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

E: info@cropwatch.org T: ++44 (0)7771 872 521

Opinion:

Citrus Ingredients Turn Sour: IFRA Takes the Pith!

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Executive summary:

IFRA, anxious not to be seen to be behind yet another industry-stopping regulatory ingredient disaster, have this time sought to spread the responsibility for a severe limitation on (citrus) furanocoumarins in cosmetics products, via attempting a collaboration between (so-far) unidentified parties within “the industry”, and the EU Commission. The reason for the proposed furanocoumarin limitation is precautionary & not based on a tide of adverse consumer reactions, but based on fears about the incompletely understood photomutagenic & photocarcinogenic potential of individual furanocoumarins. Up to now, IFRA standards for individual citrus oils have been based on their bergapten contents, & have been universally observed by the fragrance industry. Conversely, the more recent IFRA standard of 15 ppm max of furanocoumarins in cosmetic products, has been largely ignored. The prospect that a forthcoming EU Directive would impose a 1 ppm limit for any furanocoumarins (including those not thought harmful) contained within a cosmetic product has spread concern & alarm throughout the industry about the future of citrus ingredients.

Accordingly, six major marker furanocoumarins have been identified by IFRA, and their concentration in any combination within retailed fragranced cosmetics is proposed not to exceed 5 ppm for products left on the skin, and 50 ppm in wash-off products. The six chosen furanocoumarin markers are bergapten, bergamottin, byakangelicol, epoxybergamottin, isopimpinellin & oxypeucedanin. IFRA base their proposal on a stated knowledge of the toxicological profile of xanthotoxin (8-MOP), and faith in UVA filters to “eliminate the photo-toxicity of furanocoumarins”. A proposal to pioneer analytical methodology for furanocoumarin estimation by industry is also mentioned. Since three of these six marker furanocoumarins contain reactive epoxide groupings which will, for example, readily hydrate to corresponding alcohols or diols in the presence of acids (which are obviously present in citrus juices), and at

least one other is unstable in alcohol in the presence of UV-light, we can say that the furanocoumarin content of citrus oils ingredients will be processing dependent, as well as geographic location & species/subspecies dependent. Since the site of synthesis of furanocoumarins in citrus trees is not known with any degree of certainty, and since grafting is very common in the citrus plantation industry, grafting onto foreign rootstocks may throw up yet further anomalies. As it is, individual furanocoumarins may well degrade or interconvert over time in the finished fragranced product.

As far as Cropwatch can reasonably ascertain, IFRA have presented a controversial, self-serving & scientifically-slanted Risk Assessment on furanocoumarins to the EU Commission for future discussion. The Risk Assessment draws on a carefully selected narrow range of evidence (you can verify this yourself from the accompanying document) and so is not scientifically neutral, but rather is sympathetic towards the IFRA-RIFM bias for toxicological imperialism, which has helped them establish their present powerful position over the industry. Not for the first time, the Assessment also apparently contains privately commissioned research material on furanocoumarin toxicity which is not available within the public domain, in apparent contradiction to the European Transparency Initiative which includes "Access to documents" - see http://ec.europa.eu/commission_barroso/kallas/transparency_en.htm. If this hidden material is eventually published after an SCCP Opinion has been formed, or a regulatory decision is adopted, any opportunity for peer-review or for criticism by interested parties ahead of the event, will have been lost. This is not in the spirit of open government.

In his speech: "The European Transparency Initiative: an Issue for Berlin?" given in October 2007, Siim Kallas, European Commission Vice-President, announced that:

"Transparency is neither a threat nor a judgment. It simply ensures that what we do is open to public scrutiny. If we work soundly, it will enhance our credibility - It is an opportunity, offered to the lobbying profession and I sincerely hope that it will be received as such". It is not clear to Cropwatch whether the full initiative which includes access to documents is being put into practice but it is announced on the link given above that "The Commission adopted the Green Paper on a European Transparency Initiative on 3rd May 2006" (Cropwatch is awaiting clarification on the exact status of the ruling from the Vice-president's office).

The disastrous implications for severe restrictions of natural citrus ingredients in perfumery has already been previously highlighted by Cropwatch at <http://www.cropwatch.org/nlet6.htm>, but up to now, the fragrance industry would have been unable to implement any new legislation based on the 6 marker furanocoumarins stipulated above,

because it has insufficient analytical data on their occurrence within natural perfumery ingredients. Conflicting information on furanocoumarin concentrations within natural ingredients has been previously available from IFRA/RIFM sources, data which is often at variance with scientific findings published elsewhere, & which serves to underline the high variability of furanocoumarin occurrence, even within the same individual essential oil. In addition, the economic resources needed to buy sophisticated equipment to analyse natural ingredients for their furanocoumarin contents is beyond the capabilities of small companies (some furanocoumarins are too unstable to be assessed accurately by GC). Cropwatch has attempted to summarise some of the available information available to date on this topic, in an accompanying *Furanocoumarins – Properties & their Distribution in Natural Aromatic Ingredients: an A-Z Listing* document. IFRA's precautionary proposal to further restrict furanocoumarins in retailed cosmetics precedes the necessary science to back it up; the situation has all the negative potential of previous EU regulatory debacles in which IFRA-RIFM played an unfortunate part e.g. the '26 allergens' disaster, dithering over oakmoss restriction, & the validity of the 'quenching' phenomena to name but three – the first-mentioned debacle costing the industry \$ millions in reformulation costs, caused employment losses & loss of markets for essential oils. In addition the SCC(NF)P's previous partiality in its Opinions with respect to furanocoumarin toxicity has been breath-taking – for example in Opinion SCCNFP/0765/03 where selective evidence on PUVA was considered (important published work on this topic was missing), & inconvenient counter-evidence was irrationally dismissed. The aroma industry cannot allow political situations like this to keep arising, we need informed judgments & decisions based on good science. It also needs to challenge IFRA's self-appointed leadership & proposals in these matters; they are often not in the best interests of the perfumery art - they are in the best interests of toxicologists' careers.

The problem of the phototoxic potential of cosmetic products may not start & end with furanocoumarins in citrus oils, however. Hans *et al.* (2008) examined ten lipsticks & eight facial creams and found them to absorb UV/visible light, be photosensitising and be capable of generating reactive oxygen species. Verma *et al.* (2008) tested eight face creams using a DhSalpha strain of *Escherichia coli* as a test system for phototoxicity, finding one face cream phototoxic. Zinc oxide and titanium dioxide show photocatalytic properties (Theogaraj *et al.* 2007, Verma *et al.* 2008). Strangely though, it is always the natural ingredients used in cosmetics which get the over-attention from toxicologists. You might want to ask yourself why this is, who exactly are the people responsible for this promoting policy, and what do they gain by doing it.

Dufour E.K., Kumaravel T., Nohynek G.J., Kirkland D. & Toutain H. (2006) "Clastogenicity, photo-clastogenicity or pseudo-photo-clastogenicity: Genotoxic effects of zinc oxide in the dark, in pre-irradiated or simultaneously irradiated Chinese hamster ovary cells." *Mutat Res.* 607(2), 215-24.

Hans R.K., Agrawal N., Verma K., Misra R.B., Ray R.S., & Farooq M. (2008) "Assessment of the phototoxic potential of cosmetic products." *Food Chem Toxicol.* 2008 Jan 8.

Theogaraj E., Riley S., Hughes L., Maier M. & Kirkland D. (2007) "An investigation of the photo-clastogenic potential of ultrafine titanium dioxide particles." *Mutat Res.* 634(1-2), 205-19.

Verma K., Agrawal N., Misra R.B., Farooq M. & Hans R.K. (2008) "Phototoxicity assessment of drugs and cosmetic products using *E. coli*." *Toxicol In Vitro.* 22(1), 249-53.

In Slightly More Detail...

1. According to IFRA's information Letter IL 799, "the industry" (participatory identities withheld, but reportedly certain citrus concerns and fragrance customers), RIFM (the industry-funded, New Jersey-based, research organisation) and the EU Commission have reportedly embarked on "a collaboration" which has resulted in a Risk Assessment on Furanocoumarins in Cosmetics which "was shared with the European Commission at the end of 2007". The availability of this Risk Assessment to the general public is unclear, in itself quite unforgivable bearing in mind that this issue has unsettled & bitterly divided the essential oil business & its customers over the last 1-2 years.

2. A very condensed read of IFRA's reasoning in the Risk Assessment includes the point that much of what little we know about the photo-carcinogenic potential of furanocoumarins comes from psoralen – UVA (PUVA) treatments for psoriasis & other skin conditions, a conclusion previously muted by the UK's Department of Health in 1998. These studies, investigating repeated PUVA patient treatments carried out with oral or topical doses of single (& sometimes impure) furanocoumarins, sometimes together with topical application of crude coal tar, under exaggerated exposure conditions on compromised skin, tell us little about the overall risk/benefits of those complex biological materials which contain a number of furanocoumarins (some with anti-carcinogenic & other beneficial properties), used for a different purpose in fragrances. It also has to be remembered that the actual mode of action of PUVA therapy is not known (Viola *et al* 2008), and that (in spite of the information in IFRA's risk assessment) tar and repeated UV treatments alone also pose risks (see accompanying document). It is important therefore not to be swept away by fashionable dermatological opinion & toxicological dogma when trying to independently assess the overall risk associated with furanocoumarins in citrus oils & other products intended for a cosmetic purpose.

In a separate move, IFRA recommends that the addition of UVA absorbers in fragrances will reduce photo-toxicity risk, but the addition of UV absorbers to EDT's (eau de toilettes) & perfumes is already common practice by many perfume manufacturers, albeit carried out for colour & chemical stability reasons. Dubertret *et al* (1990) had previously remarked: "...despite their promising protective effect in vitro, UVB and UVA sunscreens at low concentration (0.5%-

1%) in perfumes cannot suppress the phototoxicity of bergamot oil on human skin". There is also some evidence (ignored by IFRA) that some sunscreens have actually worsened adverse user reactions of applied fragranced products. Putting these inconvenient facts to one side, it might be asked: why stop at UVA absorbers? Why not, as Cropwatch has previously suggested, also potentially modify the hazard labeling of fragrances by adding anti-irritants to perfumes containing irritating ingredients, and anti-allergens to allergen-containing perfumes?

Dubertret L., Serraf-Tircazes D., Jeanmougin M., Morliere P., Averbek D., & Young A. R. (1990) "Phototoxic properties of perfumes containing bergamot oil on human skin: Photoprotective effect of UVA and UVB sunscreens." *Journal of Photochemistry and Photobiology B: Biology* 7, 251-259.

Viola G, Fortunato E, Ceconet L, Del Giudice L, Dall'Acqua F, Basso G. (2008) "Central role of mitochondria and p53 in PUVA-induced apoptosis in human keratinocytes cell line NCTC-2544." *Toxicol Appl Pharmacol.* 227(1), 84-96.

3. The IFRA Risk Assessment apparently contains several key RIFM reports on the toxicity of individual furanocoumarins which are not available in the public domain, to the best of our knowledge. Cropwatch has previously specifically asked the Regulator for two of these individual reports, but our request has so far not been fulfilled (Cropwatch understands from contacting one of the authors of the reports, and from a member of the Brussels staff, that there might be some legal wrangle over 'ownership'). The non-publicly available reports, to the best of our belief, include the following items:

Research Institute for Fragrance Materials, Inc. (2002). "Bergamottin: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*, in the presence of ultra violet light. RIFM Report number 41130." This report has been submitted to the European Commission.

Research Institute for Fragrance Materials, Inc. (2007). "Bergamottin: Induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells in the presence of ultra violet light. RIFM Report number 52420." This report has been submitted to the European Commission.

Research Institute for Fragrance Materials, Inc. (2003). "Isopimpinellin: Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*, in the presence of ultra violet light. RIFM Report number 42994." This report has been submitted to the European Commission.

Research Institute for Fragrance Materials, Inc. (2007). "Isopimpinellin: Induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells in the presence of ultra violet light. RIFM Report number 52421." This report has been submitted to the European Commission.

We would refer readers to the "Access to documents" policy in the EU's European Transparency Initiative above, but this is not a unique occurrence: looking back over several previous SCC(NF)P Opinions, decisions made on evidence within non-publicly available documents appear commonplace.

4. **The meat of the IFRA-RIFM proposal** is to limit furanocoumarins in fragranced cosmetics to 5 ppm for leave-on products, and 50 ppm for wash-off products. Six furanocoumarin markers are to be used to estimate these levels

from natural (mainly citrus oil) sources. These are: bergapten, bergamottin, byakangelicol, epoxybergamottin, isopimpinellin & oxypeucedanin. Since cold-pressed citrus oils can contain up to several thousand ppm of these materials, this proposal would pretty-well represent the end for normal citrus ingredients within alcoholic perfumery. In spite of this, IFRA have suggested that they, "the Industry", for whom it increasingly seems to be the self-appointed spokesperson, meet with DG-Enterprise/DG-Sanco "to explain & discuss its proposals in more detail." An independent, questioning or critical voice is, apparently, not to be present at this proposed meeting. Further, from the non-scientific poll that Cropwatch has recently carried out amongst working perfumers, all have expressed the intention of not to take any notice of any further restrictions on citrus ingredients.

5. The rationale of the IFRA argument in the Risk Assessment, you will not be surprised to learn, is completely biased towards that selected evidence which suits IFRA's toxicological cause, view-point & status. An independent review of their Risk Assessment plus a full literature search is therefore absolutely essential in the interests of a correct ethical regulatory code of procedure, in case this biased Risk Assessment is subsequently spoon-fed to the SCCP 'expert' committee. So far the track-record of SCCP Opinions on furanocoumarins has been so inexpert, that their previous Opinions have not been generally supported; indeed their findings been subsequently picked apart as impractical by all interested parties (see accompanying '*Furanocoumarins – Properties & their Distribution in Natural Aromatic Ingredients: an A-Z Listing*' document).

6. Perfumers & technologists do not have the information on furanocoumarin concentration levels within citrus & other FC-containing ingredients to be able to adhere to the 5 ppm/50 ppm restrictions mentioned above. Not only is the information not available from trade ingredient suppliers, but the methodology & associated equipment to ascertain these levels are also not available as standard, in all but the largest of the aroma mega-corporations. That information which IFRA has supplied to date on FC concentration in ingredients is often at variance with IFRA's own previously supplied information, or published by researchers elsewhere (see accompanying '*Furanocoumarins – Properties & their Distribution in Natural Aromatic Ingredients: an A-Z Listing*' document). Further, no processing, geographic or botanical origins are given for the natural sources of the furanocoumarins-containing ingredients by IFRA. As Couchi & Barth remarked way back in 1975, "The content of bergapten in citrus oils is difficult to specify with any certainty because its content depends on the origin of the oil and the way in which it is identified." The authors could so easily have extended this remark to other furanocoumarins such as oxypeucedanin, oxypeucedanin hydrate, bergamottin etc. but the quote illustrates the point that IFRA-RIFM supplied data to date cannot be relied on for any sort of accurate prediction of furanocoumarins levels in natural ingredients. Ultimately, they have to be determined by the user. IFRA have foreseen this consequence, and are apparently devising an analytical procedure (Spring 2008) to determine the six

marker furanocoumarins. No doubt this will end up as another example of legislative discrimination against the interests of small companies, unable to spare the resources & expense to fulfill these proposed analytical requirements.

Chouchi D. & Barth D. (1994). "Rapid identification of some coumarin derivatives in deterpenated citrus peel oil by gas chromatography" *J Chromatogr A*. **672**(1-2), 177-83.

Conclusions. So there we have it. A slanted Risk-Assessment based on only some of the evidence, and by the sounds of it, a proposal for a forthcoming stitch-up on what to do next between shadowy & currently non-identified industry moguls & compliant fragrance customers (presumably all IFRA/RIFM members), the EU Commission & IFRA-RIFM itself. The latter two parties, of course have a *raison d'être*, which involves the perpetual generation of safety policies to justify their salaries & positions, whether needed or not. The more curious participants in all this are the representatives from big industry, some of whom have more recently expressed their concerns to Cropwatch over the fact that safety legislation which affects natural ingredients is now out of control, and is disproportionate to the consumer risks involved. So why they didn't oppose any attempts to restrict citrus oils in fragranced cosmetics, and help build up an alternative policy is completely beyond our understanding, but it possibly shows how bowed & emasculated industry leaders have actually become in the face of burgeoning programs of bewildering (over-) precautionary legislation.

The information supplied in this Opinion document is believed to be accurate, but views, comments, criticisms, corrections or additional material can be forwarded to info@cropwatch.org for consideration in future communiqués & updates.