PROPOSAL BY NTP REGARDING TALC (NON-ASBESTIFORM)

A Response by

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1. Introduction

The National Toxicology Program of the United States of America has proposed that talc (asbestiform) and talc (non-asbestiform) be listed in the 10th Report on Carcinogens as "reasonably anticipated to be a human carcinogen".

The Cosmetic, Toiletry and Perfumery Association (CTPA) has published a monograph on talc for use in cosmetic products[1] that requires, amongst other things, that cosmetic talc be free of asbestiform bodies. The cosmetics industry uses only talc that conforms to specifications that meet or exceed those for pharmaceutical grade talc. In particular, cosmetic talc is free of asbestos or other hazardous, asbestiform bodies. The toxicity of asbestos is therefore of no relevance to an assessment of the safety of cosmetic talc.

Listing of non-asbestiform talc by NTP as "reasonably anticipated to be a human carcinogen" would have serious consequences for the continued use of this material in the UK as a cosmetic ingredient. For that reason, CTPA presents this short summary document showing why the NTP proposal is not supported by the available scientific evidence and why there is no basis on which to suspect cosmetic, non-asbestiform, talc of being a human carcinogen. Several extensive reviews of the safety of talc are to be found in the scientific literature[2,3,4].

1.1 NTP Criteria for Listing

The NTP criteria which must be met for a substance to be listed as "reasonably anticipated to be a human carcinogen" are:

- There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

- There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumours:

    (i) in multiple species or at multiple sites, or
    (ii) by multiple routes of exposure, or

(iii) to an unusual degree with regard to incidence, site or type of tumour or age of onset; or

- There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however: the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogenicity as either *known to be human carcinogen*, or *reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

1.2 NTP Rationale for Listing

The rationale for the NTP proposal is stated in their "Background Document for Talc Asbestiform and Non-Asbestiform" as being:

- consistent evidence from human epidemiological studies which show an increase in ovarian cancer from women who use cosmetic talc in the perineal or genital area;

- evidence of carcinogenicity from a study in experimental animals.

1.3 CTPA Position

CTPA, on the basis of the total published scientific literature relating to this issue, only a portion of which is cited here, asserts:

- that there is neither consistent human epidemiological evidence of carcinogenicity nor evidence of carcinogenicity in experimental animals following exposure to non-asbestiform talc;
- that the NTP criteria for testing non-asbestiform talc as "reasonably anticipated to be a human carcinogen" have not been met; and,
- therefore the NTP case for such a listing should not succeed.

2. CTPA Comments

2.1 Epidemiological Studies

NTP asserts the epidemiological evidence is consistent in showing an increase in ovarian cancer in women who use cosmetic talc in the perineal or genital area. On the contrary, the epidemiological data are generally weak, inconsistent, controversial and inconclusive.

The majority of epidemiology studies in the literature are of the case-control, retrospective type and all suffer from well-known shortcomings[5]. A review of all such studies will reveal their findings are not consistent with regard to ovarian cancer and use of cosmetic talc. However, of the many epidemiological studies cited in the literature, only one - the most recently published and by far the largest - could be considered a major prospective study[6]. Participants in the Nurses Health Study formed a cohort of 78,630 women who were followed for 20 years. From within that cohort, 307 cases of epithelial ovarian cancer (the type of cancer most observed in previous case-controlled studies) were diagnosed.

The authors stated, “We did not observe an overall association with ever use of talc and epithelial ovarian cancer (RR = 1.09; 95% CI = 0.86-1.37). There was no elevation in risk among daily users of perineal talc and no trend was seen with increasing frequency of use.”

In the light of the findings of this major prospective study, it is not credible to maintain there is consistent evidence of an increased risk; manifestly, the evidence is not consistent.

2.2 Animal Carcinogenicity Studies

NTP asserts that the inhalation study in rats and mice sponsored by NTP and conducted at the Lovelace Biomedical and Environmental Research Institute[7] constitutes evidence of carcinogenicity from a study in experimental animals.

This study has been repeatedly criticised because of serious flaws in its design and conduct:

- the test material had been micronised, significantly altering its respirability and increasing deep lung deposition compared with cosmetic talc;
- the target aerosol concentrations were excessive;
- concentrations were not maintained during 19 of the 113 to 122 weeks of the study;
- for seven weeks exposure was to approximately twice the intended concentration;
- there were neither positive nor, crucially, negative dust controls.

There is ample evidence to indicate the carcinogenic response seen in the female rats exposed to the high dose of micronised talc was due to overloading of the lung and swamping of lung clearance mechanisms. Lung overload is known to lead to carcinogenic effects with inert particles such as titanium dioxide[8] and therefore the Lovelace study does not provide clear evidence that talc *per se* is carcinogenic.

Such serious shortcomings underlie the decision of the panel of experts at the ISRTP/FDA workshop[9] to declare the study as having no relevance to human risk assessment, something which the Lovelace investigators themselves have not claimed. Consequently, in the present discussion, the Lovelace study should be disregarded as having no relevance to the human safety assessment of cosmetic talc.

There are several well conducted studies showing talc is not carcinogenic on inhalation[10,11,12]: there is no reliable evidence published in the scientific literature indicating inhaled cosmetic talc may be carcinogenic.

2.3 NTP Criteria

Three criteria exist as described in 1.1 above, any one of which must be met in order to justify a substance be listed as “reasonably anticipated to be a human carcinogen”. CTPA maintains that none of the three criteria has been met and therefore any such listing is not justifiable. The reasons are:

- There is no evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to talc and any carcinogenic effect. In each epidemiology study, confounding factors, bias and chance adequately explain the small increases in odds ratio, increases which, though statistically significant, are not biologically significant, are not consistent and which, in the absence of a dose-response relationship, do not provide evidence of a causal effect.

- There is no evidence of carcinogenicity from properly conducted animal studies of relevance to human risk assessment. The single study[7] that purports to show talc is carcinogenic should be discounted for the reasons given in 2.2 above.

- The final criteria rests on talc being a member of either a well-defined, structurally-related class of carcinogenic substances or that there is convincing relevant information on a likely mechanism of carcinogenicity.

  Regarding the first point, comparison has been drawn between talc and asbestos; presumably because both are magnesium silicates. Chemical composition alone is not enough to predict biological activity; the combination of crystalline morphology and chemical composition of the surface of the crystal structure is what determines biological activity. For example, the natural mineral riebeckite is the non-fibrous and **non-carcinogenic** form of the amphibole crocidolite, or blue asbestos, a known human carcinogen. Talc is not structurally related to any asbestos mineral or to any other well-defined class of known carcinogen.

  Regarding the second point, there is no plausible mechanism by which talc can cause human cancer. Talc is not genotoxic, a point agreed by NTP. Thus, any carcinogenic activity must invoke an epigenetic mechanism, and no such plausible mechanism has been proposed. Widely reported findings of talc in ovarian tissue are not linked to the presence of ovarian cancer: talc has been found in non-cancerous ovaries too[13]. There is no plausible mechanism by which talc can migrate through the female genital tract to reach the ovaries in the absence of unusual manipulation. Finally, talc is a fibrogenic substance and fibrosis has a shorter pathogenesis than ovarian cancer yet there is an absence in the literature of reports of talc-related ovarian fibrosis.

There is, therefore, no convincing, relevant information on a likely mechanism by which cosmetic talc might be carcinogenic.

3. Summary and Conclusion

The NTP rationale for listing non-asbestiform talc "as reasonably expected to be a human carcinogen" is based on human epidemiological studies and a single rodent inhalation study. It is the view of CTPA that the total epidemiological evidence is neither consistent nor convincing; it may have generated the hypothesis than an association between cosmetic talc use and ovarian cancer exists but it fails to test that link rigorously and fails to demonstrate any causality. The rodent inhalation study is not relevant to human risk assessment and must be disregarded. No other evidence exists in the scientific literature suggesting that cosmetic, non-asbestiform talc might be carcinogenic.

Talc (non-asbestiform), on the basis on the body of scientific evidence, does not meet any of three criteria established by NTP as sufficient to justify listing as "reasonably anticipated to be a human carcinogen". Consequently, such listing is not justifiable: talc cannot be reasonably anticipated to be a human carcinogen.

CTPA submits that the proposal to list non-asbestiform talc as "reasonably anticipated to be a human carcinogen" should be rejected.

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CTPA Ltd.,
14th November, 2000
London

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