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THE FIRST TRULY INDEPENDENT WATCHDOG FOR THOSE WORKING WITH NATURAL AROMATIC MATERIALS

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Cropwatch Newsletter 16.
Disproportionate Reactions to Health & Safety Issues.

Contents:

Editorial.

Whilst Cropwatch battles with regulators who would severely restrict the use of natural aromatics in cosmetics, general household products & biocides, on the basis of a suspicion that they may cause one or two adverse skin etc. reactions on occasion per 10,000/100,000 of end-users, other much more potentially harmful substances affecting public health go completely unchecked. For example asbestos is one such substance. Whilst mechanisms for asbestos removal from UK schools or workplaces are firmly in place, asbestos removal from private dwellings is not only financially unsupported by many local authorities, but many (e.g. S. Norfolk) do not even have a policy which suitably addresses the problem. The plain fact is that over two thousand people per annum in the UK contract mesophilia from the asbestos in their homes, and although the Health and Safety Executive will direct you to their publication: the Directory of Occupational Hygiene Consultants for you to locate expert advice, as regards action and the costs of removal, you are entirely on your own. Another area of concern is the unregulated spraying of noxious pesticides by farmers in fields where school-pupils and rural house dwellers are in close proximity to the spraying operation, a practice which has severely affected the health of many individuals. The fight for justice in this matter portrays 'the establishment' at its worst, which is seemingly unable to counter the evidence submitted to the courts by potential reformers. The matter has become not about science, but about political maneuvering - in the case described below, a refusal by the court to hear the damning evidence of the plaintive Georgina Downs, in favour of the consideration of evidence solely from DEFRA. This, in our view, is absolutely shameful behaviour by the Appeal Court Judges, which goes against every

British instinct of fair play. A higher court will inevitably overturn the decision, although if it fails to do so, the European Court almost certainly will. As Cropwatch has noted previously (over the health nuisance caused farmers raising mustard seed rape crops – see http://www.cropwatch.org/Rapeseed%20Revisited.pdf), over health matters there appears to be one rule for farmers, and one rule for the rest of us, while DEFRA busily looks the other way.

§1. DEFRA vs. Pesticides Activist, Georgina Downs.

The environmental campaigner Georgina Downs runs the one-person based UK Pesticides Campaign http://www.pesticidescampaign.co.uk/ and her campaign has been frequently featured in the media (e.g. by Leake 2006). Downs, you may remember, won an impressive victory against the UK Department of the Environment, Food & Rural Affairs (DEFRA) on 14th November 2008, when the judge, Mr. Justice Collins, accepted that Downs had produced "solid evidence" that the government had failed to comply with a European Directive designed to protect dwellers in rural areas from crop spray releases. He ordered DEFRA to reassess its policy & investigate risks to people who were exposed. It appears that subsequently DEFRA has chosen not to comply with the European Directive, by not (for example) enforcing measures to impose 5m. no-spray pesticide buffer zones on the farming community, in order to increase protection to exposed by-standers from harmful spray drift.

Instead, DEFRA appear to have successfully appealed in the high court against the previous judgment. The presiding judge in the new trial, Lord Justice Sullivan, remarked that although Downs was a most effective campaigner, she had no formal or medical qualifications (but then neither, you will note, does Lord Justice Collins). The three appeal judges chose to ignore evidence of adverse health effects gathered during Down's campaigns, and relied instead on official reports to make their judgments In our opinion the hearing was thereby derailed from being a case of DEFRA vs. Downs, as Downs was effectively gagged by the appeal judges. Instead the case turned into a propaganda exercise for DEFRA.

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All this is pretty familiar territory to Cropwatch, where 'the establishment' in whatever form it manifests, tries to marginalise and exclude anyone or any group with a contrary opinion to their policies, and relies on so called 'expert' corporate-(or farmer!) friendly opinions. As Cropwatch supporters will known we have run headlong into this policy in the biocides and cosmetics areas; it is no surprise to find it within the agricultural pesticides field as well.

Reference:

Adam D. (2009). "Pesticides activist loses fight to halt spraying." *Guardian* Wed 8th July.

Leake J. (2006) "Pesticide Nun" *The Ecologist* **36**(3), 50-57. This can be seen at http://www.theecologist.org/take_action/local_hero/270564/georgina_downs_the_pesticide_nun.html .

§2. IFRA Swoops on Transgressing Members.

It seems that IFRA still doesn't trust its own members to adhere to its set of Standards (hardly surprising, since privately, many members don't agree with them), and so hires the services of an accredited analytical business to check for members' compliance. Where an IFRA members' fragranced product is found to breaks the rules, the transgressors are asked to explain themselves to a kangaroo court - so much for IFRA's pretence of 'voluntary self-regulation'. The newly appointed 'Director of Communications' Stephen Weller announced earlier in 2009 that they have (at last) identified an IFRA-member company which has marketed a product which has indeed broken the IFRA Standards. As an aside, we should mention at this juncture that IFRA membership organisations have to pledge to observe the IFRA Standards, even though (as a puzzled EU Commissioner pointed out to Cropwatch at Brussels in 2007), adherence to IFRA Standards is not a legal requirement. Safety expert Martin Watt has pointed out (private communication 2009), the scientific robustness of trade standards, such as those drawn up by IFRA, are frequently insufficient to translate into European regulatory law, and Insiders in the fragrance industry will be wondering what took the analysts concerned so long to find a transgressor (we believe we can name twenty or so such transgressors off the top of our heads). The motive for the supposed vigilance in this area becomes clear when we remember that IFRA is largely (50%) funded by a handful of super-corporate members, who use their influence to make sure that strict adherence to regulatory rules and the considerable bureaucracy & associated costs involved, disadvantages smaller competitive companies… but of course you all knew that already!

§3. Robertet Reveals its Evidence on Melissa Oil to Cropwatch. (First published on Aromaconnection 20.07.2009).

You may remember that Cropwatch was quite puzzled by any need for IFRA's new restrictive Standard for Melissa oil in IFRA's 44th Amendment, and had requested details of three unpublished toxicology reports from both RIFM & Robertet, Grasse, which were not available in the public domain, but which were cited by IFRA as containing evidence sufficient to restrict its use in perfumery. The back-story on this matter is available in the Cropwatch Files at http://www.cropwatch.org/Meliissa%20officinalis%20-%20Cropwatch%20article%20archive.pdf, but to briefly recap, although Melissa oil & extracts occupy an important place in aromatherapy and herbal medicine, Melissa oil is virtually unused in corporate perfumery. Nevertheless IFRA had previously seen fit to ban it as an ingredient on the basis of undisclosed evidence. There seemed to be no such body of evidence within the RIFM data-base to support such a ban, and it is a complete mystery to many of us how the REXPAN bunch of professors (none of whom appear to have worked in the aroma industry) could have come to such a conclusion. This ban has now been transformed into a concentration restriction under IFRA's hyper-bureaucratic QRA system. In the interests of *Freedom of Information*, Cropwatch has compiled a comprehensive bibliography of the available literature on Melissa oil in the *Cropwatch Files* section of its website, to enable any interested parties

amongst the general public at large to make their own minds up about the need for any restriction.

Although RIFM has ignored Cropwatch's request for the withheld evidence on Melissa oil as noted above, Catherine Gadras of Robertet, Grasse very kindly responded with a summary of the test data, which is displayed at http://www.cropwatch.org/Melissa%20EO%20testing%20summery.pdf, and offered to answer any further points (see below). Accordingly we asked Robertet (on 14th June) to accurately define the botanical nomenclature of the *Melissa* species employed (was it, for example, the oil from *Melissa officinalis* L. subsp. *officinalis*?), the geographical origin of the *Melissa* herbage used to steam distill the essential oil, and the compositions of the oils employed in the research (since commercial Melissa oils vary widely – see Cropwatch's Melissa oil bibliography). We also asked, in as many words, if the Robertet team would like venture any comments on the fact that there was a complete lack of adverse human reactions in the Robertet HRIPT studies, contrary to the numerical indications of possible sensitiser activity shown by the EC3 value? Without going into too many further details, this data would seem to offer further support as to the flawed ability of the LLNA test to accurately predict sensitiser potency for aromatic ingredients, and its questionable place of this animal-based test within the over-bureaucratic QRA system. But presumably, unless a notable such as Professor Axel Schnuch stands up and gives a paper on perfume ingredients with indicatory EC3 values which *do not* produce a significant number of adverse reactions per 10,000 dermatitis patients, no action will be taken by IFRA or by the `EU's 'expert' committees to scrap this flawed QRA system (we make this comment since Schnuch's evidence seems to have contributed to the pressure on the EU Cosmetics Commission to belatedly review the situation regarding notorious 26 Allergens debacle - see *Cropwatch Files*).

We promised that if we received a further reply from Robertet regarding further details of the toxicological studies on Melissa oil, we would put it on the web in the public interest. Subsequently we recently received further information on this matter from Catherine Gadras of Robertet, as follows in §4 below:

§4. Melissa Oil & IFRA Policy (cont'd): The Further Details.
(First published on Aromaconnection 6th Sept 2009).

Pre-amble.
Those of us who have worked in the aroma trade for most of their working lives, have, at times, been highly skeptical of the knowledge & abilities of those unelected officials who would impose baffling & seemingly nonsensical regulations and codes of practice upon the trade. Sometimes we felt that we were being regulated by those who had little in-depth knowledge or experience of the subject - a feeling which has never really gone away.

Perhaps safety-orientated organisations like IFRA would have gained more credibility from some of us old-timers if they had more openly owned up to their previous errors. Yes, we accept that with improvements in experimental design

and better techniques, many of IFRA's earlier (nineteen seventies') findings on ingredient toxicology are now suspect, or have been superseded. Most importantly, the failure to use rigorously purified aroma chemicals for toxicology testing by researchers reporting to RIFM, and the use of complex botanical materials from non-expertly identified botanical sources, has thrown large sections of IFRA's previous toxicological findings into doubt since impurities and adulterants have often been responsible for adverse effects rather than the pure ingredients. From a personal standpoint, when you have been drenched in perfume & essential oils on a daily basis for 30-odd years, as many of us at the coalface have, you may feel some intuition (rightly or wrongly) for what aroma materials might be posing any handling risks. This is `why many of us laughed openly over IFRA's Quenching Hypothesis (now discredited). It is why we are still cynical over the disproportionate IFRA classifications of many materials which are supposed to be sensitising, according to the corporate-toxicological methodology involved in the QRA approach. But many of these ingredients indicated as sensitisers have failed to produce any significant numbers of adverse reactions amongst the end-users of fragranced cosmetic & household products in which they occur.

Melissa Oil: Lessons Learned.

The curious` case of the previous banning of Melissa oil as a fragrance ingredient by IFRA, gave Cropwatch an opportunity to explore IFRA's ingredient policies in detail (see previous Cropwatch reports). In so many instances, a veil of secrecy obscures the detailed experimental facts on which IFRA/REXPAN ingredient status decisions are made. Following requests by Cropwatch, Robertet Grasse, to their immense credit, were willing to share their toxicological findings on Melissa oil testing, referred to in the RIFM data-base, but otherwise not available to the general public. Subsequently we can now clearly see (in our opinion) that there was no good reason to ban Melissa oil from perfumery use in the first place, and a case for its continued restriction is heavily based on Robertet's evidence, which was not comprehensive across a range of dosages, but based on a strategy to reduce costs. This involved contriving experiments at doses which were likely to produce a positive safety outcome, rather than the prospect of funding a more extensive range of tests proving its skin safety at higher dosages. That's OK - we can easily deal with this, because it represents the truth. It's just that IFRA didn't previously reveal these particular facts about the economic restraints which have materially affected the testing strategies, for this particular ingredient.

Where do we go from here? It is apparent that we need an independent body to openly ascertain the facts about 'pure' toxicological science – as against the corporate-funded version of toxicology which we are forced to follow. It is also apparent from the mail that Cropwatch receives that there are other expert opinions out there – why must these individuals be sidelined and denied places on expert committees? Above all, Cropwatch is concerned that the low standards set out in many IFRA commercial standards may be rubber stamped & adopted

by the EU Commission, as of course has happened previously, and which may come to be an increasing trend.

With a few minor punctuation changes, the reply from Catherine Gadras is set out below (we had asked for the exact botanical identification of the *Melissa* spp distilled for essential oil (since IFRA had failed to properly define it), and for its' geographic origin & compositional details. We had further asked the Robertet team for any views on the presented HRIPT & EC3 data. We also had an exchange of mails with Michel Meneuvrier of SAPAD who provided the oil for testing (see below) & who confirmed that the Melissa plants distilled for oil were produced organically from Diois region plants.

Catherine writes (remarks shaded in grey):

"As I mentioned below Melissa EO used for testing is *Melissa officinalis* subsp. *officinalis* L cultivated in the South East of France in the region of Di (Drôme). This genuine essential oil has been provided to us by the SAPAD (Société Anonyme des Plantes Arômatiques du Diois). The sample was taken from the crop 2008. 7 to 8 levels of fresh leaves plus the flower part are used for the distillation. Please find below the range of the main constituents provided to us by SAPAD and the composition of the sample used in the most recent tests. (See attached file: Melissa-EO Composition.pdf).

The crop results from the distillation of 3 "cuts: one at the end of May and the two others from the beginning of July and at the end of August/beginning of September. The producers finds that the citral content is maximum in the third cut (greater than 50%) and that citronellal is below 10%.

2) Comments regarding safety data (HRIPT and EC3)
The LLNA has been made to determine a level of concentration at which one begins to observe induction of sensitisation. In our case 4500µg/cm2. Considering the high cost of this EO (5 to 7 tons of fresh plants to produce 1 Kg of essential oil) on one hand and the fact that we did not want to risk a positive reaction in the HRIPT, we have chosen this conservative 1470µg/cm2). This is more than adequate for perfumery use which is our business. It is quite possible that a higher safe limit for melissa EO exists but in my opinion it must be verified by testing.

PS: I take advantage of our e-mail exchanges to make some comments concerning the Cropwatch report on Melissa (page 3) that I found on internet :

I have 2 comments on this sentence below: :

"Under the draft proposals for IFRA's 44th Amendment, melissa oil (which they describe as 'genuine Melissa officinalis L.') has been downgraded from an outright ban in fragrances, to a concentration restriction in the fragrance compound (as opposed to the finished

cosmetic product). QRA data for melissa oil, which is categorised as a weak sensitiser, is presented by IFRA for the various established product categories, based on a No Expected Sensitization Induction Level (NESIL) of 1400µg/cm2."

1) Did you really mean "downgraded" ? My poor English would have expected "upgraded". (***Cropwatch comments:*** downgraded from a negative position (a ban) but upgraded to more positive position (just a restriction) - it all depends on how you look at it!).

2) I confirm to you that the QRA limits are in finished consumer products and not in fragrance compounds." (***Cropwatch comments***: on this latter point we stand corrected. Thank you Catherine!).

Addenda – Analysis Data received from Robertet as attached file mentioned above 'Melissa-EO Composition.pdf.'

Analysis of Melissa EO sample used in HRIPT test.

Component	**% FID CW**
Myrcène	0,16
Limonène	0,37
Cis Ocimène	0,12
Trans Ocimène	1,14
Para cymène	0,15
Methylheptenone	1,76
Octène 1 ol 3	0,4
Citronellal	1,3
Alpha copaene	0,34
Beta bourbonene	0,4
Linalool	1,38
Cis + Trans Isocitral	1,6
Beta Caryophyllene	14,2
Neral	23,8
Methyl geraniate	0,32
Germacrene	4,3
Geranial	33
Geranyl acetate	2,2
Delta Cadinene or delta Amorphene	0,7
Citronellol	0,2
Nerol	1,1
Isogeraniol (cis+trans)	0,24
Geraniol	1,7
Epoxydes de caryophyllene (cis+trans)	1,8
Germacradienol	0,3
Muurolol T	0,4
Thymol	2,1
Carvacrol	0,25
Alpha Cadinol	0,6
Neric acid	0,1
Geranic acid	0,3
TOTAL 96,73	

Information Stat from SAPAD

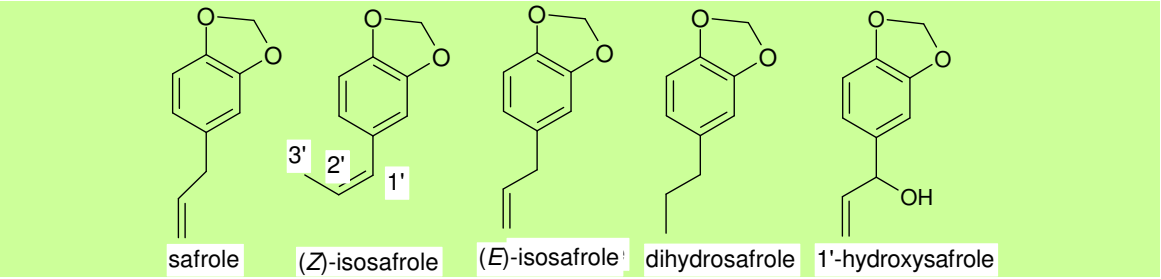
	Mini %	Maxi%	Moyenne %	Escart Type %
Methyl heptenone	**1.05**	**3.36**	**1.8**	**0.7**
Limonene	**0.04**	**0.48**	**0.18**	**0.13**
Citronellal	**0.6**	**19**	**4.9**	**4.4**
Neral +citronellol	**6.4**	**28**	**18.7**	**5.4**
Geranial + Geraniol	**9**	**38.3**	**25.6**	**7.4**
Caryophyllene beta	**10.1**	**29.6**	**18.3**	**4.4**

§5. Safrole: Human Carcinogenicity Risk Over-Stated?

[Slightly amended from its' first appearance on Aromaconnection, Sept 2009],

Pre-amble.

It almost borders on the heretical, perhaps, to suggest that the risk of human carcinogenicity from exposure to dietary safrole has been over-estimated over the years by some toxicologists, and that the existing national & international restrictions on safrole-containing ingredients & end-products can be seen as over-precautious. Weighing the evidence, a convincing case can be made that the human carcinogenic potential of safrole, if not quite negligible at low doses, is considerably less than that of ethanol (Duke 2002). As it is, the existing evidence for the carcinogenicity and genotoxicity of safrole mainly rests on a battery of experiments performed 30-40 years ago, on laboratory rodents dosed with high levels of safrole, where electrophilic metabolites generated by P450 enzymes and sulphurotransferases are identifiable as being responsible for the genotoxicity (see Cropwatch's extensive *Safrole Bibliography*, latest version at http://www.cropwatch.org/Safrole%20Bibliography%20v1.02.pdf). Different expert judgments have been made about the risk to humans from alkylbenzenes such as safrole, methyleugenol & estragole, and indeed on the relative importance for human cancer of low-dose exposures to synthetic chemicals generally (Gold *et al*. 1992). More insight into bioactivation of these (alkylbenzene) compounds in humans has been said to be required, to interpret animal data to the human situation (Jeurissen 2007).



Safrole (4-allyl-1,2-methylenedioxybenzene; CAS No. 94-59-7) is known to occurs in the following natural products:

Chinese Angelica (*Angelica sinensis* L.)
Betel oil (*Piper betle* L.)

Brown & yellow camphor oil (fractions of *Cinnamomum camphora* L.)
Yellow oil to 20%; brown oil to 80%.
Cangerana oil (*Cabralea cangerana* Saldanha)
Cinnamon leaf oil & bark oils (*Cinnamomum zeylanicum* Blume) both to 2%.
Kuromoji oil (*Lindera* spp.) to 12%
Mace oil (*Myristica fragrans* Houtt.) to 2%
Mango ginger oil (*Curcuma amada* Roxb.) to 9.5%
Nutmeg oils [E.I. & W.I.], butter & oleoresins (*Myristica fragrans* Houtt.):
E.I, oil to 2%; W.I. oil to 0.3%.
Pepper oil, black (*Piper nigrum* L.)
Piper auritum HBK oil to 90%
Sassafras oils, bark of roots, infusions of roots (*Sassafras albidum* (Nutt.) Nees
to 95%.
Sassafras oil Brazilian: *Ocotea pretosia* (Nees) Mez, to 92%
Star Anise oil (*Illicium verum* Hook f.) to 1%
Ylang-ylang oils, absolutes (*Cananga odorata* (DC) Hook. f et Thoms subsp. *genuine*) to 0.3%

…as well as in several other *Cinnamomum* essential oils (*C. burmanni*; C. *porrectum*; *C. rigidissum* etc.). It also in occurs in witch-hazel (*Hamamelis viginiana* L.), hoja santa leaves (*Piper auritum* HBK) and in many other natural herbal & spice products & preparations.

Safrole is currently classified as a carcinogen category 2 and mutagen category 3 according to the IFRA-IOFI labelling manual 2009. Since out of the three alleged human carcinogens: safrole, estragole and methyl eugenol, safrole is arguably the weakest (see below), these classifications seem somewhat arbitrary.

Substance	Hazard symbol	Risk phrases	Carcinogen category	Mutagen category
Safrole	T	R45-22-68	2	3
Estragole	Xn	R22-40-43-68*	3	3
Methyl eugenol	Xn	R22-40-68*	3	3

Classification of some Carcinogens & Mutagens according to the IFRA-IOFI Labelling Manual 2009.

[*Thanks to Penny Williams of Formpak Ltd. for drawing our attention to this labelling issue; further implications over R68 status for estragole & methyl eugenol affecting common essential oils such as Aniseed, Bay, Basil, Fennel and Pine Oil Yarmor, are discussed at http://www.formpak-software.com/active/2009/09/estragol-methyl-eugenol-r68/**].**

Previously the IARC had surmised that safrole was “Reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals” (IARC 1976); but that “No adequate human studies of the relationship between exposure to safrole and human cancer have been reported” (- IARC 1976). The weak potency of safrole as a carcinogen is illustrated by the

fact that level of safrole in the diet of rats necessary to elicit liver tumors ranges from 0.5% to 5.0% (Patri *et al.* 2002). The TD_{50} for safrole in rats was found to be 440mg/Kg/d (Gold *et al*.) compared with 51mg/Kg/d for mice. This compares with a TD_{50} value for methyl eugenol of 20mg/Kg/d for rats and 19mg/Kg/d for mice. However the TD_{50} for the proximate carcinogen 1'-hydroxysafrole was found to be 18mg/Kg/d for rats compared with 71 mg/Kg/d for mice.

The hazardous dose of sassafras oil for humans (which typically contains 80% safrole) has been put at 0.66 mg/Kg, based on experimental animal data, and a safety factor of x100; this is claimed to be way- exceeded by imbibing a standard portion of sassafras tea which has been estimated to give a dose of 3mg/Kg for a 60Kg man (Bisset 1994; Segelaman 1976). By comparison, Levy (Levy undated) gives a figure of 20 ppm safrole content of root beer before the sassafras FDA prohibition, approximating to a 5mg dose for an 8oz serving. Safrole-free extracts of sassafras have been approved by the FDA for food flavouring use, but apart from being organoleptically inferior, It is also of note that safrole-free extracts of sassafras have produced malignant mesenchymal tumors in laboratory rats (Benedetti *et al.* 1977).

Safrole & sassafras oil were banned as food & flavouring additives by the FDA on 3rd Dec 1960 (FDA Ban 21 CFR 189.180; revised April 1 2008), the ban now includes isosafrole & dihydrosafrole (the latter not being known in nature), & sassafras root bark, but in practice both sassafras oil and bark are still widely available in the US, from health food stores and internet suppliers. Safrole appears in Annex II/360 of the EU Cosmetics Directive EU 76/768, and its concentration is limited to 100ppm in finished cosmetic products (50 ppm for oral/dental use; zero for children's toothpaste). IFRA prohibits the addition of safrole to fragrances as such, and limits the safrole content of perfumes formulated with safrole-containing essential oils (basil, nutmeg, sassafras, cinnamon leaf etc.) to 0.01% (100ppm) for both skin contact & non-skin contact fragrances. These restrictions have caused a significant problem with certain fragrance styles entering the market place – for example in the deployment of cinnamon & nutmeg ingredients in masculine fougères and spicy masculine notes.

The restriction of safrole to low levels in foodstuffs was originally considered to be a threat to the economic welfare of the nutmeg trade, and so regulatory exceptions were made (note that curiously, no such exceptions are ever made for natural ingredients in the cosmetics area, presumably because the largely academic 'expert' committees in this field are unable to accurately predict the socio-economic effects of their policies since they have no commercial experience). European Council's Directive on food flavourings 88/388/EEC, amended by 91/71/EEC and implemented into UK national law in the Flavourings in Food Regulations 1992, limits safrole in foodstuffs to 1ppm, except for foodstuffs containing nutmeg (15ppm) or alcoholic drinks >25% volume alcohol (5ppm) and other alcoholic drinks (2ppm). It is of interest to note that Choong & Lin (2001) analysed 25 soft drinks, including Coca-cola and Pepsi, from

supermarkets & convenience stores in Tainan and Pingtung, for safrole and isosafrole contents in 1998, finding 20 out of 25 soft drink samples contained safrole and/or *cis*-isosafrole and the contents of safrole were up to 3-5 times the use limit of 1*μ*g/mL according to the food additive regulations.

Isosafrole (CAS No. 120-8-1), which occurs as (*E*)- & (*Z*)- geometric isomers, is a weak, non-genotoxic rodent hepatocarcinogen, classified as a carcinogen category 3 (IARC 1987) which has been alleged to occur in minor amounts in certain essential oils (such as Chinese angelica oil from *Angelica polymorpha* Max.), ylang-ylang & nutmeg oil & oleoresin, but Lawrence could not confirm its presence in nutmeg oils (Lawrence 1990), and MAFF have disputed its presence in ylang ylang & sassafras products (MAFF 1996a). However MAFF (1994) found 0.1% to 3.4% isosafrole (av. 0.3%) in 10 analysed samples of nutmeg oil and 0.1 to 2.7% (av. 0.9%) in 3 analysed nutmeg oleoresin samples (origins not disclosed). Since isosafrole usually co-occurs with safrole in certain natural products, at concentrations typically an order of magnitude lower than the safrole concentration (MAFF 1996), it was proposed by MAFF that isosafrole is an artefact formed during the processing of safrole-containing raw materials.

Safrole Metabolism.

Intraperitoneal dosing of rats and guinea pigs with safrole produces the following urinary metabolites; 1,2-dihydroxyl-4-allylbenzene, 1'-hydroxysafrole, 2-methylenedioxy-4-(2,3-dihyroxypropyl)benzene, 1,2-dihydroxy-4-(2,3-dihydroxypropyl)benzene, 2-hydroxy-3-(3,4-methylenedioxyphenyl) propanoic acid, and 3,4-methylenedioxybenzoylglycine (Stillwell *et al.* 1974). Two pathways have been proposed whereby hepatotoxic substances are produced from safrole (Dietz & Bolton 2007). The first proceeds via the P450 catalyzed hydroxylation of safrole to 1'-hydroxysafrole, and its subsequent conjugation with sulfate to produce a reactive sulfate ester, which creates a highly reactive carbocation via a SN1 displacement, which alkylates DNA. The second pathway involves the formation of hydroxychavicol via the P450 catalyzed hydroxylation of the methylenedioxy ring of safrole, which is subsequently oxidized to an o-quinone, which non-enzymically isomerizes p-quinone methide. Dietz & Bolton (2007) consider that these experiments by Bolton *et al*. (1994), Miller *et al.* (1985), Boberg *et al*. (1983), Daimon *et al.* (1997-1998) & Jeng *et al.* (2004) and the *in vitro* & *in vivo* experiments of Luo & Guenthner (1996), Gupta *et al.* (1993), Randerath *et al.* (1993), Daimon *et al.* (1998) & Daimon *et al*. (1997) prove the genotoxic effects of safrole and justify the regulatory action of the FDA & other authorities. Cropwatch takes issue with this conclusion; the mere existence of pathways in rodents fed high levels of dietary safrole which give rise to certain hepatotoxic substances does not, of itself, prove the potential for human carcinogenicity under normal living circumstances.

Although small amounts of safrole (0.63mg/Kg) have been shown to be cleared almost completely from the body within 24 hours in man & rats (Benedetti *et al*. 1977), the main urinary metabolite of safrole dosed in larger amounts is 1,2-dihydroxy-4-allylbenzene in both rats & man; 1'-hydroxysafrole and 3'-

hydroxyisosafrole were also detected in the urine of the rat, but not of man (Benedetti *et al.* 1977). Jeurissen (2007) has identified the human P450 enzymes involved in the 1'-hydroxylation of safrole, where important roles for a series of enzymes via a series of *in vitro* experiments were postulated. Lifestyles factors which may lead to poor or extensive metaboliser phenotypes, which reduce or increase the relative carcinogenicity risk, were discussed.

Also compelling evidence for humans, perhaps, lies with studies made of habitual quid chewers of betel & areca nut, where a constant body-loading of safrole may give rise to tumors over an extended time period. In particular, inflorescences of betel have been shown to contain relatively high (15mg/Kg) concentrations of safrole (Liu *et al*. 2000).

Conclusion.

The classification of safrole as a Category 2 human carcinogen and the association of risk phrase R22-45-68 with the material seems disproportionate to the risks involved to humans from its traditional uses in spices, flavours, fragrances etc. Regulators appear to be forced by some unseen hand to deny the use of any traditional natural ingredients which have been shown to carry some health risks to susceptible animals at high doses, in an attempt to construct a clean, risk-free and largely synthetic-based world of their own. That is not the world that most of us wish to inhabit, and Cropwatch believes that many will ignore any restrictions which deny us the use of those familiar materials which we associate with our lives, our heritage & our traditions.

References:

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§6. The EU Commission’s Proposals to Limit Furanocoumarins (FC’s) in (Fragranced) Cosmetic Products.

The prevention of restrictions for FC’s in cosmetic products, which occur via their presence in natural aromatic ingredients, especially citrus oils, has been the subject of a long campaign by Cropwatch (see http://www.cropwatch.org/Furanocoumarins%20-%20the%20Cropwatch%20Articles.pdf), and has included a meeting on the subject at Brussels in 2007 with EU Commission staff. Cropwatch maintains that the toxicological issues regarding photo-toxicity of FC’s are complex and incompletely understood, and that the role of photo-protective and anti-carcinogenic properties of expressed citrus oils & other FC-containing natural products have not been adequately evaluated. Many other common cosmetic materials also show photo-toxic properties, but essential oils are, once again, particularly singled out for proposed regulation (why?). We have also proposed that the answer to the problem is not the draconian limitation suggested by the EU Commission, but rather a simple labelling solution, as `already happens in the aromatherapy profession under best practice.

The Cosmetics Commissioner, Sabine Lecrenier, wrote to Cropwatch on 27th May 2009 (letter published at http://www.cropwatch.org/09-05%20Letter%20to%20Cropwatch%20signed.pdf) with a self-contradictory proposal, which on the one hand proposes that the seven marker FC’s (bergapten (5-MOP), bergamottin, byakangelicol, epoxybergamottin, isopimipinellin, oxypeucedanin and xanthotoxin (8-MOP)) should collectively not exceed 5ppm in leave-on cosmetic products and 50 ppm in wash-off products, and on the other hand, that the seven marker FC’s listed above should (also) not exceed 1ppm in products. We can only assume that the 1ppm proposal was included by mistake, but it illustrates to all concerned that the non-technical lawyer-heavy regulatory staff at Brussels have apparent difficulty in understanding the involved science. There is little more faith placed in the ‘expert’ advisory SCCP committee (now the SCCS), who are still on a learning curve after being previously criticised for failing to distinguish between linear and angular FC’s in their 2001 Opinion on FC’s.

Many of you will already be familiar with Cropwatch’s arguments on this matter. The elimination of many traditional perfume types & styles (Eau de Cologne, Eau

Fraiche and high citrus oil perfume types etc.) is inevitable if FC's are so severely restricted as proposed. The employment of real bergamot oil in fragrances, which has an FC content of up to 3.0%, will be severely curtailed. Bergamot oil's place in perfumery is unique. Its employment in male fragrances is virtually ubiquitous and represents a lot of the fresh fragrance character - examples CK One (Calvin Klein 1994), Cool Water (Davidoff 1988), Eau Savage (Dior 1966), and in female fragrances it is also virtually ubiquitous as part of top note accords e.g. Chanel 19 (Chanel 1970), Anais-anais (Cacharel 1979), Rive-Gauche (Y. Saint-Laurent 1971) & Obsession (Calvin Klein 1985). The effect of FC restrictions on the natural perfumery trade (a branch of perfumery virtually unrepresented in IFRA) will be particularly devastating. According to material seen recently by Cropwatch, IFRA and EFFA will back the EU proposals for a 5ppm FC leave on, 50ppm wash-off limit. We can say that with this departure (coupled with even more ingredient restrictions within IFRA's 44th Amendment which further impinge on natural product usage in fragrances), IFRA no longer represents the whole perfumery spectrum with its proud culture, heritage & tradition, but rather represents the narrower interests of the corporate perfumery trade, where concerns about money & profits speak louder than any considerations for defending the perfumery art. It is not to be forgotten either that the IFRA organisation got us into this mess in the first place, by introducing a Standard imposing a 15ppm limit on FC's in finished perfumes on 1st Dec 1996 (which few cosmetic/fragrance companies seem to either have been aware of, or have subsequently adhered to).

In a non-scientific appraisal of attitudes amongst aroma industry staff, Cropwatch has reason to believe that if these EU proposals on FC's are passed into law, many in the trade will simply ignore them, just as they have ignored the equally non-practical proposals over imposed peroxide limits for oils of the Pinaceae. We believe that the EU Commission is in danger of losing both its authority & credibility by proposing regulations which much of the trade will be unable to adhere to, not the least because it does not have the costly analytical equipment to (for instance), determine the byakangelicol content of expressed lemon oil (which can be considerable) or the oxypeucedanin content of bitter orange oil (which can also be considerable). In a nutshell, perfumers & regulatory staff simply do not have the necessary information to hand to be able to calculate values necessary to adhere to these proposals. N.B. In a bid to increase understanding on FC's in natural products, Cropwatch has assembled a multi-subject data-base which includes all the references we could find to the FC content of natural aromatic ingredients (see http://www.cropwatch.org/FC's%20A-Z%20listing%20v%201.05.pdf).

§7. Cropwatch's Open Letter to EU Cosmetics Commissioner Objecting to Proposed FC Limitations in Cosmetic Products.

Mrs. S. Lecrenier,
European Commission,
Head of Unit F3,

Cosmetic & Medical Services,
DG Enterprise,
BREY 10/169,
1040 Brussels.

3rd September 2009

Dear Ms Lecrenier,

I am responding to your mail to Cropwatch of 27th May 2009, regarding the proposed regulation of furanocoumarins (FC's) within the Cosmetics Directive. The proposals contained in your mail have caused some confusion for the industry, since the line restricting the seven proposed FC markers (bergapten, bergamottin, byakangelicol, epoxybergamottin, isopimpinellin, oxypeucedanin & xanthotoxin) to 1ppm is in apparent conflict to the other lines in the proposal, which limit the concentration of the sum of these markers from natural essences to 5 ppm in leave-on products, and 50 ppm in rinse-off products. Further, we consider that the inclusion of chemically unstable FC markers (such as byakangelicol, and to a lesser extent, bergamottin) is of dubious safety value, and that this proposed legislation is over-hasty, since the overall risk/benefit effects of many FC's have not been adequately evaluated by the Commission - SCCP Opinion 0942/05 for example failed to provide any direct evidence whatsoever of in-vivo human photo-carcinogenicity from FC's, and its conclusions are at variance with the findings of other researchers such as Chouroulinkov et al. (1989), Dubertret *et al*. (1990) & the EMEA (1990)(see attached file). Moreover, it is still the case that no single in vitro test currently exists which can predict the photo-carcinogenicity of furanocoumarins, and that photoclastogenicity has been associated with other very commonly used cosmetic materials such as zinc oxide and titanium dioxide (see attached file). Cropwatch does not understand why investigations into the risks posed by these inorganic materials has not been undertaken, and why it always natural aromatic ingredients which seem to be selectively singled out for investigation.

Cropwatch is opposed in principle to any proposal to regulate the FC contribution from natural ingredients within fragranced products, & our view includes the opinions of much of the natural perfumery trade (which is largely unrepresented within organisations such as IFRA, EFFA & within corporate perfumery). We feel that a labelling solution, advising users to cover up affected skin areas from actinic light for 12-24 hrs after application of FC-containing fragrances would adequately address any alleged photo-toxicity concerns. This is already best practice in aromatherapy where massage clients are treated with FC-containing citrus oils (up to 2.5% in carrier). Further, a labelling solution would also prevent accusations of 'cultural vandalism' by the EU Cosmetics Commission, if these proposals to drastically limit FC's in fragranced products result in the effective removal of indispensable natural (citrus) ingredients. This outcome would cause the disappearance of complete classes of fragrances such as Eau de Colognes, Eau Fraiche and citrus-based compositions. Further, we have identified officials

within the EU Parliament who are very concerned about the effect of such proposals on the cultural heritage and art of perfumery, a topic which we believe needs to be further considered by the EU Commission.

Since there was little comprehensive information available within the public domain on FC contents of natural perfume ingredients, and we found little knowledge of the subject amongst the professional perfumers that we contacted, Cropwatch has assembled some data-bases on the subject (one such is attached) which additionally contain some critical comments & over-views. Even now, only the larger aroma concerns have the (expensive & sophisticated) equipment required to accurately determine FC concentrations in natural ingredients and finished perfumes. So these proposals, if passed into EU legislation, would be very divisive, since they will economically discriminate against small citrus oil producers and SME's (- COLIPA has, we believe, previously commented on the socio-economic responsibilities of the Cosmetics Commission when considering the passage of this type of legislation). Cropwatch has further looked into claims made by leading aroma companies that the flavouring industry had solved the problem of FC removal from citrus oil ingredients several years ago, and found that the claim was largely unsubstantiated.

Lastly Cropwatch is concerned that evidence may be submitted to the SCCS, which is not freely available within the public domain, and that the SCCS may use such unseen evidence on which to base their opinions. One such piece of evidence (on DNA-bergamottin interactions) by Prof. David Kirkland of Covance Labs, commissioned by RIFM, has been summarised in an IFRA newsletter, but the experimental details have not been fully disclosed. Both the author of the work and RIFM have refused requests by Cropwatch to view the data. We feel that the non-publication of any such secret safety data which may be submitted to the SCCS (for their eyes only), would be completely unacceptable where matters of public safety are concerned, and would not fulfill the requirements of complete transparency.

Best regards,

Tony Burfield
Co-founder Cropwatch
www.cropwatch.org

§8. Save Our Herbs Campaign.

Cropwatch strongly supports the Save Our Herbs: the Campaign for the Protection of Herbal Medicine, and we reproduce their e-mail/press release below. Please be sure to make a visit to their website www.saveourherbs.org.uk

Save Our Herbs

The Campaign for the Protection of Herbal Medicine

A new campaign group has formed to oppose changes to UK Medicine laws and proposals for the Government to regulate herbalists.

Cropwatch, The National Health Federation – UK (NHF), International Register of Consultant Herbalist and Homeopaths (IRCH), Unani Tibb (Mohsin Institute), Alliance of Registered Homeopaths (ARH), Independent and Individual herbalists Philip Evans, Jennifer Wharam and Chris Caton, have formed an Alliance 'Save Our Herbs; the Campaign for the Protection of Herbal Medicine' www.saveourherbs.org.uk

We urge everyone, worldwide to take a look at our website, sign our petition, respond to the DH recent consultation document http://www.dh.gov.uk/en/Consultations/Liveconsultations/DH_103567 , write to their MP's, join our supporter's forum and spread the word!

Your Traditional Herbal Medicines Need You.

Without your support our traditional herbal medicines could become obsolete, inaccessible and your freedom of choice taken from you.