Potential Carcinogenicity of Fragrance and Heavy Metals from Cosmetic Talc

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He has over 33 years of experience as a professional toxicologist focusing on:

- Multi-disciplinary research in fate/transport, exposure assessment and toxicokinetics;
- Design and implementation of studies to characterize exposure/dose and toxicity;
- Human health and ecological risk assessments including complex indirect pathways;
- Evidence-based approaches for analysis of epidemiologic studies; and
- Disease causation analysis using the Hill Criteria and alternative cause assessment.

A board-certified toxicologist since 1994, Dr. Kerger has extensive experience in evaluating scientific issues involving claims of chemical causation or increased risk of diseases in humans in regulatory and litigation settings. He has thoroughly researched key toxicological issues surrounding human exposures to a broad range of chemicals and mineral dusts. Dr. Kerger guides the optimized research capabilities and access to resources (expertise and information) that promote an integrated, multi-disciplinary perspective to addressing scientific issues.

Abstract: We have performed a risk assessment for potential upper-bound cancer risks posed by added fragrance ingredients (benzophenone, coumarin, and styrene) and naturally occurring heavy metals (cobalt, chromium, and nickel) reported to be present in cosmetic talc. In conjunction with claims of asbestos contamination, Plaintiffs' experts have alleged that these agents in a variety of talc-containing products may cause or substantially contribute to ovarian cancer and/or mesothelioma. Review of the scientific literature pertaining to these fragrance materials and heavy metals, however, does not support a causal connection with ovarian cancer or mesothelioma. Our upper-bound risk assessment assumes conservatively that the fragrance ingredients were each present at 1% by weight of the talc, and that all chromium metal present was chromium (VI), for a 70-year lifetime of daily cosmetic talc use as face powder or body powder. We found the upper-bound cancer risk estimates for each fragrance or metal component were less than one in a million and thus can be considered *de minimis* for public health purposes.

Introduction:

Plaintiffs' experts in recent litigation have identified fragrance chemicals and heavy metals in cosmetic talc products that they considered as probable contributors to the cancer risks posed to product users. These experts did not rigorously analyze the available carcinogenicity evidence or classifications among regulatory agencies for these fragrance compounds or metals, nor did they quantify potential risks from fragrance and metal exposures among talc product users. In this analysis, we performed an exposure and carcinogenic risk assessment for three added fragrance ingredients found to have sufficient evidence of carcinogenicity in animals and the three naturally occurring heavy metals alleged by Plaintiffs' experts to contribute to cancer risks of cosmetic talc inhalation. All three of the metals are considered by regulatory agencies to be potential animal or human carcinogens, but have not been specifically associated with either ovarian cancer or mesothelioma.

Definitions: Hazard Identification, Exposure Assessment, and Risk Assessment

Toxicologists evaluate potential health risks of chemicals using the concepts of hazard identification, exposure assessment, and risk assessment as defined below.

Hazard Identification	Assessing animal and human studies for insights on the inherent property of a chemical to cause cancer and related outcomes. Importantly, exposure/dose is NOT considered in hazard identification.
Exposure Assessment	Quantifying the reasonable upper-bound dose of a chemical with known carcinogenic potential (hazard) relevant to Plaintiffs' claimed exposures. This effort may require specific testing, simulations, modeling and uncertainty analysis to be scientifically validated.
Risk Assessment	Quantifying the upper-bound probability of increased cancer risk from Plaintiffs' claimed exposures. The exposure assessment is

	combined with dose-response evidence from epidemiologic and/or controlled animal studies to estimate Plaintiffs' cancer risk probability. Demonstration of very low cancer risks for upper-bound exposures can strongly argue against specific causation, but not vice versa.

Hazard identification is akin to a determination of general causation for legal purposes. The body of scientific evidence in animal or human studies of potential carcinogenicity for the subject chemical is interpreted by scientific experts to answer the question: Does this chemical – regardless of dose considerations -- cause the subject cancer to a reasonable degree of scientific certainty? The answer to this question is often complicated by lack of adequate study, conflicting evidence, and seemingly reasonable differences in expert interpretations of the weight of evidence. Legal arguments on whether or not general causation of cancer is supported with reasonable scientific certainty may not be addressed by Courts as a gatekeeping requirement, leaving the jury to determine the veracity of expert opinions pro or con. In some instances, Plaintiffs may argue that it is Defendant's burden to 'prove the negative' with respect to general causation, which may be a daunting or impossible task from a scientific perspective.

Exposure assessment and risk assessment can provide more detailed science-based information to address the question of specific causation: Did this chemical cause the Plaintiff's cancer considering the specific exposure conditions at issue? Quantification of chemical exposure and probability of cancer risk inherently involves the application of assumptions about the most relevant and applicable parameters to include in the calculations, which leads to some degree of uncertainty. Use of a balanced set of upper-bound assumptions leads to health-protective estimates for dose and cancer probability that can help assure a very low potential for underestimation of risk. Thus, risk assessment inherently involves a margin of safety to account for uncertainties, making the upper-bound estimates health protective to a reasonable degree of scientific certainty. Due to this margin of safety, risk assessment-based estimates cannot be assumed to accurately predict risks, but those estimates can be considered protective of human health. Accordingly, appropriately designed upper-bound cancer risk calculations can be used to exclude the likelihood of specific causation, but cannot be used to establish specific causation.

Fragrance Materials in Face and Body Powders: Fragrance materials can vary from complex mixtures to single chemicals. Cosmetic talc products contain a variety of fragrance materials. A given fragrance added to a cosmetic product may contain up to 300 different ingredients, any one of which may give the product a certain aesthetic character that consumers find appealing (Bickers et al. 2003). Thus, the details of the specific ingredients and amounts used are often regarded as proprietary information.

Fragrance materials can be natural products, meaning that they are extracted or obtained directly from plant or animal sources. Fragrance materials can also be nature-identical, meaning that they are produced synthetically but they are chemically identical to their natural counterparts (Bauer et al. 2001). The majority of the compounds used in fragrances are those identified as components of natural products, for example, constituents of essential oils or resins.

There are many chemical compounds that are used as fragrance ingredients as part of a fragrance formulation that may not be generally recognized as fragrances. In this analysis, an original list of eight fragrance additives for a particular talc body powder product was evaluated for evidence of carcinogenic potential in animals or humans, and only three ingredients were found to have sufficient evidence of carcinogenicity (based on animal studies showing increased lung or liver tumors in treated rats or mice). The three compounds we identified were benzophenone, coumarin, and styrene, none of which are generally recognized as fragrances. Notably, these three compounds may be perceived to provide a pleasant odor at the low concentrations in a fragrance formulation, although higher concentrations in each case might be perceived as unpleasant. The added concentration of each of the three fragrance chemicals in the body powder product was not provided; only an upper-bound value of 'less than one percent by weight' was identified. Thus, our upper-bound risk assessment approach conservatively assumed that each of the three fragrances was present in the product at 1% by weight.

Heavy Metals in Face and Body Powders: The three carcinogenic heavy metals found to be present at naturally occurring concentrations in cosmetic talc were cobalt, chromium, and nickel.

Carcinogenic potential can be dependent on the species or valence state (i.e., charge) of the metal. This is especially important for chromium. Chromium exists largely as chromium (III), or trivalent chromium, and chromium (IV), or hexavalent chromium. Chromium (III) is a naturally occurring trace nutrient and is the food of the chromium found in foods (Agency for Toxic Substances and Disease Registry (ATSDR) 2012); this form is not associated with animal or human carcinogenicity. However, chromium (VI) is predominantly found as a by-product of industrial processes, such as the manufacturing of stainless steel, pigments, chrome plating, and certain other industrial processes. Chronic animal bioassays provide evidence that chromium (VI) is a lung carcinogen when administered via the inhalation route and a GI tract carcinogen when administered by the oral route (ATSDR 2012). In humans, occupational inhalation exposure to chromium (VI) has been consistently associated with increased lung cancers (IARC 2012). Thus, the carcinogenic potential of chromium is demonstrated to be dependent on the hexavalent valence state. Only chromium (VI) is considered by regulatory agencies to be an animal and human carcinogen (NTP 2016; IARC 1990, 2012; US EPA 1998).

Trivalent chromium is the predominant naturally occurring form and is present in rocks and soils, and it is considered an essential element for human nutrition. Chromium (III) is most likely the form of chromium present in talc products. This was confirmed by Petrucci and Senofonte (2015), who analyzed the naturally occurring heavy metals content in a cosmetic these talc product and reported no detectable chromium (VI), although total chromium [as chromium(III)] was confirmed to be present. As a conservative assumption in our upper-bound risk assessment, we assumed that the detected concentrations of total chromium in talc was entirely present in the carcinogenic hexavalent form.

The opinions of regulatory agencies on cobalt carcinogenicity are not as clear. Like chromium, cobalt is a naturally occurring element and is considered an essential metal (it is a cofactor in vitamin B12). In chronic bioassays, rats and mice developed lung and adrenal tumors from inhalation exposures to cobalt metal (widely dispersed in the environment but also used in industrial processes) and cobalt sulfate (used in electroplating and as a pigment in ceramics, paints, and other materials) (NTP 1998, 2014). OEHHA (2020) derived inhalation unit risk factors for cobalt metal and water-soluble cobalt compounds based on limited animal studies;

however, NTP (2016) did not find sufficient evidence of cobalt carcinogenicity and the USEPA has not produced a cancer slope factor for cobalt inhalation. IARC (2006) concluded that cobalt metal in combination with tungsten carbide was "probably carcinogenic" to humans (Group 2A). As no data were found of the cobalt species present in cosmetic talc, our upper-bound risk assessment conservatively assumed the more conservative inhalation unit factor for cobalt metal was applicable for this analysis.

Nickel is another naturally occurring element; exposure to the general population is from ambient air, water, food, and smoking of cigarettes and use of smokeless tobacco. Chronic bioassays have been conducted in rats and mice with various nickel compounds, including nickel subsulfide (component of nickel refinery dust), nickel oxide (used in stainless and alloy steel production), and nickel sulfate hexahydrate (used in industrial processes, including nickel plating, dying and printing textiles, and manufacture of organic nickel salts). Inhalation exposure to nickel subsulfide and nickel oxide induced lung and adrenal tumors in rats but not in mice (NTP 1996a,b). Nickel sulfate hexahydrate was not carcinogenic in rats or mice (NTP 1996c). Epidemiologic data indicate that occupational cohorts in certain industries that refine, produce or use nickel had increased risks of lung cancer; types of nickel compounds that have been reported to increase risk of lung cancer are sulfidic, oxidic, water-soluble, and metallic forms of nickel (Goodman et al. 2011). IARC (2012) concluded that nickel compounds are carcinogenic to humans (Group 1); NTP (2016) concluded that nickel compounds are known human carcinogens and that metallic nickel is "reasonably expected to be a human carcinogen." USEPA (1987a,b) has derived inhalation unit risk factors for nickel subsulfide and nickel refinery dust, but these refined forms would not be expected in cosmetic talc. Our upper bound risk assessment conservatively assumed that the inhalation unit risk factor for nickel and nickel compounds derived by OEHHA (2011) was applicable for this analysis.

Methods:

Published data from Burns et al. (2019) on talc use patterns were used to estimate fragrance and metal exposures from various cosmetic talc use scenarios. Burns et al. (2019) reported on adult exposures to talc from use of baby powder and body powdering. It has been reported that Johnson's Baby Powder and Shower to Shower talc products include 173 unique fragrance ingredients. The combination of all fragrance ingredients was $\leq 0.22\%$ in Johnson's Baby Powder. The combination of all fragrance ingredients was present at a maximum of 1% in Shower to Shower. As fragrance ingredients were reported to be present at a higher percentage in the Shower to Shower product, the use scenarios for adult face and body powdering were used to calculate the risk estimates reported here for coumarin, styrene, and benzophenone. Although the combination of all fragrance ingredients is reported to be present at a cumulative maximum of 1%, our upper-bound risk calculations assumed that coumarin, styrene, and benzophenone were each present at 1% in cosmetic talc. Use scenarios and measured dust concentrations associated with those scenarios are summarized in Table 1. Only studies that reported total or respirable dust concentrations (Aylott et al. 1979, Anderson et al. 2017, Russell et al. 1979) were considered in this analysis.

Table 1. **Representative Dust and Fiber Exposure Measurement Data Associated with Adult Application of Cosmetic Talcum Powder (adapted from Table 1 of Burns et al. 2019)**

Description	Powdering time	Sample duration (min)	N	Measured airborne dust concentration (mg/m^3)	Reference
Face powder					
loose face powder	10-25 sec	5	16	0.48	Aylott et al. 1979[a]
Body powder					
"Typical fashion"	13-47 sec	6	20	1.46	Anderson et al. 2017[b]
"normal way"; container with sprinkle closure	15-80 sec	5	32	1.13	Aylott et al. 1979[a]
upper body; shaker container	55 sec	5	1	NA	Gordon et al. 2014[c]
upper body; puff applicator	57 sec	4	2	NA	Gordon et al. 2014[c]
upper body; puff applicator	57 sec	3.3	1	NA	Gordon et al. 2014[c]
"normal way"; twist-top container	1.23 ± 0.55 min	1.23 ± 0.55 min	44	2.03	Russell et al. 1979[d]

[a] Aylott et al. 1979. Normal use levels of respirable cosmetic talc: preliminary study. Int J Cosmet Sci 1: 177-186.

[b] Anderson et al. 2017. Assessment of health risk from historical use of cosmetic talcum powder. Risk Anal 37: 918-929.

[c] Gordon et al. 2014. Asbestos in commerical cosmetic talcum powder as a cause of mesothelioma in women. Int J Occ Environ Health 20: 318-332.

[d] Russell et al. 1979. The determination of respirable particles in talcum powder. Food Cosmet Toxicol 17: 117-122.

Hepp et al. (2014) reported on the several metals in various cosmetic products, including 5 body powders and 5 face (compact) powders. This study was funded by the US FDA. The valence states/species of metals were not identified in this study, although the 3 metals at issue (Cr, Co, and Ni) were present (Table 2). For each powder type, our upper bound risk assessment utilized the maximum concentration of each metal compound based on the cosmetic talc data reported by Hepp et al. (2014). Although Petrucci and Senofonte (2015) reported on Cr levels in talc, they did this for only a single talc sample and they did not report on any other metals; thus, we used the Hepp et al. (2014) study in this work.

Table 2. Data on metal content of body and face powder data from Hepp et al. (2014)

Body powders			
	% present in talc		
Brand	Cr	Co	Ni
1	0.00039	0.00014	0.00046
2	TR[1]	ND[2]	TR
3	0.00019	0.00011	0.00016
4	0.000029	0.0000073	0.000022
5	0.00017	0.00016	0.00038
Maximum	0.00039	0.00016	0.00046
Face powders			
	% present in talc		
Brand	Cr	Co	Ni
1	0.0016	0.00044	0.0012
2	0.00014	0.00018	0.00039
3	0.00048	0.0014	0.0028
4	0.0011	0.000082	0.0006
5	0.00047	0.0003	0.00087
Maximum	0.0016	0.0014	0.0028
[1] Trace (greater than detection limit but less than quantification level)			
[2] Not detected			

Upper-bound cancer risk estimates were calculated using the measured airborne dust concentrations and sample duration times in Table 1. It was assumed that each fragrance ingredient (styrene, benzophenone, and coumarin) was present at 1% in the talc formulation as explained above. It was assumed that each metal was present in the maximum concentrations reported by Hepp et al. (2014). The authors of this paper were did not report on specific species of chromium; however, it was assumed that all of the Cr reported was Cr(VI).

The sample durations reported by Burns et al. (2019) were assumed to be the exposure times (ET; hours per day). Exposure frequency (EF; uses per year) was assumed to be once per day (or 365 days per year) and exposure duration (ED; years of use) was assumed to be 70 years (consistent with the US EPA default lifetime exposure of 70 years; USEPA 2005).

Estimated upper-bound cancer risk is calculated by the following:

$$Risk = Fragrance\ exposure\ concentration\ \left(\frac{\mu g}{m^3}\right) * TWF * IUR$$

Where the fragrance exposure concentration is the inhalation concentration of the fragrance ingredient or metal in μg/m^3.

TWF is the time-weighting factor and is the fraction of the year during which exposure from a particular activity can occur. This was calculated by the following:

$$TWF = \frac{ET\ \left(\frac{hr}{day}\right) * EF\ \left(\frac{day}{year}\right)}{24\frac{hr}{day} * 365\ \left(\frac{day}{year}\right)}$$

IUR is the inhalation unit risk factor (per μg/m^3), which is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to a substance at a concentration of 1 μg/m^3 in air. The interpretation of inhalation unit risk is as follows: If unit risk = 2 x 10^{-6} per μg/m^3, excess cancer cases (upper-bound estimate) would be expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 μg of the chemical per m^3 of air (USEPA 2011). A 10^{-4} risk level corresponds to the upper end of the USEPA's generally acceptable risk range of 10^{-6} to 10^{-4} (USEPA 2020). Table 3 outlines the inhalation unit risk factors used for fragrance ingredients and metals.

Table 3. Inhalation Unit Risk (IUR) Factors used for Fragrance Ingredients and Metals

Fragrance ingredient	**IUR (per μg/m^3)**	**Source**
Benzophenone	6.57E-06	Michigan Department of Environmental Quality[a]
Styrene	5.70E-07	Michigan Department of Environmental Quality[b]
Coumarin	3.40E-05	California Office of Environmental Health Hazard Assessment[c]
Metal	**IUR (per μg/m^3)**	**Source**
Chromium (VI)	1.2E-02	USEPA Integrated Risk Information System[d]
Cobalt (metal)	7.7E-03	California Office of Environmental Health Hazard Assessment[e]
Nickel	2.6E-04	California Office of Environmental Health Hazard Assessment[f]

[a] http://www.deq.state.mi.us/aps/downloads/ATSL/119-61-9/119-61-9_annual_ITSL_IRSL.pdf
[b] https://www.michigan.gov/documents/deq/deq-rrd-chem-StyreneDatasheet_527586_7.pdf
[c] No IUR is available for coumarin. As coumarin is thought to induce mouse tumors by a similar mode of action as naphthalene (Lake 1999), the IUR as derived by the OEHHA for naphthalene was used (https://oehha.ca.gov/media/CPFs042909.pdf)
[d] https://iris.epa.gov/static/pdfs/0144_summary.pdf
[e] https://oehha.ca.gov/air/crnr/notice-adoption-cancer-inhalation-unit-risk-factors-cobalt-and-cobalt-compounds
[f]https://oehha.ca.gov/chemicals/nickel-and-nickel-compound

Tables 4 and 5 summarize the estimated cancer risks from the three fragrance ingredients and three metals resulting from a lifetime of daily use of cosmetic talc. The upper-bound cancer risk estimates are within or below the USEPA acceptable risk range of 10^{-6} to 10^{-4} (USEPA 2020), and all below the California Proposition 65 acceptable safe harbor limit of 1 in 100,000 (10^{-5}).

Table 4. Estimated Cancer Risks for Fragrance Ingredients from Various Cosmetic Talc Use Scenarios

Use Scenario—face powder	Reference for measurement data	Estimated cancer risk for styrene	Estimated cancer risk for benzophenone	Estimated cancer risk for coumarin	Summed cancer risk for fragrances
Loose face powder	Aylott et al. 1979	9.5E-09	1.1E-07	5.7E-07	6.8E-07
Use scenarios—body powdering					
"Typical fashion"	Anderson et al. 2017	3.5E-08	4.0E-07	2.1E-06	2.5E-06
"normal way"; container with sprinkle closure	Aylott et al. 1979	2.2E-08	2.6E-07	1.3E-06	1.6E-06
"normal way"; twist-top container	Russell et al. 1979	1.4E-08	1.6E-07	8.5E-07	1.0E-06

Table 5. Estimated Cancer Risks for Metals from Various Cosmetic Talc Use Scenarios

Use Scenario—face powder	Reference for measurement data	Estimated cancer risk for chromium	Estimated cancer risk for cobalt	Estimated cancer risk for nickel	Summed cancer risk for metals
Loose face powder	Aylott et al. 1979	3.2E-07	1.8E-07	1.21E-08	5.1E-07
Use scenarios—body powdering					
"Typical fashion"	Anderson et al. 2017	2.8E-07	7.5E-08	7.28E-09	3.6E-07
"normal way"; container with sprinkle closure	Aylott et al. 1979	1.8E-07	4.8E-08	4.69E-09	2.3E-07
"normal way"; twist-	Russell et al. 1979	1.2E-07	3.1E-08	3.00E-09	1.5E-07

top container					

Discussion:

Our upper-bound risk assessment of fragrance chemicals and heavy metals with carcinogenic potential in cosmetic talc indicates that they present a negligible cancer risk for lifetime users of face or body powders. The upper bound risk estimate is extremely low despite the use of conservative upper-bound assumptions pertaining to exposure levels, chemical species, and dose-response factors from relevant scientific studies. Moreover, no association has been established between any of these components and excess ovarian cancer or mesothelioma in controlled animal studies or in epidemiological studies to date. No strong or consistent evidence supports a toxicological link between the relatively low level daily exposures to these fragrance compounds or metals and increased risk of cancer generally. Thus, Plaintiff experts' opinions that added fragrance chemicals or naturally occurring heavy metals in face or body powder products can cause or substantially contribute to cancer risks among users is false and unsupported by scientifically sound methodology and support based on toxicological considerations. In sum, an upper-bound cancer risk assessment for the three fragrance ingredients and three metals considered here indicates that negligible cancer risk probabilities would result from intake of these fragrance chemicals by daily talc users for a 70-year lifespan.

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