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Call for Journal of New England Medicine to publish a retraction re the recent article: ***Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oil***. (published: New England Journal of Medicine 365 (5) pp 480-485 D. V. Henley, Ph. D., Natasha Lipson, M. D., Kenneth S. Korach, Ph. D. and Clifford A. Bloch, M. D.)

A critique after consultation with numerous research scientists by Christopher Dean, Chairman of the Australian Tea Tree Oil Industry Technical and Safety Committee. February 2007

The recent reports alleging that Lavender and Tea Tree Oil may be causing breast growth in very young boys has very little substance, is a product of poor reasoning, and is cast into doubt on many grounds. The following article challenges the poor conclusions and methodology, and calls on the New England Journal of Medicine for a retraction of this data and the unwarranted conclusions that give the impression that this has the endorsement reserved for thorough, well reviewed science. This article focuses on the Tea Tree Oil allegations in particular, which is the special knowledge area of the author.

Many researchers and scientist have looked at this article, and raised concern and alarm at the poor methodology and conclusions which are certainly not supported by science.

When such science is amplified by publication in a respected Journal, and the media beats up the story, it has damaging consequences out of all proportion to the facts. This article was uncritically reported around the world causing alarm and commercial impacts and fear. Is this responsible?

One doctor in one town reports 3 cases in close succession and promotes as a scientific conclusion that Tea Tree Oil is a causative agent – even though only one of the 3 had any, and that a very tiny, exposure to Tea Tree Oil. There is no good science to link this with the Gynecomastia, while there are dozens of other plausible hypotheses that are not even considered. From this poor reasoning this expert is able to make a claim and create a climate of fear that is responsible for causing millions of consumers to be fearful of what they are using and avoid an excellent proven therapeutic product which offers them major benefit. Bad science outcome indeed. The Tea tree industry around the world has a long history of documenting all adverse events reported – and two of the largest companies selling retail products, with global sales of over 150 million units of tea tree products over three decades, have never had a single instance of this bizarre side effect reported.

Let's review the facts:

This article does not provide the type of scientific reasoning which one might expect from a respected medical journal. It suggests an association but not a logical connection between prepubertal Gynecomastia and lavender and tea tree oils. **The application of lavender oil and of tea tree oil in the case studies is purely anecdotal. In only one case was tea tree oil involved even anecdotally.** This does not seem to fit with the title of the article or with the unsupported conclusion in the summary.

This paper consists of two separate parts which have no scientific connection. Part one describes three clinical case studies of prepubertal Gynecomastia. Part two describes a cell culture assay of the estrogenic activity of lavender oil and tea tree oil. In the summary we find the statement "We conclude that repeated topical exposure to lavender and tea tree oils probably caused prepubertal Gynecomastia in these boys." **No scientific basis for this conclusion is stated** nor can it be found in the article.

A scientific basis would require that dosages and routes of administration could be related to each other quantitatively. The cell culture studies show quantitative dosages for lavender oil and for tea tree oil. There are no quantitative dosages in the clinical case studies. The route of administration is defined in the cell culture study. It is by direct application to unprotected cell culture medium. The routes of

administration for the case studies and even the materials applied in the three case studies are different. They are only by applied by topical administration. In two of the case studies only lavender oil was applied. In one case a product containing unstated amounts of lavender oil and tea tree oil was applied via shampoo and hair gel. In only one of the cases was any amount of any oil product applied via a leave-on skin topical treatment. In the other two cases only a rinse-off product was used. The quantities of oils used in the cell culture are vastly greater than would be possible to achieve by normal cosmetic application of products yet there is no acknowledgement of this.

Skin Penetration studies show that only 3 components of this complex mixture penetrate the skin when applied topically, and further that evaporation removes over 90%.¹ Even if the results seen in the in vitro MCF-7 test is correct (which it may not be), it is unlikely that a TTO mixture is able to cause oestrogen receptor activation in the body since the TTO complex is altered following breakdown/metabolism on the skin. Skin penetration studies for Tea Tree Oil conducted at the University of Queensland by Dr Sheree Cross (unpublished) have clearly shown that only extremely small amounts of 3 of the over 100 components found in TTO have been found to penetrate the surface of the skin so that any oestrogen receptor activity by TTO in vitro is not relevant to topical application of TTO products. This may well be true with Lavender as well. There is nothing in the literature that indicates that these components (terpinen-4-ol, alpha-terpineol and 1,8-cineole) have estrogenic receptor activity in vitro or in vivo.

The paper discusses three case studies - only Patient 2 was exposed to TTO and only in a styling gel & shampoo. From the usage of styling gel, the possibility of skin absorption is very low (as the gel is applied to the hair, not scalp). The composition of the actual shampoo that was used is known - it is a well formulated product of less than 1% TTO (not a commercial secret - it is easy to determine by solvent extraction & GC of T4-OI). The expected deposition rate of TTO from a normal surfactant based shampoo like that used by Patient 2 is very low - shampoos are, after all, designed to remove hydrophobic materials, not deposit them - so the likelihood of skin absorption of tea tree oil resulting from use of this shampoo is very low. Additionally, Patients 1 & 3 were exposed only to lavender oil, Patient 2 to lavender & TTO. Alternatively, all three cases may be due to some other material in these boys environment. The fraternal twin of one of the boys apparently using the same materials was not affected. Note that all 3 affected boys lived in the Denver area, yet no other environmental or health factors were considered.

When they received this information from Bloch, Henley and Kenneth Korach, both researchers at the National Institute of Environmental Health Sciences, performed test tube experiments of the effects of lavender oil on breast cancer cells. They also decided to test tea tree oil because of Dr. Bloch's request. They observed that both oils exhibited "estrogen-like" qualities on the cells. At the annual meeting of the National Endocrine Society held in Boston in June 2006, Henley reported the results of the research, which was subsequently published on February 1, 2007. What Henley's report failed to mention is that there are literally thousands of harmless natural oils and other natural plant substances that exhibit similar "estrogen-like" qualities when applied directly to a cell culture. Just a few common examples of products that have similar effects as essential oils in similar tests are: soy, hops, garbanzo beans, red clover, lentils, flaxseed, sunflower seeds, alfalfa sprouts, liquorice, and ginseng. Were these boys screened for liquorice consumption or garbanzo beans or one of these other hundred of suspect substances each?

Dr. Henley told a representative from Melaleuca Inc, a USA corporation selling Tea Tree oil products, that while he was being interviewed by reporters about the report, he had the definite impression that they were trying to get him to say that lavender oil and tea tree oil cause Gynecomastia so that they could publish a headline that these products should not be used. Scaring consumers about dangers of 'safe' products sells papers (and gives exposure to scientific Journals in the face of their credibility). Mainstream Channel 10 news in Australia carried a 3 minute prime time segment on this article warning mothers of the risk of using tea tree oil products. Henley told Melaleuca Inc. that he was concerned about how the stories had come out as they just took portions of what he said instead of publishing everything he said. Henley emphasized that the research does not conclude that either lavender oil or tea tree oil are the direct cause of the Gynecomastia in the young boys - but that there "may" be a correlation. He pointed out that the only common ingredient among all of the products used by the patients was lavender oil and that only one boy had used a product that contained both lavender oil and tea tree oil. In his report Henley cautioned patients of prepubertal Gynecomastia to avoid repeat exposure to these essential oils, but in the phone interview he said there is not nearly enough evidence to indicate that people should stop using products with lavender oil or tea tree oil, even young boys.

It seems very odd to us that tea tree oil was even mentioned in this story. It appears that lavender oil is the only common substance identified as being used by the three boys in question. It appears that the only reason that tea tree oil was mentioned in the story was because the source of lavender for one of the three boys was a Tea Tree Hair Gel and Shampoo. There does not appear to be any evidence whatsoever that the symptoms of that one boy had anything to do with Tea Tree Oil. Industry records certainly support this conclusion. Over the past 21 years the two leading companies supplying tea tree products, Melaleuca Inc and TP Health Ltd, have sold over 150 million bottles of product containing Tea Tree Oil. Both companies maintain meticulous adverse event reporting records. At the time of writing there has never been a single case of prepubertal Gynecomastia reported to either company anywhere in the world in all those years.

Additional poor methodology and erroneous conclusions are to be found in the in-vitro study – the second part of this flawed research. This is a unique protocol with no relationship to any other body of work. Apart from flawed technique, there is the absurd conclusion that to achieve equivalence in the human clinical situation would require 40 bottles of shampoo per dose for a 20Kg child (see below). No responsible scientist should draw conclusions on such grossly distorted comparisons.

The procedure for dosing the essential oils into the cell culture medium is not fully described in the article. It is stated that the oils were dissolved in dimethylsulfoxide before addition to the cell culture in the text. In the figures it is stated that the solvent control was ethanol. It is not clear which of these solvents was actually used. Nor is it clear whether the same amount of solvent was added to the cell culture at the different dose levels. Dismissing this discrepancy there is a technical problem with the cell culture studies in that the quantities of oils added to the cell cultures exceed the solubility of the oils in water and presumably also the solubility in the culture media. For example the addition of 0.01% of lavender oil corresponds to 100 mg/l of oil. This is a considerable quantity of free, insoluble oil. Thus the distribution of the components of the oils in the cell culture is not controlled and free droplets of oil would be floating around at the higher concentrations. The potential effects of this on the assays are unclear. It could certainly either add to the variability of the assay or possibly lead to unpredictable results. The authors note that lavender oil was cytotoxic at levels above 0.025% oil. They do not state whether they tested for long term cytotoxicity at the lower levels. By comparison the addition of nanomolar amounts of estradiol (0.28 micrograms per litre) would not lead to apparent physical separation.

If we attempt to equate the level of 0.01% lavender oil used in cell culture to a human dosage the quantity would be 0.01% of the body weight or a systemic dose of 100 mg/ kg. The quantity of topically applied lotion or cream required to achieve this type of a systemic dose would, of course, be enormous. Even if the lotion contained the improbably high amount of 10% lavender oil and even if the transdermal delivery were as improbably high as 10% a 20 Kg child would require a single dose of 200 g of lotion.

In the case of a rinse off product such as a shampoo or bar soap the quantities become quite ridiculous. The maximum amount of tea tree oil which is practically incorporated into a shampoo or bar soap is about 1%. Further since these are administered as rinse off products the potential for transdermal transport is much less than for a lotion or cream. Let us estimate it with the improbably high figure of 1%. To achieve the 2.0 g systemic dosage required for a 20 Kg child via 1% transdermal delivery of a 1% product we would require an application of 20 Kg of product. Attempt to visualize this process. This would correspond to about 80 bath sized soap bars or 40 bottles of shampoo.

To summarize:

- In only one of the case studies does the product claim to contain tea tree oil even qualitatively. The conclusion that Tea Tree is a causative agent with only one case study is preposterous. It ignores

numerous other hypotheses.

- There is no discernable dosage of lavender oil or tea tree oil in the three case studies.
- The authors make no attempt to relate the dosages of lavender oil and tea tree oil in the case studies to the dosages used in the cell culture experiments
- The authors do not account for the improbability of transdermal delivery of oil components from a lavender oil lotion (Case 1) or from a lavender oil and tea tree oil shampoo (Case 2) or from a lavender oil soap bar (Case 3) Nor do they note that what transmits is very different from the whole oil mixture applied directly to a cell, and nor do they consider other materials in these products.
- The actual components of lavender oil and of tea tree oil are almost totally chemically distinct from each other; it is unlikely that they would have similar effects. The paper claims the opposite.
- The quantities of lavender oil and tea tree oil which elicited a response in the cell culture studies are vastly greater than the quantity of estradiol in the positive control treatment. The difference is a factor of 100,000 to 1,000,000. Thus if the studies do show any estrogenic activity it is at a level one hundred thousand to one million times less than that of estradiol, the positive control.
- The amounts of lavender oil and tea tree oil which elicited a positive response are stated as concentrations as 0.01% to 0.025%. At these nominal concentrations these water insoluble oils will physically separate from water and presumably from the cell culture medium. Thus there will be droplets of pure oil floating around in the culture. It is incorrect to refer to these amounts as concentrations due to this fact.
- The authors do not state exactly how the oils were added to the cell cultures. In the text they state that they were dissolved in dimethylsulfoxide before addition to the cell culture. In the figures they state that the solvent was ethanol. It is not clear which was used or whether the amounts of solvent added to the different concentrations were the same. In either case however one would expect physical separation of oil droplets at concentrations as high as 0.005% and above.
- The authors make no reference to these huge differences in dosage and in potency or the physical difficulties in the cell culture experiments cited above.
- There is no supporting field data from decades of actual exposure that supports this conclusion. None.

In short the authors ignore numerous alternate possibilities and draw an unsound conclusion from non significant and very noisy data.

This publication is, to say the least, unscientific. The conclusion stated in the summary is not supported by the cell culture studies. The authors show no curiosity at all about the enormous difficulties in attempting to connect the cell culture studies with the case studies scientifically. It is disappointing to see the New England Journal Of medicine publishing such work uncritically, allowing such material to damage its own reputation and to create unwarranted alarm and commercial damage around the world. A retraction is warranted.

¹ Cross S. and Roberts M. (2005). In-vitro human epidermal membrane penetration of tea tree oil components from pure oil and a 20% formulation. A report to RIRDC (Australian Rural Industry Research and Development Corporation)