities against all organisms.

**Discovery of parabens**
Parabens are esters of p-hydroxybenzoic acid where the ester can be methyl, ethyl, propyl butyl, etc. They were discovered in the 1920s mainly due to frustrations at the use of benzoic acid which was ineffective at high pH. Scientists discovered that substituting and forming an ester instead of the acid form meant that the pH effectiveness could be improved up to 8.5. This was the single most important development in the long history of preservatives, and we still use parabens today.

This esterified molecule had the added advantage in that the effectiveness was improved over a wide pH range while the safety profile was still similar to benzoic acid. It is not surprising that parabens soon became accepted globally in not only cosmetic formulations but also food and pharmaceutical applications and up to the present day they are still approved in all cosmetic, food applications and most pharmaceutical applications. The scientists later formed Nipa Laboratories and since then all the parabens are still
manufactured under the Nipa name, now acquired by Clariant.

Safety and toxicology summary
- **Acute oral**: LD$_{50}$ R > 2000 mg/kg for all parabens. LD$_{50}$ R isothiazolinones mixture 64 mg/kg.
- **Subchronic/chronic**: Low order of toxicity.
- **Irritancy**: Mild – negative up to 5-12%.
- **Sensitisation**: Non-sensitising.
- **Mutagenicity**: Non-mutagenic.
- **Carcinogenicity**: Non-carcinogenic.
- **Teratogenicity**: Non-teratogenic.
- **Phototoxicity**: No evidence.

By 1984 the Cosmetic Ingredient Review (CIR 1984) reviewed and approved the safety of parabens citing over 350 safety publications on parabens alone and in 2002 Soni also cited more than 350 publications. As recently as early 2005 parabens were reviewed by the Scientific Committee of Consumer Products with no change in status and still approved in all applications with no further restrictions. This is quite significant since this was requested by authors of papers claiming adverse health effects of parabens.

From Table 5 it can be seen that with regard to sensitising potential, parabens, phenoxyethanol and benzoic acid are amongst the least sensitising preservatives available today. The most common complaints from cosmetic consumers is irritation and sensitisation and this causes a lot of concern for the cosmetic industry which wants to keep products that cause little or no irritation or sensitisation.

Another 10 year study involving 50,000 patients in 10 countries also looked at the sensitisation potential as recently as 2002 (Fig. 1). In fact due to the significant increase in sensitisation reported for methyldibromo glutaronitrile, the material was restricted for rinse off applications with no further restrictions. This is quite significant since this was requested by authors of papers claiming adverse health effects of parabens.

The above two examples demonstrate the good toxicological profile of parabens, which is why it has global approval even today and is still widely used.

Efficacy of parabens:
- **Overall good broad spectrum**.
- **Very good efficacy against yeast and mould** – MIC 0.05% - 0.1%.
- **Effective but slightly weak against gram-ve bacteria**.
- **Often blended with good anti-bacterial preservatives**.
- **Good synergistic/optimum blends with formaldehyde donors**.
- **Combination of parabens show improved efficacy**.

Blends with suitable solvents show improved efficacy.

Better pH stability than organic acids such as benzoic, DHAA, Sorbic acid, etc. (see Fig. 2 and 3).

Figure 2 shows the dissociation of organic acids. This is why parabens were invented in the first place since dissociation of acids occurs at pH as low as 5.1 while parabens are still 85% active up to pH 8.5.

Combinations of parabens

Blending of parabens also improves efficacy and this is one of the advantages of using various blends of parabens to improve efficacy. As shown below some mixtures of parabens reduce efficacy while other mixtures show synergistic performance. This explains why there are so many blends of parabens on the market today.

Are parabens the ideal preservative?

Obviously not, but a look at all the advantages and disadvantages of available preservatives today shows that they are the closest we have within the industry. It is truly amazing that despite new preservatives launched during the last 30 years, parabens remains the first choice of preservative in the present climate.

Ideal preservative or not?

- **Broad Spectrum** – (weak against gram negative).
- **Safe at use concentrations** – non-irritating, non-sensitising, etc
- **Cost-effective**
- **Global approval, particularly EU, USA and Japan**
- **Stable and effective over product shelf life**
- **Easy to use and handle**
- **Effective at target pH of product (pH 4-8.5)**
- **Raw material and formulation compatibility** – (creams, lotions, cleansers, toothpaste, shower gels, lipsticks, baby products, etc.)
- **Readily soluble in water** (low water solubility).
- **Heat Stable**
- **Applications – leave on, rinse off, oral, food, pharmaceutical**

Recent safety concerns on parabens

Unfortunately, the time has come within the chemical industry where any publication in any journal or on the internet may be seized on and used by the media, pressure groups and even governments to further their own profile or interests. Chemicals from everyday life have come under scrutiny due to some of these reports carried out by academic institutions, pressure groups or even individuals. It appears that authors and researchers are looking at areas where they could generate the maximum publicity by highlighting implausible and sometimes exaggerated risks.

In the UK for instance, if you consider the negative publicity surrounding MMR created by a single doctor involving very few patients, and even after 10 years of sound scientific counter arguments with more credibility and involving analysis of data from millions of children around the world, there are still doubts in parents’ minds about using the triple vaccine. Parents have become so concerned that some of them cannot comprehend and balance both sets of risks. On the one hand there is a higher risk of catching diseases which, until the vaccine was found, crippled millions of children in Third World countries and on the other hand the concerns about a report published where it may not even have been statistically significant.

Some parents sadly put their children at greater risk by either not allowing them to be given the vaccine or preferring the single vaccine alternative that has not been proven nor tried and there is no guarantee that after 30 years’ use the effect will not be worse than what they have just switched from which is proven worldwide.

It looks like I am digressing but there are similarities. If parabens are banned or restricted there are no effective options which are safer and in fact customers will move to unsafe and untried options only to find out that they were better off not switching in the first place. The increase in sensitisation with regards to methylidibromo glutaronitrile demonstrates this fact where parabens were replaced by this new preservative in sunscreens only to encounter numerous incidents of sensitisation and irritation as the usage increased.

Many preservatives have been banned by some regulatory authorities or governments where the science does not quite add up. However, it is of great benefit that with regard to parabens safety, all sections of the industry – customers, manufacturers, suppliers, industry associations (such as Collipa, CTFA, CTPA) and even regulatory bodies – and governments have continued to defend the use of parabens in all applications and in some cases reviewing and dismissing misleading articles such as the Darbre paper. (This paper published misleading research linking parabens in underarm cosmetics to breast cancer which does not make any sense when 95% of all underarm applications do not contain preservatives and the author completely missed that important point).

This and other reviews hopefully puts the parabens issue to rest in the
meantime but unfortunately there will still be individuals and institutions who will continue to carry out research claiming adverse effect on not only parabens but all cosmetic raw materials as well.

The future of preservatives

It is looking likely that all preservatives will become scrutinised against today's safety requirements and that new research, however implausible will be considered and decisions made by regulatory bodies around the world.

Seen already has been the effect of key preservatives such as IPBC and methyldibromo glutaronitrile being threatened with extinction, a situation made worse by the fact they are not being defended as vigorously as parabens.

Another review in 2005 by the SCCP stated that parabens are safe for use in all cosmetics and personal care applications and the use concentrations should remain. There is still data required for butyl and isobutyl but these are more likely to have their use concentrations reduced rather than an outright ban.

Here are a few other examples of what is happening within SCCP in Europe:

- IPBC-based formulations – iodine concerns due to effect on thyroid gland.
  - In 2004 SCCNFP opinion concluding limitation on concentration and also ban on children’s products. This is looking likely.
- DBDCB (MDGBN) – sensitisation and irritation issues following clinical trials and safety experiments.
  - Already banned on leave-on products by EU in 2003.
  - In 2005 another SCCNFP opinion concluded that a safe limit could not be established for rinse-off hence possible ban on all products.
- Tea Tree oil – concerns over sensitisation/irritation.
  - In 2005 SCCP opinion recommended not to be used neat.
- Isothiazolinones – concerns over sensitisation already addressed by limiting concentration to 15 ppm but still reluctance for use in leave-on formulations by consumers.
- Formaldehyde donors – concerns over carcinogenicity of free formaldehyde.
  - Not substantiated but SCCC now debating the ban on all Cat 3 CMR substances including formaldehyde. Formaldehyde donors will probably not be affected but free formaldehyde might need tightening.

Summary and conclusion

Despite all the bad press associated with preservatives, they still play a vital role within all cosmetic formulations. Some formulations claim to be self-preserved but even these have those properties because some of the raw materials used have preservation properties in their own right.

The beginning of this article highlighted the pitfalls of micro-contamination of cosmetic products and the risk of contamination needs to be balanced with the overall safety of the product. Although thankfully very few incidents like these occur today, care still needs to be taken when formulating to ensure that formulations are adequately preserved.

There is no doubt that the increased awareness and use of effective preservatives in today’s cosmetic and personal care formulations have led to these incidents being extremely rare and this is a credit to not only the product manufacturers but also to preservative suppliers who have developed safe, effective preservatives for use in all formulations today. Parabens have been leading the way since their discovery in the 1920s in ensuring that cosmetic products are adequately preserved.

Fortunately common sense still prevails and despite all the adverse publicity there is still global acceptance and support from all parts of the industry including governments around the world. It is still widely accepted that in the future parabens will still be the most commonly used group of preservatives globally.

Alternatives developed or being developed do not have the historical in use proven safety in actual formulations/consumer feedback. Just to reiterate this point, new preservative actives such as IPBC and methyldibromo glutaronitrile developed only 10-15 years ago are now being banned or severely restricted as historical in use data is being compiled. Customers have no option but to continue and support parabens with a proven safety record going back to the 1920s. If with all the wealth of safety information and in use historical data compiled since then, parabens are still being questioned, then no cosmetic material let alone preservative is exempt especially when most have only just been developed with little or no historical safety profile.

References

8. SCCP Opinions No. 0874/05 and No. 0873/05 – March 2005 – Toxicological review of parabens following claims associated with breast cancer article by Darbre.
REFERENCES

NATURAL Parabens

1. In a data sheet from Nipa Laboratories received from Malcom Irvine Dec 1994. "Parabens - the natural preservatives".

In the plant world 4-hydroxybenzoic acid and its derivatives are commonly found in various vegetable foods, such as barley, strawberries, blackcurrants, peaches, carrots, onions, cocoa-beans, vanilla; further in foods prepared from fruit plants such as grapes and fruit juices, yeast extract, wine vinegar and also in cheeses. The distribution of the acid in plants, as derivatives of alkaloids, natural colourings etc. was reviewed by Banfield. Tomaszewski investigated 122 plant species and found the acid present in all the plants. Billek concluded that 4-hydroxybenzoic acid is the most widely distributed aromatic organic acid in the vegetable kingdom. Baardseth showed that the Scandinavian cloudberry contained benzoic acid, sorbic acid, salicylic acid, 2-hydroxybenzoic acid, as well as methyl and propyl parabens, which accounted for the superior resistance of cloudberries to microbial spoilage.

The total organic acids were present at a level of 600 ppm.

Recently, Schafers reported an elegant technique (GC/MS) for the detection of methyl and ethyl esters of hydroxybenzoic acid in vegetable and potato peelings.

In the animal kingdom, Schildknecht found Dytiscus marginalis, the yellow beetle, produced in the secretion of its glands a disinfecting mixture of benzoic acid, 4-hydroxybenzoic acid, 4-hydroxybenzaldehyde and methyl paraben, which protected the glands from bacterial infection. Staddon likewise found methyl paraben in the stink gland secretions of the British water bug, Ilyocoris cimicoides.

The presence of 4-hydroxybenzoic acid in urine of healthy, normally fed human beings has been known for many years and is due to the decomposition of the amino acid, tyrosine, and from dietary sources.

Goodwin identified methylparaben in the vaginal secretions of female dogs in oestrus. It was proposed that methylparaben was an essential part of the complex odour profile generated by the secretions of the vaginal glands. It is more likely, as in the water bug and yellow beetle examples, that methylparaben was produced as antimicrobial protection of the microbiologically labile odoriferous components of the secretions.

Research worker suspected a vital role for 4-hydroxybenzoic acid. Davis found it an essential growth factor (bacterial vitamin) for E. coli and as sulphamides were an antagonist to 4-aminobenzoic acid (bacterial vitamin H), so methyl paraben was to its parent acid. Many other workers supported these findings, culminating in Simonart & Wiaux detecting the occurrence of 4-hydroxybenzoic acid in Penicillium griseofulvum which emphasised the fundamental importance of this acid in biochemistry.

It was eventually resolved that 4-hydroxybenzoic acid was the precursor building block for ubiquinones (coenzyme-Q) which is essential for the oxidative phosphorylative process in all respiring organisms. Ubiquinones were found in microbes, in the heart muscle and in the normal
skin. It was concluded that:-

"All respiring vegetable and animal species require 4-hydroxybenzoic acid. Without it there are no ubiquinones and hence no respiration. 4-hydroxybenzoic acid is a natural vital ingredient of aerobic life, it is no foreign substance to them."

Bose reported that 4-hydroxybenzoic acid exhibited marked synergy with auxins, in promoting root growth of chrysanthemums, tomatoes and marigolds. Another interesting report by Kickuth isolated and identified nine aromatic compounds from the rhizomes of bullrushes S. lacustris which had microbiocidal activity (especially against E. coli and Salmonella spp.) and therefore would make these plants important in maintaining water quality and protecting against pollution from disease producing organisms. The nine compounds identified were derivatives of benzaldehyde, 4-hydroxybenzoic acid and cinnamic acid (0.025 wt % of rhizomes). The aromatic acid function had the greatest activity and had bactericidal activity against E. coli at concentrations as low as single ppm levels.

Da & Vialle studied the flavour components of natural vanilla extracts. They showed that, unlike the Bourbon vanilla, the Tahiti vanilla contained methyl paraben as one of the four major flavour components. Harbourne found methyl paraben a constituent of lignin in some gymnosperms and woody dicotyledons.

Aldrich, studying the 7th-8th ventral abdominal gland secretions of adult males of the leaf-footed bugs, Leptoglossus and related species, found a preponderance of aromatic compounds, contrasting sharply with the aliphatic compounds which comprise the metathoracic gland defensive secretions of male and female leaf-footed bugs. It was later found that methyl paraben was a major component of the ventral abdominal gland secretion.

Perkins, investigating the major components of the rectal glandular secretions of male fruit flies found methyl, ethyl and propyl parabens. He found that the glandular extracts of the S.E. Asian fruit fly (Dacus albistirigatus) was rich in methyl paraben. In another Dacus zeugodacus sp. (a large unidentified Malaysian fruit fly) the glandular extract contained 66% ethyl paraben. Dacus cucurbitae, the melon fly, is the major fruit fly pest of melon and other cucurbits. Analysis of the rectal gland secretions showed ethyl paraben as the major component and propyl paraben as a minor one. Hancock, studying African cucurbit pests, found Dacus vertebratus Bezzi to be highly attracted to methyl paraben. This discovery was initially observed when the fly was attracted to a locally manufactured cosmetic product.

Methyl paraben has now joined three other previously identified fruit fly attractants, "Cue-lure" [4-(4-acetoxyphenyl)butan-2-one], "Willison's lure" [4-(4-hydroxyphenyl) buutan-2-one] and methyl eugenol. Methyl paraben has been called "Vert-lure".

The article continues with a discussion of the biodegradability and the 4-hydroxybenzoic acid biocycle.

It was concluded that 4-hydroxybenzoic acid and derivatives have a well reported and proven biocycle and are intrinsic and fundamental to all respiring and anaerobic life.

See the reference list in the data sheet.

Parabens used to preserve medicaments and cosmetics may sensitisise and cause contact dermatitis at the site of application. It has been suspected that persons sensitised to parabens may experience flares of dermatitis from parabens in food and systemic medicaments.

From 1.1.90 to 31.12.94 we performed a placebo-controlled oral challenge with a mixture of 100 mg methyl p-hydroxybenzoate and 100 mg propyl p-hydroxybenzoate in 14 patients with least a+ positive patch test to the paraben mixture in the European Standard Series. 7 of the patients had hand eczema; 1 also had dermatitis of the face and 1 also had axillary eczema. 3 patients had dermatitis of the lower legs, 3 had dermatitis of the face and/or scalp, and 1 had dermatitis of the forearms.

The capsules containing the paraben mixture or a placebo were given an interval of 1 week. This interval was longer if there was a flare of dermatitis after the 1st. capsule. The sequence of capsules was randomised. The oral challenge was carried out when the dermatitis was quiescent. The patients themselves recorded whether or not aggravation occurred following the oral challenge.

2 of the 14 patients had flares of their usual dermatitis after challenge with the paraben mixture but not after the placebo. Both had hand eczema of the recurrent, vesicular type. Both had a severe eruption of vesicles on the sides of the fingers within 24 hours of ingesting the paraben capsule. 1 of the patients also has a flare at a paraben patch test site on the back. 1 patient had doubtful reactions to both the paraben mixture and the placebo, while 11 patients did not have any reaction to the oral challenge.

The 2 patients with specific reactions to the challenge were informed about food and medicaments that may contain parabens. These preservatives are permitted in amounts up to 300 mg/kg of foods such as mayonnaise and ready-to-serve salads containing mayonnaise, water-based ice cream, preserved fish, preserved vegetables, including ketchup and mustard, marmalade, fruit and vegetable juices and cider as well as candy and cakes.

At follow-up visits after the patients had attempted to avoid the above-mentioned food items for a period of 1 to 2 months, neither patient of physician could see that the dermatitis had improved as a result of the diet.

Using the method described in the current study, we have not found oral challenge with parabens to be a useful test procedure in patients sensitive to the paraben mix. Although specific reactions were seen in 2 paraben-sensitive patients with recurrent vesicular hand eczema, the significance of this finding remains uncertain.

The European Cosmetic Toiletry and Perfumery Association COLIPA stated that the Routledge work was 'irrelevant' as 'Parabens are hydrolysed in the skin and we have data to show that none are entering the blood stream', and said that the Industry had no plans to follow up the work.

Further information is attached for a considered opinion.
We are aware of the new research published by Dr Phillippa Darbre and the concern this may cause to consumers\(^1\). The research does not find a causal link between underarm cosmetics containing parabens and breast cancer.

Parabens are preservatives that are used in cosmetics because of their excellent safety profile. They are very rarely used in deodorant and antiperspirant products because these products are, essentially, self-preserving. However, where parabens are used in cosmetic products they are declared in the ingredient listing by the name ‘paraben’.

Dr Darbre reports finding parabens in samples of human breast tumour tissues but she also found quantities of parabens in “blank” samples that did not contain any tissue at all. Thus, the significance of her results is not easy to ascertain. Extensive independent research has previously shown that any traces of parabens that might enter the skin are completely broken down by skin cells to harmless substances that cannot pose any risk of breast cancer.

According to a number of leading cancer research organisations, there is no plausible biological mechanism by which antiperspirants and deodorants could cause breast cancer. Other risk factors, including smoking, drinking and obesity, are well known to have an impact on the rising incidence of breast cancer.

Dr Chris Flower of the CTPA said “Extensive research available to our members continues to indicate that there is no proven link between rising breast cancer rates and the use of antiperspirants or deodorants. Dr Darbre’s research is based on an extremely small sample of 20 breast tumour cases and does not include any reference samples from normal tissues.”

Safety is the number one priority for CTPA members who manufacture antiperspirants and deodorants. Parabens are officially approved for use under the Cosmetics Directive (76/768/EEC), the European legislation that regulates all cosmetics and toiletries. We can reassure the public that all cosmetic and toiletry products containing parabens may continue to be used safely.

Expert comment regarding latest reports on parabens and breast cancer

“The findings of parabens in tumour samples are additional results in line with the general hypothesis that there may be a link between oestrogenic compounds commonly used in underarm cosmetics and other consumer products and breast cancer. The results alone, however, do not suggest that these chemicals caused the tumours in these patients. Darbre et al.’s findings invite several questions: how did the parabens get into the breast, are they persistent and could they do harm? The answers require further research.”

Philip W. Harvey and David J. Everett
General considerations and conclusion from the Editorial of the Journal of Applied Toxicology where the research was published

“We are all exposed to all kinds of chemicals but it doesn’t mean that they all cause cancer. The question is here whether the chemicals would have an impact on the hormones, and also what level you would see in a healthy breast tissue. A causal link has by no means been proved.”

Karol Sikora, Professor of Oncology at Imperial College London
The Observer
Sunday, 11th January 2004

“Although this is an interesting study the sample size is very small. No causal link has been found between underarm cosmetics containing parabens and breast cancer. There is also no robust population-based evidence to suggest a link. Should any notional risk exist it would be insignificant when compared to other avoidable environmental risks for the disease, such as obesity.”

Dr Richard Sullivan, Head of Clinical Programmes at Cancer Research UK
The Sun, The Star, Daily Mail, The Independent, The Observer
Monday, 12th January 2004

“This extremely small study does not demonstrate a direct or causal link between deodorant or anti-perspirant use and developing breast cancer. Further research is needed to establish the source of the chemicals found in the breast tumour samples and what, if any, the relationship is to breast cancer.”

Delyth Morgan, Breakthrough Breast Cancer
Daily Mail, Daily Mirror
Monday, 12th January 2004

“We conclude from our results that the above mentioned paraben esterase III of keratinocytes (a skin enzyme that breaks down parabens) is sufficient to completely hydrolyse the traces of parabens that may enter the skin from topically applied ointments.”

Hydrolysis of parabens by extracts from differing layers of human skin.

The Cosmetics Directive 76/768/EEC
Annex VI specifically permits 4-hydroxybenzoic acid and its salts and esters (the parabens) for use as preservatives in all cosmetic products. The maximum authorised concentration is 0.4% (as the acid) for any one ester and no more than 0.8% (as the acid) for mixtures of
esters.
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e/state/ingr/parabens 12.1.04


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MORE PARABEN ISSUES

Dear Tony,

Whilst Professor Morganti specifically requested a reply on the parabens question from someone from Nipa Laboratories (which no longer exists), I would like to reply in my capacity as an ex-Nipa employee!

Firstly a general comment. I think that the Board of Directors of Avon are to be congratulated on their calm and sensible response to the current scare. Too often in these cases a knee-jerk response is given without any careful thought or consideration of the facts. It seems to me to be a great shame that some "scientists" feel that they have to publicise their theories before they have any proof, especially in these times when the media delight in seizing on any "scare" or "scandal".

Good science is the formulation of a theory, then testing to prove the theory, then publication of the results with conclusions. The current concerns over the safety of parabens is just sensationalism using an unproven theory.

I question the validity of the use of some of the papers used in support of Dr. Darbre's case, notably the Routledge et al paper (Tox. Appl. Pharm 153 (1998) 12 - 19). This paper has been used many times to justify the statement that "parabens are oestrogenic". I think it is important to place this paper in context before addressing Dr. Darbre's own work. Whilst the workers did find some oestrogenic activity in certain paraben esters, the dose levels used and the strength of oestrogenic response must be borne in mind. Routledge's in vitro study showed comparative activities of parabens with oestradiol ranging from 10,000 (butylparaben) to 1,000,000 (methylparaben), and the in vivo study showed no oestrogenic activity for methylparaben and the activity for butylparaben was 100,000 times weaker than oestradiol. The lowest observed effect level of butylparaben (200mg/kg/bw/day) in this study was achieved using a subcutaneous dose approximately 50,000 times greater than is ever likely to be employed by the consumer. A further study by Houssaini et al ((Food & Chem. Tox. 38 (2000) 319 - 323) repeated the subcutaneous application used by Routledge et al and found only a weak response with butylparaben at 400mg/kg/bw/day and a clear response at 600mg/kg/bw/day - much higher than that observed by Routledge. I think the telling part of the Houssaini study was part of the conclusion - "owing to...rapid metabolism and excretion it is conceivable that concentrations high enough to produce an oestrogenic effect in target tissues will not be reached unless excessive doses are used". In the case of butylparaben, the excessive dose required to exhibit an oestrogenic effect was 150,000 times the highest typical application rate in humans - surely an excellent margin of safety!

Many papers have been published demonstrating that parabens are rapidly absorbed through skin, metabolised and excreted - mostly within 24 hours. The huge doses employed in these studies, plus the dosing method employed further distort the picture, resulting in more of the dose added actually reaching target organs intact.
Dr. Darbre's study itself raises some interesting questions, having put to one side the dubious question of oestrogenic activity of parabens. I have read this paper and find some of the aspects of the work rather questionable. I ignore the results for benzylparaben as this compound is hardly ever used in personal care preservation, if at all. In the results table many of the blank samples showed a paraben presence - which is questionable in itself, and I find it difficult to accept the explanation that they carried over from the detergents used to wash the glassware employed in the study - when the figure for the blank was subtracted from the test sample a negative figure resulted. This occurred in 26 out 120 data points, leaving us with the interesting concept of "minus parabens". To have so many meaningless data points (over 20%) must surely throw a question mark over the validity of the data?

Part of the claims for this study is that it demonstrates bioaccumulation of parabens. Even if it is accepted that the parabens were found in breast tissue, it is not possible to claim any form of accumulation from a single data point, and the findings could be background levels present during the metabolic process. Dr. Darbre draws comparison between parabens and PCB's and OCP's, quoting mean levels of 20, 267 and 707 ng/g tissue respectively, claiming this as evidence of bioaccumulation. I would argue that this proves precisely the opposite. Human exposure to parabens must be several orders of magnitude greater than exposure to PCB's and OCP's, yet the latter have significantly higher residual levels than parabens. If parabens were bioaccumulative, surely this would be reflected in mean levels much higher than those of PCB's and OCP's?

One of the most questionable aspects of this work is the use of a "corrected average level of parabens" on the basis that 4 of the 20 tumours contained more than twice the average level of total parabens, and she then allows for only a 50% recovery of parabens through the analytical procedure. The "corrected average level" of 100ng/g only uses the data from the 4 tumours with the highest levels of parabens, so this is not a corrected figure at all, but a gross distortion which is then used as a comparison with data from other studies. The true "corrected average level" of parabens should be 41.2ng/g if it is accepted that only 50% of parabens are recovered by analysis. I note that there was no justification or demonstration of the basis for the 50% recovery claim. The distorted average was used for comparison with a study that found levels of 150ng/ml of propyl, butyl and isobutylparaben to stimulate growth of MCF7 human breast cancer cells. However, 62% of the total paraben found in the breast tumours was methylparaben and almost 10% was ethylparaben, for which there are no data on their capacity to stimulate MCF7 human breast cancer cells, so only 28% of the total parabens found were relevant to the comparison actually made, which surely calls into question the validity of the comparison?

The comments about the reasons for the detection of higher levels of methylparaben are very interesting. The initial conclusion is probably correct in part, ie. that methylparaben is the more widely used in consumer products (but it is also used in higher concentrations), but this is followed by the astonishing claim that methylparaben has a greater ability "to be absorbed into body tissues and to resist hydrolysis by esterases of human skin and subcutaneous fat tissue". Basic chemistry tells us that longer chain esters are increasingly resistant to hydrolysis, therefore methylparaben is much more likely to be hydrolysed than the higher esters, and less likely to be absorbed by fatty tissue.
Dr. Darbre has been told on more than one occasion that the vast majority of underarm products contain neither parabens, nor any other preservatives, but she chooses to ignore this fact and to continue to court publicity for her cause. To paraphrase Phillip Day's comments - "I applaud Phillipa Darbre's intentions, but her scientific approach is highly questionable". I take great issue with Mr. Day's comments as it is clearly scaremongery to publicise Dr. Darbre's theories across the world without any scientific proof that her theory is correct as this study only demonstrates that parabens appear to be present in breast tumours - it does not prove that they are the cause. I also take equal issue with his assertion that "chemical products (are) being sold without a care in every supermarket around the world". This is complete rubbish, and deserves no further comment.

I admit that I have no ready explanation for the possible finding of parabens in breast tumour tissue, as it appears to conflict with the many studies that have claimed complete metabolism and excretion. It may be that parabens remain stable within tumour tissue for some reason, but this would not prove that they are responsible for the tumour itself, as the tumour would need to be present before the parabens migrated there! Dr. Darbre should have tested normal breast tissue to provide a control for her study, and she should use a more reliable method of analysis as it is easy to achieve much greater than 50% recovery of parabens in analytical studies. I would also like to see the basis for the claim of only 50% recovery in her method.

I am not a toxicologist and the above observations have been made on the basis of discussions with expert toxicologists, past experience and basic common sense, but I hope that I have clarified my point that the study in question has some very important failings, and more work is required, possibly by someone less evangelical and more rational about the subject of breast cancer, in order to finally put this to rest.

I live in hope that, should it ever be proven unequivocally that parabens do not contribute to breast cancer, I hope the media give it the same degree of attention that they have to the alleged negative aspect of their use.

I shall now go and lie down for a while!

Best regards

Dene Godfrey
Sales & Technical Director
MGS MicroPure Ltd.

ANOTHER ANSWER FROM MY USA FRIEND

1. I am not aware of any underarm antiperspirant or deodorant that contains parabens. The use of the CIR report was taken without any understanding of the data. All of this is junk science.

2. The major use of parabens as food preservatives is in Soy Sauce in Japan. (The US does not use parabens in US made soy sauce). For the paper to have a snow balls chance in hell of any truth, than All Japanese's women should have breast cancer! We
rarely use parabens in foods because they really screw up our taste buds. Not a good idea for foods!

David C. Steinberg
Steinberg & Associates, Inc.
16 Mershon Lane
Plainsboro, NJ 08536
Phone 1-609-799-1575
Fax 1-609-799-5271
www.SteinbergConsult.com

MORE ON PARABENS

Hi Tony,

Parabens & breast cancer

Thanks for highlighting this emotive subject (I had also seen reports in the UK press). While I believe that this is a study worthy of our attention, I think this is another case of poorly conducted or half-done science. The researchers have forgotten one thing, that was strongly stressed to me throughout my university career: 'correlation DOES NOT prove causation' - just because 2 events are linked, this is no proof that one causes the other!

While the postulated link is interesting, I'm sure that many of us can see weaknesses - the primary one for me, is that the majority of AP/deo products do not contain parabens. As you know from formulating, most varieties of stick and aerosol don't have any preservatives at all. I have just searched 2 online sources of information - drugstore.com (which handily gives ingredient listings for products) and GNPD Mintel, a marketing company we use that has a searchable online database of new personal care products from around the world. Of the 3,324 'deodorants' products launched in the last 6 months (includes AP), only 12 contain any parabens! These are 5 varieties of wipes, 1 powder, 4 roll-ons, 1 cream and 1 spray (some deo, some AP).

Therefore, it should be very easy for an epidemiological study to find people using different formats of deodorant, and monitor their cancer levels. Also, since men are supposed to be more oestrogen sensitive, shouldn't we be seeing many more cases of breast cancer in men?

They say debate is a good thing, but I am worried that most consumers are not scientists, and take all of these studies as 'gospel', without ever looking at their scientific rigour.

Kind regards

Heather
PARABENS

Information for patients allergic to PARABENS.

What causes allergy?

Although many people may have contact with chemicals, only a very few develop an allergy to them. In these people the body’s defence mechanisms learn to recognise this chemical. They therefore develop a reaction when the chemical contacts the skin again. The allergy is 'remembered' by the body for many years.

What are 'Parabens'?

Parabens are a group of closely related chemicals which are 'esters' of p-hydroxybenzoic acid. They are used widely as preservatives for cosmetics, foods and drugs. They work as preservatives by inhibiting the growth of organisms. As different esters inhibit different organisms, they are often used as a combination of different esters.

The most commonly used 'parabens' are methylparaben, ethylparaben, p-hydroxybenzoic acid, propylparaben and butylparaben.

Parabens sensitivity is usually caused by medicaments used to treat eczema. Although parabens are found in many cosmetics, they are used in low concentration, insufficient to cause an allergy.

What are parabens in?

a] Pharmaceutical preparations, including:

<table>
<thead>
<tr>
<th>Paraben</th>
<th>Product Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphosyl HC cream</td>
<td>Locoid Lipocream</td>
</tr>
<tr>
<td>Aureocort ointment</td>
<td>Mildison Lipocream</td>
</tr>
<tr>
<td>Barquinol HC cream</td>
<td>Neo-medrone cream</td>
</tr>
<tr>
<td>Betnovate lotion</td>
<td>Nerisone cream</td>
</tr>
<tr>
<td>Betnovate N lotion</td>
<td>Synalar gel and lotion</td>
</tr>
<tr>
<td>Carbo-cort cream</td>
<td>Synalar C cream</td>
</tr>
<tr>
<td>Cobadex cream</td>
<td>Synalar N cream and lotion</td>
</tr>
<tr>
<td>Dome-cort cream</td>
<td>Siladerm cream</td>
</tr>
<tr>
<td>Efcortelan lotion</td>
<td>Synalar forte cream</td>
</tr>
<tr>
<td>Epifoam</td>
<td>Tarcortin cream</td>
</tr>
<tr>
<td>Eurax-Hydrocortisone cream</td>
<td>Temtex cream</td>
</tr>
<tr>
<td>Fucidin H gel</td>
<td>TerraCortril Nystatin cream</td>
</tr>
<tr>
<td>Genticin HC ointment and cream</td>
<td>Timodine cream</td>
</tr>
<tr>
<td>Haelen-C cream</td>
<td>Tridesilon cream</td>
</tr>
<tr>
<td>Leder cort cream and ointment</td>
<td>Ultradil cream</td>
</tr>
<tr>
<td>Locioid cream</td>
<td>Ultralanum plain cream</td>
</tr>
</tbody>
</table>

b] Barrier creams.

c] Cosmetics. Many cosmetics contain parabens.

d] Many drugs given by injection.

How can I prevent further problems?

Try to identify possible sources of contact and avoid them.

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REFERENCES

Propylparaben
NIPASOL M

In a material safety data sheet from Nipa Laboratories Ltd.

It is N-Propyl-4-hydroxybenzoate or propyl paraben. It is a fine, white, crystalline powder.

Toxic hazard

Practically non-harmful by ingestion (Acute oral toxicity in rat LD_{50} above 8g/Kg).

Tasteless, but producing a slight burning sensation in the mouth and tongue, followed by a local numbness.

Non-irritant to the skin. Slightly irritant to the eyes.

First aid

Skin contact: Wash thoroughly with soap and water
Eye contact: Irrigate with water for 10 minutes
Inhalation: Remove to fresh air.


Martindale adds no further to the information above.


It is slightly soluble in boiling water, freely soluble in alcohol, soluble in 2000 parts of water. It is used as a pharmaceutic aid (antifungal). Preservative in foods.


W.P. Jordan reported that hand eczema may be contact dermatitis. The prognosis is not good if - after avoidance of offenders identified by patch test - eczema does not clear. As a rule, preservatives contribute to hand eczema. In his opinion, the safest preservatives are the parabens. Psoralen-UV(A) therapy of palm eczema can be very effective.


The action is predominantly fungistatic. Solubility in water is lower at 0.05% at 20°C than that of the methyl ester.
Propylparaben.

4-Hydroxybenzoic acid propyl ester; propyl p-hydroxybenzoate; Nipasol M (Nipa); Solbrol P (Bayer); Propyl Parasept (Tenneco). C_{10}H_{12}O_{3}; mol wt 180.20. C 66.65%, H 6.71%, O 26.64%. Prepn: Stohmann, J. Prakt. Chem. 36, 368 (1887); L. Nobli, Giorn. Farm. Chim. 84, 168 (1935), C.A. 30, 34239 (1936).

White crystals, mp 96-97 deg. Sol in 2000 parts water; freely sol in alcohol, ether; slightly sol in boiling water.

PROPOSAL 7—RESOLUTION REQUESTING REPORT ON PARABENS

The Company is informed that Domini Social Investments LLC, whose address and share ownership will be furnished promptly upon receipt of any oral or written request therefore, together with another shareholder co-proponent, whose name, address and share ownership will be furnished promptly upon receipt of any oral or written request therefore, intend to introduce at the Annual Meeting the following resolution:

“WHEREAS:

According to Avon Products’ website, 82 products, including Auto Focus Light Adjusting Foundation, Beyond Color Illuminating Radiance Vitamin C Foundation, Beyond Color Vertical Lift Foundation, Perfect Wear Total Coverage Concealer, Clear Finish Great Complexion Pressed Powder contain parabens.

Parabens are preservatives that have been identified as estrogenic and disruptive of normal hormone functions.\(^1\) Estrogenic substances are chemicals foreign to the body that mimic the function of the naturally occurring hormone, estrogen.\(^2\) Estrogen has been shown to control the growth of breast cells.\(^3\) and exposure to external estrogens has been shown to increase the risk of breast cancer.\(^4\)

According to a report by the National Research Council, some estrogenic substances are associated with adverse reproductive and developmental effects in wildlife and other animals.\(^5\) The US National Toxicology Program lists steroidal estrogens as ‘known human carcinogens.’\(^6\) Although parabens are not ‘steroidal estrogens,’ studies have shown that they can mimic steroidal estrogens in animal studies, including in mammals (see, e.g., Pedersen et al. (2000) and Routledge et al. (1998), cited above).

There is substantial scientific evidence to suggest that increased exposure to substances that behave like estrogen in the body may elevate an individual’s risk of developing cancer.\(^7\) Parabens are among these substances.\(^8\)

BE IT RESOLVED

The shareholders request that the Board of Directors prepare a report (at reasonable cost and omitting proprietary information), available to shareholders by October 2003 evaluating the feasibility of removing, or substituting with safer alternatives, all parabens used in Avon products.”

The proponents have furnished the following statement in support of the resolution:

“Our company deserves high praise for its commitment to women’s health. Avon has raised approximately $190 million for women’s health programs in 30 countries through a variety of fundraising programs. Avon states on its web site, “No other company has committed as much money to the cause of women’s health.” Our Company has done more in the breast cancer fight than any other company.
Chemicals that may pose higher-than-average risk to human health, and particularly those that may increase the risk of breast cancer, could undermine our Company’s good efforts to support women’s health, especially in the breast cancer arena. We believe that they do not belong in our products.”


4 NRC Report, cited above.

5 Id.


7 NRC Report, cited above.


Board of Directors Statement on Proposal 7

Consumer safety is Avon’s number one priority. As a responsible cosmetics manufacturer, the Company has an extensive formal process for review of the safety and integrity of all of our products and ingredients. Toxicologists at Avon thoroughly evaluate safety data for all ingredients before they are approved for use in any of our products. Also, the Company’s scientists participate in industry-wide and professional scientific organizations in order to access and evaluate the latest information to ensure the continued safe use of all our product ingredients. In addition, Avon microbiologists strive to ensure that our products do not present potential health risks from contamination by harmful microorganisms by using preservative systems such as parabens.
Parabens have an extensive history of use in a wide variety of consumer products, foods and beverages for over 70 years. Parabens provide a critical role in frontline defense for preventing disease and infection in humans by preventing fungal and bacterial contamination.

Avon, along with the rest of the cosmetic industry, has widely used parabens due to what we believe to be their ability to reduce the risk of microbial contamination effectively at low concentrations. Parabens are recognized as safe by the World Health Organization as well as government agencies throughout the world. In the United States, the Cosmetic Ingredient Review (CIR) expert panel (an independent body of internationally recognized medical and scientific experts in safety evaluation) has reviewed parabens and concluded they are safe for use in cosmetic products. Importantly, the FDA considers a CIR decision of safety as a significant basis for the use of ingredients in cosmetic products.

There are many published studies conducted by both independent scientists and agencies on parabens, some of which specifically address the issue of carcinogenicity.\textsuperscript{1,2} We believe that these studies do not support the proponents’ assertion that there is substantial scientific evidence linking exposure to parabens with increased health risk.

Avon has a strong commitment to women’s health and is a leader in the fight against breast cancer. The safety of our products is of primary concern to Avon. We believe that discontinuing the use of parabens and replacement with inferior preservatives would present a potential health risk to our consumers that is neither necessary nor warranted.

Your Board of Directors recommends that you vote AGAINST Proposal 7

\textsuperscript{1} JECFA 1974 17th Report of the FAO/WHO expert Committee on Food Additives, Technical Report Series 539, World Health Organization showed no evidence of tumors after a lifetime feeding study in rats up to 1.5g/kg/day.

\textsuperscript{2} Homberger 1968 National Technical Information Service PB No. 183 027 showed no evidence of cancer in rats fed ethylparaben at 1g/kg day over their lifetime.
REFERENCES

Methylparaben
NIPAGIN M

In a material safety data sheet from Nipa Laboratories Ltd.

It is sodium methyl-4-hydroxybenzoate or sodium methyl paraben. It is a white hygroscopic powder, readily soluble in water and having a pH (0.1% solution) in water of 9.5-10.5.

Toxicity hazard

Slightly harmful by ingestion (acute oral toxicity in mouse LD₅₀ 2g/Kg). Tasteless, but producing a slight burning sensation of mouth and tongue, followed by local numbness.

Non-irritant to the skin. Slightly irritant to the eyes and to nasal passages.

First aid

Skin contact: Wash thoroughly with soap and water.
Eye contact: Irrigate with water for 10 minutes.


The solubility in water is given as 0.25% w/w at 20°C and as 0.3% w/w at 25°C. It is used as a preservative in foods, beverages and cosmetics.


gives no further information to reference 1.


W.P. Jordan reported that hand eczema may be contact dermatitis. The prognosis is not good if - after avoidance of offenders identified by patch test - eczema does not clear. As a rule, preservatives contribute to hand eczema. In his opinion, the safest preservatives are the parabens. Psoralen-UVA (PUVA) therapy of palm eczema can be very effective.


Methylparaben (INCI)GEN-60
Methylparaben (INCI)

CAS 99-76-3; EINECS 202-785-7

Synonyms: Methyl 4-hydroxybenzoate; 4-Hydroxybenzoic acid, methyl ester; Methyl
parahydroxybenzoate

Definition: Ester of methyl alcohol and p-hydroxybenzoic acid

Empirical: C₈H₈O₃

Formula: CH₃OOCC₆H₄OH

Properties: Colorless crystals or wh. cryst. powd., odorless or faint char. odor, sl. burning taste; sol. in alcohol, ether; sl. sol. in water, benzene, CCl₄; m.w. 152.14; m.p. 125-128 C; b.p. 270-280 C (dec.)

Toxicology: LD50 (oral, dog) 3000 mg/kg; mod. toxic by ingestion, subcutaneous, and IP routes; mutagenic data; heated to decomp., emits acrid smoke and fumes

Uses: Food additive (preservative); cosmetics; antimicrobial agent

Regulatory: FDA 21CFR §150.141, 150.161, 172.515, 181.22, 181.23, 184.1490, GRAS, limitation 0.1%, 556.390, zero limitation in milk; USA CIR approved, EPA reg.; Japan listed; Europe listed

Trade names: Aseptoform; Unisept M

Trade names containing: Killitol; Varifoam® SXC


Toxicity

ADI (Acceptable Daily Intake) 2 - 7mg per kf body weight (FAO).

One must proceed on the premise that the effective concentration lies near the solubility limit (0.2%).


Methylparaben.

4-Hydroxybenzoic acid methyl ester; methyl p-hydroxybenzoate; Nipagin M; Tegosept M; Methyl Chemosept; Methyl Parasept (Tenneco). C₈H₈O₃; mol wt 152.15. C 63.15%, H 5.30%, O 31.55%. Prepn: Ladenburg, Fitz, Ann. 141, 247 (1867); Zbarskii, C.A. 33, 93123 (1939). Identification in the vaginal secretions of female dogs in estrus: M. Goodwin et al., Science 203, 559 (1979).

White needles, mp 131 deg. bp 270-280 deg (dec). One gram dissolves in 400 ml water, 40 ml warm oil, about 70 ml warm glycerol; freely sol in alcohol, acetone, ether. The soly in
water is also given as 0.25% w/w at 20 deg, and as 0.30% w/w at 25 deg.

USE: As preservative in foods, beverages and cosmetics.
Nipa Esters
the original Parabens
Benefits of Nipa Esters

- Broad spectrum antimicrobial activity - effective against Gram-positive and Gram-negative bacteria, yeasts and moulds.
- Effective at low concentrations.
- Low order of toxicity
- Non-irritating to the eyes, skin and mucous membranes at normal use levels.
- Chemically stable - compatible with a wide range of formulation ingredients.
- Stable in aqueous solution, retaining antimicrobial activity across pH range 4-8.
- Colourless and odourless.
- Activity maintained in the presence of gums, mucilages, fats and oils.

Combinations of Nipa Esters exhibit increased activity compared with individual esters.

Biodegradable at low concentrations presenting no environmental hazard.

Well documented toxicological and dermatological acceptability allowing application in some foods, oral medicines, eye products and skin preparations as well as cosmetics and toiletries.

p-hydroxybenzoic acid and a number of its esters occur naturally in a variety of plants and animals.

Nipa Esters have not been tested on animals by, or on behalf of Clariant.

Trade Name | Chemical Name | INCI Name
--- | --- | ---
Nipagin M | Methyl p-hydroxybenzoate | Methylparaben
Nipagin A | Ethyl p-hydroxybenzoate | Ethylparaben
Nipasol M | Propyl p-hydroxybenzoate | Propylparaben
Nipabutyl | Butyl p-hydroxybenzoate | Butylparaben

Preservatives for cosmetics, toiletries and pharmaceuticals

The Nipa Esters are a range of antimicrobial preservatives comprising the four lower alkyl esters of p-hydroxybenzoic acid (often referred to as ‘parabens’).

They are used extensively throughout the cosmetics, toiletries and pharmaceutical industries and are the most widely used and accepted cosmetic preservatives in the world.
Antimicrobial Activity

Minimum Inhibitory Concentrations (%)

<table>
<thead>
<tr>
<th>Gram-negative Bacteria</th>
<th>Nipagin® M</th>
<th>Nipagin® A</th>
<th>Nipasol® M</th>
<th>Nipabutyl®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0.2</td>
<td>0.10</td>
<td>0.08</td>
<td>&gt;0.02</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0.1</td>
<td>0.05</td>
<td>0.04</td>
<td>&gt;0.02</td>
</tr>
<tr>
<td>Klebsiella aerogenes</td>
<td>0.075</td>
<td>0.05</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>0.1</td>
<td>0.05</td>
<td>0.025</td>
<td>0.015</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>0.075</td>
<td>0.05</td>
<td>0.04</td>
<td>0.2</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>0.10</td>
<td>0.06</td>
<td>0.025</td>
<td>0.015</td>
</tr>
<tr>
<td>Salmomella enteritidis</td>
<td>0.15</td>
<td>0.05</td>
<td>0.04</td>
<td>&gt;0.02</td>
</tr>
<tr>
<td>Salmomella typhi</td>
<td>0.15</td>
<td>0.10</td>
<td>0.06</td>
<td>&gt;0.02</td>
</tr>
<tr>
<td>Gram-positive Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0.15</td>
<td>0.07</td>
<td>0.04</td>
<td>0.015</td>
</tr>
<tr>
<td>Streptococcus haemolyticus</td>
<td>0.1</td>
<td>0.06</td>
<td>0.04</td>
<td>0.015</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>0.075</td>
<td>0.025</td>
<td>0.025</td>
<td>0.015</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
<td>0.10</td>
<td>0.10</td>
<td>0.025</td>
<td>0.015</td>
</tr>
<tr>
<td>Lactobacillus buchneri</td>
<td>0.10</td>
<td>0.06</td>
<td>0.025</td>
<td>0.01</td>
</tr>
<tr>
<td>Yeasts and Moulds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>0.1</td>
<td>0.07</td>
<td>0.013</td>
<td>0.013</td>
</tr>
<tr>
<td>Saccharomyces cerevisiae</td>
<td>0.1</td>
<td>0.05</td>
<td>0.013</td>
<td>0.005</td>
</tr>
<tr>
<td>Aspergillus niger</td>
<td>0.1</td>
<td>0.04</td>
<td>0.02</td>
<td>0.020</td>
</tr>
<tr>
<td>Penicillium digitatum</td>
<td>0.05</td>
<td>0.025</td>
<td>0.006</td>
<td>-0.005</td>
</tr>
<tr>
<td>Rhizopus nigricans</td>
<td>0.05</td>
<td>0.025</td>
<td>0.013</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Applications of Nipa Esters

Cosmetics and Toiletries

In widespread use for over 60 years, Nipa Esters are particularly suitable for the preservation of cosmetic products, where low toxicity, compatibility with a wide range of ingredients and activity over the desired pH range are important. Microbial contamination during the use of cosmetics may reach a very high level, thus requiring a powerful preservative system with microbiocidal activity. Experience has shown that most personal care products can be effectively preserved by Nipa Esters, including creams, lotions, solutions, pastes, gels, shampoos, deodorants, toothpastes, eye make-up, baby products etc.

The use of Nipa Esters continues to grow due to their many desirable properties. In the 10 years to 1992, for example, the use of all four esters has increased; most notably in the USA where the frequency of use of one higher ester increased by almost 400%.

In contrast, the use of some more recently introduced preservatives, after an initial increase, have shown fluctuations due to concerns over toxicological properties. The continued increased use of Nipa Esters is, therefore, a reflection of the confidence placed in the products by the personal care industry.

Research has shown that combinations of p-hydroxybenzoate esters are particularly effective in cosmetics. In some products combinations of Nipagin® M and Nipasol® M (for example) will be satisfactory, whereas products which are more difficult to preserve are more effectively protected by a Nipa Ester combination such as Nipastat®. This preservative shows good microbiocidal activity in the majority of cosmetic formulation types. Information on Nipastat® is available on a separate Technical Information Sheet. In common with many preservatives, the Nipa Esters show reduced antimicrobial activity in the presence of some nonionic surfactants, which are often used in cream formulations. This may be overcome by using more powerful preservative combinations such as Nipaguard MPA® or Phenonip®, liquid preservatives based on the Nipa Esters. These preservatives may be used at increased concentrations in the presence of nonionics. In some cosmetic products it may be necessary to evaluate Nipa Esters in combination with other cosmetic preservatives.

Pharmaceuticals

Nipa Esters have widespread applications as preservatives in pharmaceuticals. For example, the Nipa Esters, their sodium salts and combinations may be used to preserve ointments, creams, syrups, eye drops/ lotions, vitamin solutions and antacid suspensions. Nipa Esters have also been successfully used to preserve veterinary products.

Regulatory Status

Methyl, ethyl, propyl and butyl parabens are permitted for use in preservatives in cosmetics and toiletries worldwide.

<table>
<thead>
<tr>
<th>Maximum Permitted Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nipa Esters</td>
</tr>
<tr>
<td>Nipagin® M</td>
</tr>
<tr>
<td>Nipagin® A</td>
</tr>
<tr>
<td>Nipasol® M</td>
</tr>
<tr>
<td>Nipabutyl®</td>
</tr>
</tbody>
</table>

*0.4% is the maximum concentration of the individual esters. The maximum permitted concentration of combinations of esters in total is 0.8%.
Dissolving in Organic Solvents

The Nipa Esters are readily soluble in polar organic solvents. Where such a solvent is already part of a formulation an ester concentrate may be made up prior to addition. If a suitable solvent is not already part of the formulation, a highly concentrated solution may be made up e.g. a 50% w/w solution of Nipasol® M in ethanol, which would give insignificant residual levels of ethanol in the end product.

Solubilisation in Oils, Emulsifiers etc

Nipa Esters are readily soluble in lipophilic ingredients and may be introduced to a formulation by adding to the oil phase with some warming before any emulsification stage. In multiphase systems, such as emulsions, it is often advisable to use a combination of aqueous dissolution with either of the other methods to ensure adequate preservation. The ester may be incorporated in the water to its maximum solubility and any further quantities may be dissolved in the oil phase, or solvent, as appropriate.

Nipa Esters are also available as their respective sodium salts which are more soluble in cold water (in excess of 30% w/w at 25°C).

The sodium salts are ideal for use in cold processes where heating to dissolve the free esters is not desirable.

Toxicological Information

The Nipa Esters have not been tested on animals by, or on behalf of, Clariant. Data have been taken from the scientific literature in order to assess the hazards to man and the environment.

Under European Union Regulations none of the four esters are classified as ‘harmful’, nor are they classified as primary skin or eye irritants.

Paraben esters are found in many plants and animals and, being naturally occurring, biodegradability is assumed to occur readily. It has been demonstrated that some bacteria can exist in an environment containing low levels of parabens as the sole carbon source. Aquatic toxicity data has demonstrated that paraben esters present a very low risk to the environment. More detailed toxicological data is available on request.

Whilst the information contained herein is accurate to the best of our knowledge, no warranty is either expressed or implied. It is the responsibility of the individual to ensure that their products will remain preserved over the anticipated shelf life.
About Clariant

Clariant is a leading global speciality chemicals company with more than 30,000 employees and annual sales of over CHF 10 billion. The company resulted from the merging of the Sandoz chemicals division and the Hoechst speciality chemicals business. Clariant is domiciled and headquartered in Muttenz near Basle, Switzerland and operates worldwide with Group companies in more than 60 countries. Clariant comprises of five divisions: Textile, Leather & Paper Chemicals; Pigments & Additives; Masterbatches; Functional Chemicals and Masterbatches of Clariant which, together, offer a broad range of specialty chemicals for all major applications.

Technical Service

At our global network of well-equipped technical service laboratories, our dedicated and experienced microbiologists support the full Nipa product range with shelf-life stability tests along with biocide efficacy studies. Our expert advice and guidance is well known and respected by chemists wherever a biocide or preservative is needed.

Nipa Biocides is a business unit within the Functional Chemicals Division of Clariant. The company was originally established in 1924 to commercialise paraben esters as antimicrobial preservatives and gallate esters as antioxidants. Nipa held the original patents on these applications and today the company enjoys a worldwide reputation for the quality of its preservatives for the cosmetics, toiletries and pharmaceutical markets. Strong emphasis on the quality of its products and the reliance on highly trained staff and modern equipment maintain our position as a respected market leader.

Nipa Preservative Products are listed below:

<table>
<thead>
<tr>
<th>NIPA Product</th>
<th>INCI Name</th>
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<tbody>
<tr>
<td>Nipagin M*</td>
<td>methylparaben</td>
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<tr>
<td>Nipagin A*</td>
<td>ethylparaben</td>
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<tr>
<td>Nipasol M*</td>
<td>propylparaben</td>
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<td>Nipabuty*</td>
<td>butylparaben</td>
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<tr>
<td>Nipastat*</td>
<td>methylparaben, butylparaben, ethylparaben, propylparaben, isobutylparaben</td>
</tr>
<tr>
<td>Nipasept*</td>
<td>methylparaben, ethylparaben, propylparaben</td>
</tr>
<tr>
<td>Phenonip</td>
<td>phenoxyethanol, methylparaben, ethylparaben, butylparaben, propylparaben, isobutylparaben</td>
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<tr>
<td>Phenoxetol</td>
<td>phenoxyethanol</td>
</tr>
<tr>
<td>Nipa Bispure 100</td>
<td>imidazolidinyl urea</td>
</tr>
<tr>
<td>Nipa Bispure 200</td>
<td>diazolidinyl urea</td>
</tr>
<tr>
<td>Nipaguard CMB</td>
<td>triethylene glycol, benzyl alcohol, propylene glycol, chloromethylisothiazolinone, methylisothiazolinone</td>
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<tr>
<td>Nipaguard PDU</td>
<td>propylene glycol, diazolidinyl urea, methylparaben, propylparaben</td>
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<td>Nipaguard SMG</td>
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<td>Nipaguard BPX</td>
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<td>Nipaguard DCM</td>
<td>phenoxyethanol, methylglycidyl ether, glutaraldehyde</td>
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<td>Nipaguard DMDM</td>
<td>DMDM hydantoin</td>
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<td>Nipaguard MPA</td>
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<tr>
<td>Nipaguard TBK</td>
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<tr>
<td>Nipaguard IFM</td>
<td>PEG-4 laurate, isopropylbutylcarbamate</td>
</tr>
</tbody>
</table>

* These products are also available as the sodium salts of the esters.

The information in this publication corresponds to the present state of our knowledge and is intended to describe our products and their possible applications. It is not intended to guarantee the suitability of particular products characteristics for a specific use. Any existing industrial rights are to be taken into consideration. Quality is guaranteed in accordance with our general conditions of sale.
Uses

This group of chemicals are used as preservatives in cosmetics, and are antibacterial agents in some antibacterial toothpastes. Four main parabens are in use: methyl, ethyl, propyl and butylparabens; many products will have 2 or more of these chemicals as part of a preservative system. As preservatives in cosmetics are on the label in the EU it is easy to find out which products contain these chemicals.

Oestrogenic effects

In late 1998 John Sumpter's group at Brunel University, UK, published a paper identifying parabens as oestrogen mimics (Routledge et al., 1998). The authors state:

"Given their use in a wide range of commercially available topical preparations, it is suggested that the safety in use of these chemicals should be reassessed, with particular attention being paid to estimation of the actual levels of systemic exposure of humans exposed to these chemicals. The acquisition of such data is a prerequisite to the derivation of reliable estimates of the possible human risk of exposure to parabens."

In a screen with a human estrogen receptor expressed by yeast cells the potency of the parabens group was butylparaben>propylparaben>ethylparaben>methylparaben. When methylparaben and butylparaben were injected into immature or ovariectomized rats, butylparaben led to an increase in uterus weights (an oestrogenic effect), whereas methylparaben had no detectable effect.

Another study examining effects on excurrent ducts of the rat testis through puberty to adulthood found no effects from butylparabens (Fisher et al, 1999); however this used much lower doses than the Routledge work.

Industry response

The European Cosmetic Toiletry and Perfumery Association COLIPA stated that the Routledge work was 'irrelevant' as 'Parabens are hydrolysed in the
skin and we have data to show that none are entering the blood stream', and said that the Industry had no plans to follow up the work.

Professor Sumpter replied that

'What we really want to know is what effects may come from low exposures over a long period of time. That is the realistic exposure mechanism' (ENDS, 1999a).

AstraZeneca toxicologist Dr John Ashby, who is very engaged in the science and policy debates on endocrine disruption, said at a conference in March that he had decided not to use parabens-containing products on his young daughter (ENDS, 1999b).

---

This page was last updated in October 1999

Return to the hormone disrupting chemicals home page

References


URL: http://website.lineone.net/~mwarhurst/parabens.html
The Registry of Toxic Effects of Chemical Substances

Benzoic acid, p - hydroxy - , methyl ester

RTECS #: DH2450000

CAS #: 99-76-3

UPDATE: January 1997

MW: 152.16

MF: C₈H₈O₃

NOTE:

- TOXICITY DATA HAVE NOT BEEN EVALUATED. OMISSION OF A SUBSTANCE OR NOTATION DOES NOT IMPLY ANY RELIEF FROM REGULATORY RESPONSIBILITY.

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7. **STATUS IN FEDERAL AGENCIES:**

8. **REFERENCES:**

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**SYNONYMS:**

| 2. p-Hydroxybenzoic acid methyl ester | 15. Methyl chemosept |
| 4. Moldex | 17. Metaben |
| 5. Aseptoform | 18. Maseptol |
| 9. Methyl parasept | 22. Paridol |
| 10. Methyl parahydroxybenzoate | 23. Septos |
| 11. Methylparaben | 24. Tegosept M |
| 12. Methyl p-oxybenzoate | 25. p-Oxybenzoesauremethylster (German) |
| 13. Methylester kyseliny p-hydroxybenzoove (Czech) | |

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**SKIN AND EYE IRRITATION DATA AND REFERENCES:**

<table>
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<th>DOSE</th>
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<td>hamster lung</td>
<td>125 mg/L/27 hour</td>
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### REPRODUCTIVE EFFECTS DATA AND REFERENCES:

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### ACUTE TOXICITY DATA AND REFERENCES:
The Registry of Toxic Effects of Chemical Substances (RTECS)

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<td>Peripheral Nerve and Sensation: Flaccid paralysis without anesthesia (usually neuromuscular blockage) Behavioral: Somnolence (general depressed activity) Behavioral: Ataxia</td>
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<td>oral guinea pig</td>
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<td>oral mouse</td>
<td>lethal dose (50 percent kill): &gt;8 gm/kg</td>
<td>Peripheral Nerve and Sensation: Flaccid paralysis without anesthesia (usually neuromuscular blockage) Behavioral: Ataxia</td>
<td>JAPMA8 45,260,1956</td>
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<td>oral rabbit</td>
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<td>AIPOTAK 128,135,1960</td>
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<td>subcutaneous rat</td>
<td>lethal dose (50 percent kill): &gt;500 mg/kg</td>
<td>N/R</td>
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OTHER MULTIPLE DOSE DATA AND REFERENCES:

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<tr>
<td>Toxicoology Review</td>
<td></td>
<td>ARZNAD 4,575,1954</td>
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### Standards and Regulations:

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<th>Organization</th>
<th>Standard</th>
<th>Reference</th>
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<tr>
<td>Environmental Protection Agency (EPA) Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) 1988</td>
<td>Pesticide Subject to Registration or Re-Registration</td>
<td>FEREAC 54,7740,1989</td>
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</table>

### NIOSH Documentation and Surveillance:

<table>
<thead>
<tr>
<th>Organization</th>
<th>Standard or Survey</th>
<th>Reference</th>
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<tbody>
<tr>
<td>National Occupational Hazard Survey 1974</td>
<td>National Occupational Hazard Survey 1974: Hazard Code: 80461; Number of Industries 33; Total Number of Facilities 4,469; Number of Occupations 50; Total Number of Employees Exposed 57,029</td>
<td></td>
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### National Occupational Exposure Survey 1983

- **Hazard Code:** 80461
- **Number of Industries:** 94
- **Total Number of Facilities:** 15,369
- **Number of Occupations:** 117
- **Total Number of Employees Exposed:** 590,361
- **Total Number of Female Employees Exposed:** 398,916

### STATUS IN FEDERAL AGENCIES:

<table>
<thead>
<tr>
<th>ORGANIZATION</th>
<th>REFERENCE</th>
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<tbody>
<tr>
<td>EPA TSCA Section 8(b) CHEMICAL INVENTORY</td>
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### REFERENCES:

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<th>REFERENCE</th>
</tr>
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<tbody>
<tr>
<td>AIPTAK</td>
<td>Archives Internationales de Pharmacodynamie et de Therapie. (Heymans Institute of Pharmacology, De Pintelaan 185, B-9000 Ghent, Belgium) V.4- 1898-</td>
</tr>
<tr>
<td>CTOXAO</td>
<td>Clinical Toxicology. (New York, NY) V.1-18, 1968-81. For publisher information, see JTCTDW.</td>
</tr>
<tr>
<td>ESKHA5</td>
<td>Eisei Shikenjo Hokoku. Bulletin of the Institute of Hygienic Sciences. (Kokuritsu Eisei Shikenjo Kagaku, 18-1 Bushitsu Johobu, Setagaya-ku, Tokyo 158, Japan) V.1- 1886-</td>
</tr>
<tr>
<td>FEREAC</td>
<td>Federal Register. (U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402) V.1- 1936-</td>
</tr>
<tr>
<td>JAPMA8</td>
<td>Journal of the American Pharmaceutical Association, Scientific Edition. (Washington, DC) V.29-49, 1940-60. For publisher information, see JPMSAE.</td>
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<tr>
<td>MUREAV</td>
<td>Mutation Research. (Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands) V.1- 1964-</td>
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**Used as a pharmaceutical and preservative**

**RTECS Compound Description:**
- **Drug**
- **Mutagen**
HYPOTHESIS:
Underarm Cosmetics are a Cause of Breast Cancer
by Philippa D Darbre

THE HYPOTHESIS
I propose a novel hypothesis that the chemical constituents of antiperspirant/deodorant cosmetics applied to the underarm area are a cause of breast cancer.

BACKGROUND
Breast cancer is the major cancer of women in the western world, but shows a rising incidence all over the world (Ursin et al, 1994). Epidemiological evidence demonstrates that 90% of breast cancers are environmental in origin (Lipworth, 1995) and linked to a western lifestyle, but the specific environmental causes have never been identified. In recent years, two tumour suppressor genes, BRCA1 (Miki et al, 1994) and BRCA2 (Wooster et al, 1995), have been cloned which confer susceptibility to breast cancer, but loss of function of these genes accounts for a maximum of 5-10% of breast cancer (Easton et al, 1993). The main identified risk factors are hormonal and linked, in particular, to lifetime exposure to oestrogen through variations in menarche, menopause, childbirth and personal choices such as use of the contraceptive pill or hormone replacement therapy (Lipworth, 1995). Diet, smoking and alcohol can also exert influences (Lipworth, 1995). However, these known risk factors confer only a small increased risk and the main causative agents of breast cancer remain unaccounted for.

A novel, unexplored but plausible explanation for the cause of breast cancer is the use of underarm cosmetics. These chemicals are applied repetitively and frequently to an area directly adjacent to the breast area. They are not rinsed off but left always on the skin. They are used by women with ever increasing frequency and by ever younger girls before puberty. They are now also being used by some men in increasing amounts. The progressive increase in use of these cosmetics in the western world over the past 100 years is illustrated by US sales figures (Laden and Felger, 1988). Sales in 1914 reached sufficient levels to support national advertising, and rose from there to US business worth $30million in 1947 to $300million in 1970 to over $1billion in 1983 (Laden and Felger, 1988). Although these cosmetics are regulated as over-the-counter drugs (Laden and Felger, 1988), there are no indications on the containers of the safe level of usage or whether the constituent chemicals are safe for prolonged use by young children before puberty. Contrary to common belief, there is great diversity in use of these cosmetics across the population. My own unpublished survey within the University of Reading shows that women use a variety of different products, each containing different types and amounts of chemicals and that frequency of use varies from never to more than 5 times a day. Such diversity in usage provides ample possibility for cancer to arise through quantity used, through pattern of usage or through individual susceptibility to specific product formulations.

ANATOMICAL SITE OF BREAST CANCER
The strongest supporting evidence for a role for underarm cosmetics in breast cancer comes from published clinical observations showing disproportionately high incidence of breast cancer both in the upper outer quadrant of the breast and in the left breast. Numerous clinical studies, dating back decades, have shown that the upper outer quadrant of the breast is the most frequent site of carcinoma. This basic observation has now become textbook fact (Haagensen, 1971) and for countries as different as India (Hussain et al, 1994), the West Indes (Raju and Naraynsingh, 1989), and Italy
(Azzena et al, 1994), and irrespective of race within any one country (Patterson et al, 1998). The upper outer quadrant is also the most frequent site of breast cancer in men as well as in women (Jaiyesimi et al, 1992; Rizk et al, 1994). The accepted explanation is that this region of the breast contains a greater proportion of the epithelial target tissue but evidence for this explanation seems to be largely anecdotal and as written by Haagensen himself (Haagensen, 1971) "This is a purely anecdotal explanation, but I know of no other".

An alternative explanation of these studies could simply be that the upper outer quadrant is the local area adjacent to which the underarm cosmetics are applied. Since they are applied in large amounts, they may simply penetrate through the skin of the local area without even invoking any major physiological carrier such as blood or lymphatics. It is interesting to note that the disproportionate incidence of female breast cancer in the upper outer quadrant rises with year of publication, from 30.9% in 1926 (Lane-Claypon, 1926) to 43-48% in 1947-1967 (Truscott, 1947; Harnett, 1948; Nohrman, 1949; Smithers et al, 1952; Donegan and Spratt, 1967) and to 60.7% in 1994 (Azzena et al, 1994). If this observation of published trends is not just a reflection of different study populations and reflects some real increasing incidence in the upper outer quadrant relative to other quadrants with time, then this would question the explanation as being due always to more epithelial tissue in that region. Other workers have also queried explanatory dogma through their studies showing an even distribution of cancer between quadrants in large and small breasts, despite the less marked quadrant distribution of tissue in the smaller breasts (Rimsten, 1976).

Another set of numerous studies, also without adequate explanation, show that the left breast is more prone to development of cancer than the right breast in both female (Busk and Clemmesen, 1947; Harnett, 1948; Smithers et al, 1952; Garfinkel et al, 1959; Haagensen, 1971) and male (Busk and Clemmesen, 1947; Jepson and Fentiman, 1998) breast cancer. This has been attributed to more epithelial cells on the left side of the breast due to preferential vascular supply to the left side of the body during intrauterine cardiac development (Jepson and Fentiman, 1998) but a simpler and equally plausible reason could relate simply to the right-handed nature of a majority of the population resulting in a greater application of chemicals to the left underarm area. This could be tested by study of the quadrant incidence in left- and right-handed people, if such data were available.

Lastly, the reasons for enhanced risk of (Chen et al, 1999) or even coexistence of (Fenig et al, 1975) contralateral breast disease have yet to be explained. This type of pathological pattern is more consistent with a general intolerance to chemicals of cosmetics applied under both arms than to the equivalent of several coincidental monoclonal initiation events (Ponten et al, 1990).

CONSTITUTENTS OF UNDERARM COSMETICS AND POSSIBLE ROLE IN CARCINOGENESIS:

i) Chemical constituents

If underarm cosmetics play any role in breast cancer, then the challenge will be to identify specific chemical culprits. All ingredients will have been tested by current safety guidelines (Laden and Felger, 1988), but the effects of long-term use over an entire lifetime by the whole global population of women (and increasingly by men) can only be investigated retrospectively. The main active ingredients of underarm cosmetics are:

1) Antiperspirant agents
2) Deodorant agents
3) Preservatives

Minor components include fragrance and colourings.

The antiperspirant component acts to block the sweat ducts, so preventing escape of sweat onto the body surface (Laden and Felger, 1988). The main active agents are metal salts, principally aluminium chloride and the aluminium zirconium chloride glycine complexes. Their mechanism of action is not fully established but is thought to involve the formation of a physical plug at the top of
the sweat duct (Laden and Felger, 1988) which is composed of a combination of precipitated salts and damaged cells. This plug then prevents the secretion of sweat. The deodorant components are antimicrobial agents which act to kill bacteria on the body surface (Laden and Felger, 1988). Since it is the bacterial action on sweat which generates the undesirable odour from sweating, the deodorant is designed to eliminate the smell (Laden and Felger, 1988). Finally, since consumers expect long shelf life from these cosmetics, preservatives are added, especially to stick, roll-on and cream formulations, to prevent microbial and fungal growth in the containers during long-term storage.

ii) Possible mechanism of action
Any carcinogenic action by the constituent chemicals of underarm cosmetics would require a minimal combination of initiating and promoting agents. The simple suggestion would be that underarm cosmetics act by delivering to the breast area a regular supply of components capable of both initiation and promotion of breast cancer, and which are simply absorbed through the skin into the local breast area. However, it is also possible that there would be interactions with other physiological, dietary and environmental agents, possibly with the underarm cosmetics acting as the final insult.

iii) Initiation
Initiation would require agents capable of binding to DNA and causing DNA damage and mutation. The active antiperspirant agents include aluminium and zirconium salts (Laden and Felger, 1988), and there is evidence that aluminium can bind to DNA (Karlik et al, 1980; Ahmad et al, 1996). There are also reports of accumulation of aluminium in human breast material (Mulay et al, 1971) and in mammary tumours of rats (Ogoshi et al, 1994). Another alternative source of initiating agents could arise from chemicals secreted in the sweat itself (Stowe and Plaa, 1968) if they could accumulate at the point where sweat ducts are blocked by the antiperspirant agents. This has been suggested in an anonymous e-mail widely circulated across the world over the past two years, but although it has stimulated discussion, most conclusions have been negative due to the fact that the source of the e-mail has, unfortunately, never been identified.

iv) Promotion
Promotion of breast cancer would require agents capable of enabling growth of breast epithelial cells. In view of the well established role of oestrogen in growth of breast cancer cells both in vivo and in vitro (Miller, 1996), the most likely promotional candidate would have oestrogenic properties. It is possible that promotion could result from exposure to physiological oestrogens, since established risk factors for breast cancer include lifetime exposure to oestrogen (Lipworth, 1995). However, the human population is now also exposed to a variety of pollutant chemicals which can mimic the action of oestrogen and which, due to their lipophilic nature, are stored in human breast fat (Darbre, 1998). These include a variety of pesticides such as DDT (Smith, 1999) and polychlorinated biphenyls (PCBs) (Dobson and van Esch, 1993). Some PCB congeners can mimic the action of oestrogen (Nesaretnam et al, 1996; Nesaretnam and Darbre, 1997) and can enhance breast cancer in an animal model (Nesaretnam et al, 1998). Such chemicals accumulate in body fat over a lifetime but can be released during times of fasting or dieting and can be released into breast milk during lactation (Darbre, 1998).

However, it is also possible that underarm cosmetics contain themselves oestrogenic chemicals capable of being absorbed through skin and acting locally. There is now evidence that parabens (alkyl esters of p-hydroxybenzoic acid) can mimic the action of oestrogen (Routledge et al, 1998; Byford et al, 2001) and parabens are used as preservatives in over 13,000 cosmetic formulations including underarm cosmetics in concentrations of up to 1% (Elder, 1984). Parabens have been shown to bind to the oestrogen receptors of rat uterus (Routledge et al, 1998; Blair et al, 2000) and of MCF7 human breast cancer cells (Byford et al, 2001). They show oestrogenic activity in yeast cell assays (Routledge et al, 1998) and in regulating gene expression and growth of oestrogen-responsive human breast cancer cells (Byford et al, 2001). Their oestrogenic activity has also been detected in vivo in fish (Pedersen et al, 2000) and in the immature rodent uterine weight assay (Routledge et al, 1998; Hossani et al, 2000). Interestingly, oestrogenic activity in the latter assays was found only when administration was subcutaneous and not oral (Routledge et al, 1998; Hossani et al, 2000) suggesting
that topical application of parabens in cosmetics could provide an oestrogenic stimulus. The issue of penetration of parabens through the human underarm skin needs now to be studied, but parabens have been shown capable of penetrating skin in animal studies (DalPozzo and Pastori, 1996) and our own preliminary unpublished work has shown that parabens can be detected in human breast fat by either simply thin-layer chromatography or by high-pressure liquid chromatography followed by mass spectrometry.

**INHERITED SUSCEPTIBILITY TO BREAST CANCER**

About 5-10% of female breast cancer is inherited as a genetic susceptibility with an increased risk of developing breast cancer (Easton et al, 1993). In recent years, two of the susceptibility genes BRCA1 (Miki et al, 1994) and BRCA2 (Wooster et al, 1995) have been cloned and sequenced. BRCA1 has been implicated to play a primary role in maintenance of DNA repair; BRCA2 is a DNA binding protein but its function has yet to be fully understood (Hilakivi-Clarke, 2000). Both these genes act as tumour suppressor genes in that loss of their function is associated with increased risk of breast cancer (Hilakivi-Clarke, 2000), presumably through an inability to maintain normal DNA repair systems. Although much has therefore now been learnt about the inheritance of susceptibility, the question remains as to susceptibility to what? It is possible that the explanation lies in susceptibility to use of underarm cosmetics. Loss of BRCA1 or BRCA2 will have compromised the ability of the breast cells to repair DNA damage and it is possible that this could lead to increased sensitivity to any DNA damaging chemicals of underarm cosmetics.

**BENIGN BREAST DISEASE**

Breast cancer represents only around 5% of clinical abnormalities of the breast (Haagensen, 1971). Other major problems of the breast include fibroadenomas and breast cysts (Haagensen, 1971). Interestingly, the upper outer quadrant is not only the most common site of the tumour in cancer but also of the abnormalities in many benign breast conditions including fibroadenoma and breast cysts (Rimsten, 1976) and phyllodes tumour (Stebbing and Nash, 1995). It is interesting to note that breast cysts are caused by blocked breast ducts (Haagensen, 1971). The reason for their high incidence rate remains unknown but they are of considerable concern since their presence can be an indicator of cancer to come (Dixon et al, 1999). Since antiperspirants act by blocking sweat ducts (Laden and Felger, 1988) and breast cysts result from blocked breast ducts (Haagensen, 1971), it is possible that breast cysts might also arise from underarm cosmetic use. Application of underarm cosmetics is rarely so precise that ingredients fall only on the underarm site and not partly also on adjacent breast areas. There is no reason to believe that antiperspirants should not do the same to adjacent breast ducts as to the sweat ducts, if sufficient cosmetic is applied and if the cosmetic is applied carelessly to areas beyond the immediate underarm site, particularly since breast is essentially a modified sweat gland (Anderson, 1991).

**CONCLUSIONS:**

Whether or not this hypothesis proves to be correct, it deserves serious testing by both scientists and clinicians. The nature of the chemicals in these cosmetics and the lack of any advice about safe quantity or frequency of application should be of major concern alone. However, their use by ever younger children before puberty is also an extremely worrying trend. There is evidence that the origin of breast cancer can be many years before the symptoms become visible and that there may even be a specific time period before puberty when the breast is particularly susceptible to carcinogenesis (Russo and Russo, 1987). Studies of Japanese survivors of the atomic bomb in 1945 have shown that the highest risk of radiation-induced breast cancer was in girls who were prepubertal at the time of exposure (Tokunaga et al, 1979).

If there proves to be any truth in the hypothesis, then underarm cosmetics can be given up without addictive or life-threatening consequences. Furthermore, since these cosmetics are applied voluntarily, then women would have, for the first time, an opportunity to choose to reduce their own personal risk of breast cancer.


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PHILLIP DAY’S COMMENT: Ms Darbre is to be applauded for producing her hypothesis which I believe deserves to be rapidly distributed around the world. So many chemicals used in personal care products have not been adequately tested for their long-term effects. This is also true for many foods we consume, such as white bread, sugar, coffee and others, that are taken for granted. My own investigations into the antiperspirant/deodorant conundrum have led me actively to encourage the public to seek safe alternatives to the chemical products being sold without a care in every supermarket across the world. Stay natural with safer, gentler products. And if you have chronic body odour, investigate a colon cleanse, a change of diet to raw fruits and vegetables, and increase water intake to 2-3 litres a day.

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Statement of the Scientific Committee on Food

on the Parabens

(expressed on 4 April 2003)
Parabens have been used as preservatives in food for over 50 years. Under EU Directive 95/2/EC, Annex III, the parabens (E214-219) are conditionally permitted for use in a limited number of foods in combination with either sorbates or sorbates and benzoates, i.e. in jelly coatings of meat products, surface treatment of dried meat products, cereal- or potato-based snacks and coated nuts, confectionery (excluding chocolate), and liquid dietary food supplements. They are not permitted for use as the sole preservative in any foods.

Following a review of the published literature, the SCF expressed an opinion on the parabens in 1994 in which it concluded that the available data showed some inadequacies and uncertainties (Reports of the Scientific Committee for Food, Thirty-fifth series). A temporary ADI of 0-10 mg/kg bw was allocated for the sum of methyl, ethyl and propyl p-hydroxybenzoic acid and their sodium salts. Further studies in the rat to investigate cell proliferation in the forestomach and developmental toxicity were requested.

The situation was reviewed again in 2000 when the Committee reiterated its wish to review the safety of both benzoates and the parabens (Minutes of the 123rd Plenary Meeting of the Scientific Committee on Food, October 2000). Subsequently, data were submitted by industry in support of the benzoates and a favourable opinion allocating a group ADI for the benzoates was adopted (Minutes of the 134th Plenary Meeting of the Scientific Committee on Food, September 2002). No data have been submitted in support of the parabens.

It is unclear whether the lack of support for the parabens indicates that they are no longer used in food sold in the EU. The Committee recommends that the Commission take steps to ascertain whether or not the parabens are still used in food before any further scientific advice is sought. In the event that the parabens are still used in food, the Committee draws attention to its statement of October 2000, that the temporary ADI should be withdrawn if no further data are submitted.
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NATURAL Parabens

1. In a data sheet from Nipa Laboratories received from Malcom Irvine Dec 1994. "Parabens - the natural preservatives".

In the plant world 4-hydroxybenzoic acid and its derivatives are commonly found in various vegetable foods, such as barley, strawberries, blackcurrants, peaches, carrots, onions, cocoa-beans, vanilla; further in foods prepared from fruit plants such as grapes and fruit juices, yeast extract, wine vinegar and also in cheeses. The distribution of the acid in plants, as derivatives of alkaloids, natural colourings etc. was reviewed by Banfield. Tomaszewski investigated 122 plant species and found the acid present in all the plants. Billek concluded that 4-hydroxybenzoic acid is the most widely distributed aromatic organic acid in the vegetable kingdom. Baardseth showed that the Scandinavian cloudberry contain benzoic acid, sorbic acid, salicylic acid, 2-hydroxybenzoic acid, as well as methyl and propyl parabens, which accounted for the superior resistance of cloudberries to microbial spoilage.

The total organic acids were present at a level of 600 ppm.

Recently, Schafers reported an elegant technique (GC/MS) for the detection of methyl and ethyl esters of hydroxybenzoic acid in vegetable and potato peelings.

In the animal kingdom, Schildknecht found Dytiscus marginalis, the yellow beetle, produced in the secretion of its glands a disinfecting mixture of benzoic acid, 4-hydroxybenzoic acid, 4-hydroxybenzaldehyde and methyl paraben, which protected the glands from bacterial infection. Staddon likewise found methyl paraben in the stink gland secretions of the British water bug, Ilyocoris cimicoides.

The presence of 4-hydroxybenzoic acid in urine of healthy, normally fed human beings has been known for many years and is due to the decomposition of the amino acid, tyrosine, and from dietary sources.

Goodwin identified methylparaben in the vaginal secretions of female dogs in oestrus. It was proposed that methylparaben was an essential part of the complex odour profile generated by the secretions of the vaginal glands. It is more likely, as in the water bug and yellow beetle examples, that methylparaben was produced as antimicrobial protection of the microbiologically labile odoriferous components of the secretions.

Research worker suspected a vital role for 4-hydroxybenzoic acid. Davis found it an essential growth factor (bacterial vitamin) for E. coli and as sulphonamides were an antagonist to 4-aminobenzoic acid (bacterial vitamin H), so methyl paraben was to its parent acid. Many other workers supported these findings, culminating in Simonart & Wiaux detecting the occurrence of 4-hydroxybenzoic acid in Penicillium griseofulvum which emphasised the fundamental importance of this acid in biochemistry.

It was eventually resolved that 4-hydroxybenzoic acid was the precursor building block for ubiquinones (coenzyme-Q) which is essential for the oxidative phosphorylative process in all respiring organisms. Ubiquinones were found in microbes, in the heart muscle and in the normal
It was concluded that:

“All respiring vegetable and animal species require 4-hydroxybenzoic acid. Without it there are no ubiquinones and hence no respiration. 4-hydroxybenzoic acid is a natural vital ingredient of aerobic life, it is no foreign substance to them.”

Bose\textsuperscript{21} reported that 4-hydroxybenzoic acid exhibited marked synergy with auxins, in promoting root growth of chrysanthemums, tomatoes and marigolds. Another interesting report by Kickuth\textsuperscript{22} isolated and identified nine aromatic compounds from the rhizomes of bullrushes \textit{S. lacustris} which had microbiocidal activity (especially against \textit{E. coli} and \textit{Salmonella} spp.) and therefore would make these plants important in maintaining water quality and protecting against pollution from disease producing organisms. The nine compounds identified were derivatives of benzaldehyde, 4-hydroxybenzoic acid and cinnamic acid (0.025 wt \% of rhizomes). The aromatic acid function had the greatest activity and had bactericidal activity against \textit{E. coli} at concentrations as low as single ppm levels.

Da & Vialle\textsuperscript{23} studied the flavour components of natural vanilla extracts. They showed that, unlike the Bourbon vanilla, the Tahiti vanilla contained methyl paraben as one of the four major flavour components. Harbourne\textsuperscript{24} found methyl paraben a constituent of lignin in some gymnosperms and woody dicotyledons.

Aldrich\textsuperscript{25,26}, studying the 7th-8th ventral abdominal gland secretions of adult males of the leaf-footed bugs, \textit{Leptoglossus} and related species, found a preponderance of aromatic compounds, contrasting sharply with the aliphatic compounds which comprise the metathoracic gland defensive secretions of male and female leaf-footed bugs. It was later found that methyl paraben was a major component of the ventral abdominal gland secretion.

Perkins\textsuperscript{27}, investigating the major components of the rectal glandular secretions of male fruit flies found methyl, ethyl and propyl parabens. He found that the glandular extracts of the S.E. Asian fruit fly (\textit{Dacus albistrigatus}) was rich in methyl paraben. In another \textit{Dacus zeugodacus} sp. (a large unidentified Malaysian fruit fly) the glandular extract contained 66\% ethyl paraben. \textit{Dacus cucurbitae}, the melon fly, is the major fruit fly pest of melon and other cucurbits. Analysis of the rectal gland secretions showed ethyl paraben as the major component and propyl paraben as a minor one. Hancock\textsuperscript{28}, studying African cucurbit pests, found \textit{Dacus vertebratus} Bezzi to be highly attracted to methyl paraben. This discovery was initially observed when the fly was attracted to a locally manufactured cosmetic product.

Methyl paraben has now joined three other previously identified fruit fly attractants, "Cue-lure" [4-(4-acetoxyphenyl)butan-2-one], "Willison's lure" [4-(4-hydroxyphenyl) buutan-2-one] and methyl eugenol. Methyl paraben has been called "Vert-lure".

The article continues with a discussion of the biodegradability and the 4-hydroxybenzoic acid biocycle.

It was concluded that 4-hydroxybenzoic acid and derivatives have a well reported and proven biocycle and are intrinsic and fundamental to all respiring and anaerobic life.

See the reference list in the data sheet.

Parabens used to preserve medicaments and cosmetics may sensitise and cause contact dermatitis at the site of application. It has been suspected that persons sensitised to parabens may experience flares of dermatitis from parabens in food and systemic medicaments.

From 1.1.90 to 31.12.94 we performed a placebo-controlled oral challenge with a mixture of 100 mg methyl p-hydroxybenzoate and 100 mg propyl p-hydroxybenzoate in 14 patients with least a+ positive patch test to the paraben mixture in the European Standard Series. 7 of the patients had hand eczema; 1 also had dermatitis of the face and 1 also had axillary eczema. 3 patients had dermatitis of the lower legs, 3 had dermatitis of the face and/or scalp, and 1 had dermatitis of the forearms.

The capsules containing the paraben mixture or a placebo were given an interval of 1 week. This interval was longer if there was a flare of dermatitis after the 1st. capsule. The sequence of capsules was randomised. The oral challenge was carried out when the dermatitis was quiescent. The patients themselves recorded whether or not aggravation occurred following the oral challenge.

2 of the 14 patients had flares of their usual dermatitis after challenge with the paraben mixture but not after the placebo. Both had hand eczema of the recurrent, vesicular type. Both had a severe eruption of vesicles on the sides of the fingers within 24 hours of ingesting the paraben capsule. 1 of the patients also has a flare at a paraben patch test site on the back. 1 patient had doubtful reactions to both the paraben mixture and the placebo, while 11 patients did not have any reaction to the oral challenge.

The 2 patients with specific reactions to the challenge were informed about food and medicaments that may contain parabens. These preservatives are permitted in amounts up to 300 mg/kg of foods such as mayonnaise and ready-to-serve salads containing mayonnaise, water-based ice cream, preserved fish, preserved vegetables, including ketchup and mustard, marmalade, fruit and vegetable juices and cider as well as candy and cakes.

At follow-up visits after the patients had attempted to avoid the above-mentioned food items for a period of 1 to 2 months, neither patient of physician could see that the dermatitis had improved as a result of the diet.

Using the method described in the current study, we have not found oral challenge with parabens to be a useful test procedure in patients sensitive to the paraben mix. Although specific reactions were seen in 2 paraben-sensitive patients with recurrent vesicular hand eczema, the significance of this finding remains uncertain.
Keeping Well-Preserved

Cosmetic preservatives makers offer alternatives as widely used parabens come under scrutiny

Marc S. Reisch

Cosmetics ingredients must be above suspicion. As with Julius Caesar and his wife, even the hint of scandal is enough to precipitate a divorce—be it between man and woman or between cosmetics maker and suspect ingredient.

Cosmetics formulators have used esters of \( p \)-hydroxybenzoic acid as preservatives for more than 20 years. They are reliable and cost-effective, and most regulatory agencies and oversight bodies have approved their use. The tiniest amount of these preservatives keeps skin creams, shampoos, conditioners, and similar products free of bacteria,
mold, and other contaminants.

But despite their long years of service, these preservatives, widely known as parabens, have raised a few eyebrows recently. Some cosmetics makers have either cut out parabens and switched to alternative preservatives or are moving in that direction largely because of two small studies.

The first appeared in the *Journal of Applied Toxicology* [2004, 24, 5] about two years ago. Researchers studied breast tumors from 20 patients and detected the presence of minute amounts of parabens in the tissue. Since parabens are known to be weak estrogen mimics, the paper suggested a connection between the presence of parabens in breast tissue and breast cancer.

Then in September, Japanese researchers presented a paper at a conference of the *International Federation of Societies of Cosmetic Chemists* in Florence, Italy, that added to concerns over parabens. The researchers, mostly from the Kyoto Prefectural University of Medicine, applied lotion containing just one type of paraben—methylparaben—twice a day for a month to the skin of 12 Japanese volunteers. They found that methylparaben did not metabolize in the stratum corneum, the outermost layer of the epidermis, and suggested that its presence accelerated skin aging.

Critics point out that it is difficult to reach any broad conclusions about parabens based on the small number of samples in the two studies. For this reason, a number of large cosmetics makers, such as Avon and Estée Lauder, have hesitated to make changes in their formulations and have assumed a wait-and-see attitude.

At least one activist group, however, says it has heard all it needs to hear and has mobilized against firms that formulate cosmetics with parabens. A San Francisco-based group called Breast Cancer Action has encouraged consumers not to use products from Avon and Estée Lauder because many of them incorporate parabens. Breast Cancer Action, along with Domini Social Investments, which describes itself as a socially responsible investment firm, forced a vote at Avon's annual meeting in May 2003 on a resolution that would have required Avon to seek “safer” alternatives to parabens. The group was concerned about parabens even before the two studies were reported.

Avon management opposed the shareholder resolution and argued that “there are many published studies conducted by both independent scientists and agencies on parabens, some of which specifically address the issue of carcinogenicity. We believe that these studies do not support the proponents’ assertion that there is substantial scientific evidence linking exposure to parabens with increased health risk.”

The resolution did not pass. But Breast Cancer Action continues to put pressure on cosmetics makers to reformulate. The group recommends that people use cosmetics that do not contain parabens and that they patronize cosmetics firms that formulate without an ingredient that at one time seemed nearly ubiquitous. In fact, some products now on the market boast they are “paraben free.”

The cosmetics ingredient supplier International Specialty Products has been closely following the controversy over the use of parabens, according to Patrick Bowers, corporate development director. “Some of our customers are concerned, and some are not,” he says.

“Parabens are economical, broad-spectrum preservatives. They are the most widely used preservatives worldwide.”
For decades, ISP has been selling preservatives such as Germaben II, a blend of methylparaben and propylparaben with diazolidinyl urea in a propylene glycol base. The formula is active over a wide pH range. Other paraben-containing preservatives include ISP’s LiquaPar paraben oils.

“Safety is always paramount,” Bowers says. “But different customers have different needs. In our industry, perception often trumps science.” So to address customer concerns, ISP has alternatives to traditional preservatives available.

For instance, the firm’s Optiphen preservative contains phenoxyethanol in an emollient base of caprylyl glycol. Optiphen Plus adds sorbic acid to the base formulation. Optiphen is best in formulations in a pH range of 6 and above, while Optiphen Plus is targeted at products with a pH of 6 and below. “We focus on systems and blends tailored to our customers' needs,” Bowers points out.

“Parabens are economical, broad-spectrum preservatives,” asserts Reith Karl, international manager for Germany-based preservatives specialist Schülke & Mayr. “They are the most widely used preservatives worldwide,” he says, and have until recently been considered safe. It is no surprise that parabens would have been found in breast tissue, he adds, since parabens are approved for use in pharmaceutical creams.

While Schülke & Mayr's product line includes a range of parabens, it also includes alternatives. For instance, Euxyl PE 9010 contains phenoxyethanol and ethylhexylglycerin. The second ingredient “is used for better wetting action on the microbes and so kills them more effectively,” Karl says.

Though some ingredient suppliers are offering alternatives to parabens, Rohm and Haas has moved against the trend. It introduced the Neolone line of methylisothiazolinone-based preservatives and included one containing parabens. Neolone MxP, launched a year ago, is a blend of methylisothiazolinone, phenoxyethanol, methylparaben, and propylparaben. It is “cost-effective,” Business Manager Dianne Carmody says. It remains in Rohm and Haas's line because, while some customers may be avoiding parabens, some are not, she says.

Mark Chandler, technical manager for Uniqema Personal Care, a unit of specialty chemical firm ICI, says, “As far as we know, there is no technical argument against the use of parabens in cosmetic formulations.” The few studies that question the use of parabens “do not definitively point to any problems with this traditional preservative.”

But where formulators feel the pressure to remove or minimize the use of traditional preservatives, Uniqema says it can help. The firm does not make preservatives, but it has recently developed a coconut-derived phospholipid, Arlasilk Phospholipid PTM, that it says dramatically cuts down on the use of preservatives.

Each cosmetics product is different, Chandler says, and requires a customized approach. Arlasilk Phospholipid PTM has cleansing, emulsifying, and conditioning properties. “In carefully formulated hair and skin care products, it can be utilized to minimize preservative requirements and to develop self-preserved systems,” he adds.

Mike Curtis, commercial development manager for Mason Chemical, says the consumer backlash over parabens provides a lesson on how the personal care market works. When consumers look askance at an ingredient, “it is not always science that drives cosmetic reformulation.” As a result, “enhancing a formulation so that it doesn't need preservatives seems to really resonate with personal care product formulators.”
But scientists have come up with alternatives to traditional preservatives, which, in addition to parabens, include isothiazolinone and formaldehyde donors such as imidazolidinyl urea. Some studies have cast suspicion on isothiazolinone as a skin sensitizer and possible mutagenic compound. Formaldehyde donors are also thought to cause skin reactions in sensitive individuals.

At Mason, scientists combine conditioning, moisturizing, thickening, and pH-control ingredients under the Enhansys brand to make possible self-preserving cosmetics that do not require traditional preservatives. For instance, Enhansys C-110 is a blend of the exfoliant gluconic acid, the moisturizer glucono delta lactone, and the stabilizer and conditioning agent C4–18 perfluoroalkylethyl thiohydroxypropyltrimonium chloride.

Many cosmetics formulators now have programs to review and remove parabens when they can, says Jim Plaza, vice president of technology and innovation for Body Blue, a Canadian contract manufacturer of cosmetics. The firm first developed a paraben-free deodorant stick using a natural blend of ingredients. In doing so, Plaza says, it “stumbled” on a system of all-natural ingredients that is self-preserving.

By themselves, the materials “have no discernible activity,” Plaza says. “But when these ingredients are coupled, they develop unexpected synergies.” Body Blue has patented the blend and will eventually promote it under the Naturbak name. While he won't divulge the ingredients, Plaza says the firm has been working on Naturbak for three years. “Major players have tested and validated our findings” on the odorless and colorless ingredient system, he says.

Ever since the Journal of Applied Toxicology article came out, the effort to replace parabens and other traditional preservatives “got legs because of consumer perception,” says Stephen D. Hinden, commercial development director for Arch Personal Care Products. Arch has developed three new preservatives. The first, Mikrokill PCC, is a blend of phenoxyethanol, chloroxylenol, and caprylyl glycol. It is compatible with a range of skin care, hair care, and sunscreen formulations at use levels of 0.5–1%.

Another preservative, Cosmocil CQ, is based on polyaminopropyl biguanide. Approved for use in the U.S., Europe, and now in Japan, this bactericide originally replaced thimerosal in contact lens solutions and came to Arch when the firm bought Avecia's biocide business last year.

The third new preservative, Biovert, mimics a natural enzyme system that keeps bacteria at bay in saliva, tears, and breast milk. Biovert consists of glucose, glucose oxidase, and lacto peroxidase. Activated in the presence of oxygen, a biological cascade leads to an attack on fungi and bacteria, Hinden says.

“Formulators don't want to lose parabens, but they are under pressure to change because of public perception,” says Carl Cappabianca, personal care global marketing vice president at Lonza. Alternatives, he says, include the firm's Geogard Ultra, which is specifically meant to address concerns over traditional preservatives. Targeted for “leave-
on” products, Geogard Ultra combines a glucose-derived lactone potentiator that works synergistically with sodium benzoate. The glucose-derived lactone provides an added benefit: It is a skin moisturizer, too.

Despite the large number of alternatives available, parabens are not about to disappear. It will take larger studies and government action to really force formulators to find alternatives, and so far that doesn’t appear to be happening. While parabens are no longer above suspicion, most formu-la-tors are not ready to uniformly replace them.

**COVER STORY**

![Image](image_url)

**Specialty Chemicals - Introduction**

**Clean Chemistry**

Approaches abound for replacing perchloroethylene in dry cleaning

**Fresh Faces**

The often-fickle consumer drives the market for cosmetics preservatives

**Staying Flexible**

Phthalate ester plasticizers hold their own despite intense scrutiny

**Phthalate Assessed**

New report by safety panel reinforces conclusions from five years ago

Chemical & Engineering News
ISSN 0009-2347