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DOCUMENT DESCRIPTION: Letter to Gene M. Williams, Lawyer, from Innovant Research - Founded by a Former J&J Toxicologist Employee and Current Independent Consultant, Defending the Use of Asbestos as Non-Toxic in Relation to Ovarian Cancer



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Dear Mr. Williams:

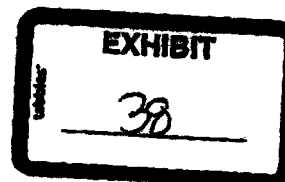
I have prepared the following for the case of *Blaes v. J&J, et al.*

I hold a Bachelor of Science degree with Honors in Chemistry & Biochemistry from the University of St. Andrews, Scotland, U.K. I also hold a Ph.D. degree in Toxicology from the University of Dundee, Scotland, U.K. I am a Chartered Biologist, holding the Diploma, C. Biol. and my academic background is in the field of toxicology. I am also a member of the Society of Biology. I have 41 years experience as a Toxicologist in Pharmaceutical, Medical Device and Consumer product areas.

During the period 1976 – 2000, I was in the employment of Johnson & Johnson (U.K., 1976-1994; U.S.A., 1995-1998; and France 1999-2000). Prior to that, I undertook some teaching to medical students followed by employment as a Toxicologist in the Pharmaceutical industry. I was a founding member of the British Toxicology society in 1979.

From the time I became employed at Johnson & Johnson as a Toxicologist in 1976, I have been familiar with the literature and discussion as to talc safety. I am also familiar with the history and background of the sourcing, standards and specification of talc as used by Johnson & Johnson on a worldwide basis. During my employment for Johnson & Johnson in the U.K., I was based in the medical department and was in regular contact with medical and scientific colleagues in the United States and kept updated on all matters relating to talc safety. I also sat on a talc issue task force, which dealt with various issues, including talc safety. I was a participant at the FDA sponsored Talc Safety workshop held in 1994 in Washington, D.C. I was also involved in the collation of scientific data via the CTPA (U.K. Trade Association) for the NTP review of talc safety in December 2000. I retired from Johnson & Johnson as Worldwide Category Director, Infant & Children's Products, in 2000.

Since 2000, I am the President of my own company, Innovant Research, which is an independent consultancy in the field of toxicology, product safety, and risk assessment. Through my company, I have continued to serve as a consultant to Johnson & Johnson both in Europe and in



the United States on safety matters, including talc safety, and continue to maintain a strong interest in talc safety today.

I am also a Member of the U.K. Trade Association, the CTPA. I am a Member of the CTPA Scientific Advisory Committee and the CTPA Talc Committee and the CTPA Toxicology Panel. My Curriculum Vitae is attached, which provides further details about my education, training and experience. I have testified as an expert witness one time in the last four years (*Berg vs. Johnson and Johnson*).

JOHNSON & JOHNSON TALC SOURCING

Johnson's Baby Powder has been manufactured since 1894.

The purity of talc is based on its source. There are only a limited number of talc mines in the world that provide the high grade of talc that meets the requirements of talc for pharmaceutical applications (Talc USP) and for cosmetic applications (compliance with the CTFA monograph). Mines that include geological structures other than pure talc are not suitable as a source of cosmetic and pharmaceutical grade talc.

Beginning in approximately 1946, talc for Johnson & Johnson in the U.S. was sourced from the Italian mine at Val Chisone. In approximately 1967, Johnson & Johnson in the U.S. began to acquire its cosmetic grade talc from the Windsor mine in Vermont, U.S.A. From approximately 2003 until the present, Johnson & Johnson in the U.S. has been acquiring talc through Luzenac (now Imerys) from the Guangxi mine in China. All of these sources have undergone rigorous testing by Johnson & Johnson in order to become an approved source of talc.

TESTING OF JOHNSON & JOHNSON TALC

The records indicate that as far back as 1949, there is documented evidence that the specification for Johnson & Johnson cosmetic talc should be free from asbestos and asbestiform minerals. Although asbestos and talc share the same chemical components, their physical structure differs significantly in that asbestos and asbestiform minerals are needle-like in appearance, whereas talc is flat and plate-like. ~~The needle-like structure of asbestos and asbestiform minerals is the quality that gives it the ability to embed in pulmonary tissue and potentially lead to mesothelioma.~~ On the other hand, the flat, plate-like structure of talc gives it a soft, slippery quality that is desired in personal care products.

Although asbestos was ~~not known as a hazard in 1949~~, the presence of asbestos was, even at that time, considered highly undesirable, as its feel on the skin is regarded as unpleasant and cosmetically unacceptable. As a part of a program to ensure that the talc used in Johnson & Johnson products was free from asbestos, an independent geological audit of the talc mine both in Italy and in Vermont was conducted in 1972 by Professor Fred Pooley from the Department of Mineral Exploitation, University of Wales, U.K. Professor Pooley is considered a world class expert in talc mineralogy and geology. The conclusion of the audits, for both the Italian and the Vermont mines, was that there was zero evidence of asbestos in the geology and mineralogy of

the mines. Additionally, Professor Pooley examined a sample of Italian talc dating from 1949, as used by Johnson & Johnson in the U.K. Dr. Pooley reported that the quality of the talc had not changed.

Since 1975, Johnson & Johnson Consumer Companies, Inc. (and its predecessors) has conducted a regular monitoring program of samples of talc from mines supplying talc for its products in the U.S. The monitoring program, which is conducted by independent external laboratories, includes assay for asbestos, silica and quartz. These independent laboratories, McCrone & Associates and RJ Lee, have never reported quantifiable asbestos in any of the samples tested. In addition, it has been a requirement of Johnson & Johnson's Raw Material Specification since 1975 for each batch of talc supplied to Johnson & Johnson to be free from asbestos and in compliance with the CTFA Talc Monograph. This has required the supplier to confirm purity of every batch supplied using state of the art techniques. There is no evidence of asbestos contamination of any batch sampled, as certified by the suppliers.

In summary, there has never been a documented instance of asbestos contamination in Johnson & Johnson Consumer Products.

OVARIAN CANCER AND TALC

Studies

Johnson & Johnson Consumer Companies, Inc. has closely tracked safety issues related to talc, including studies suggesting that talc may be associated with a higher risk of ovarian cancer. The Company has a safety team that, among other things, searches for any new literature or published articles that pertain to the safety of talc. There are publications on the safety and non-toxic nature of talc going back to 1944. Since the first Cramer study was published in 1982, J&J CC has thoroughly investigated the results and has retained independent, outside consultants to analyze each publication and provide a detailed opinion on the methods and results of each of the studies and/or publications and the strength of any association between talc and ovarian cancer.

None of the independent consultants have concluded that there is any causal relationship between talc and ovarian cancer. For one thing, many of the studies have shown absolutely no association. Even the studies that show a statistical association, however, show only a very low relative risk (approximately 1.3), which could easily have resulted from bias or some other confounding factor. This is supported by the lack of a dose-response correlation in virtually all the studies. Indeed, none of the authors concluded in their studies that there is a causal relationship between talc and ovarian cancer and most acknowledged the limitations of their studies in terms of potential biases.

There are other concerns regarding the validity of many of the studies. For instance, there is some question whether the researchers in the Purdie and Green study used properly matched controls, as there is no evidence that some of the known risk factors for ovarian cancer, such as oral contraceptive use, dietary fat intake, body weight, and number of children, was taken into

account when matching controls. These factors, alone, could account for the slightly elevated relative risk reported.

The results of the studies involving miners and millers also support a lack of association between talc and any cancer. While miners exposed to high levels of talc in talc mines sometimes developed fibrosis (which can occur with any dust), there was no excess of pulmonary tumors. Rats exposed to similar levels of talc likewise did not develop an excess of pulmonary tumors (1).

A two-day scientific workshop on "Talc: Consumer Uses and Health Perspectives," co-sponsored by the International Society of Regulatory Toxicology and Pharmacology and the United State Food and Drug Association, concluded that talc is not carcinogenic and that there is no causative connection between talc and ovarian cancer. The workshop consisted of leading experts in epidemiology, safety assessment, toxicology, and clinical medicine, who participated as speakers or as panel members. A number of epidemiologic studies investigating a possible association between talc and ovarian cancer were reviewed. The workshop concluded that, when taken together, the results of these studies are insufficient to demonstrate any real association. In addition, participants agreed that there is no basis to conclude that talc is capable of migrating to the ovaries in the first place (2).

Studies conducted by the National Toxicology Program (NTP) have likewise concluded that talc does not migrate to the ovaries. The authors reported that "...extensive lifetime exposure to talc does not result in the deposition of talc in the ovary. Since the animals were exposed for 6hr per day with talc covering the fur and cage bars, there was ample opportunity for perineal as well as a oral and respiratory exposure...." (3). This confirms an earlier study in monkeys using radio-labeled talc which showed no vaginal translocation from deposition in the vaginal fornix to the uterine cavity (4).

In recent years the safety of cosmetic talc has been further validated. A Safety Assessment Report by the independent Cosmetic Ingredient Review (CIR) panel published in 2013 (5) reviewed all relevant published reports at that time and concluded that talc is safe in the present practices of use and concentration described in this safety assessment. It is noteworthy that the reviewers are independent academic experts in their fields and in compiling the Report cited some 219 peer reviewed scientific publications. Since the publication of the CIR Report, other recent publications have further confirmed the conclusions.

A recent publication from 2014 has investigated talc use and ovarian cancer. In a prospective cohort study of 61,576 women (6), the authors concluded there was no influence of talc on ovarian cancer risk, thus confirming the Conclusions of the CIR Report.

Cramer (7) has suggested that an increased number of estimated ovulatory cycles correlates directly with risk for both endometrial and ovarian cancer, suggesting that reproductive tissue turnover with an accumulation of PTEN or p53 mutations represents a possible common mechanism. However, recently published studies clearly show no relationship between talc usage in the perineal areas and endometrial cancers in women (8,9). In the first of these studies (8) a population of 48,526 women was studied and the conclusion was there is no association of

8. Crawford L et al. Perineal Powder use and risk of endometrial cancer in post-menopausal women. *Cancer Causes Control*, 23(10):1673-80, 2012.
9. Neill AS et al. Use of talcum powder and endometrial cancer risk. *Cancer Causes Control*, 23(3):513-19, 2012.
10. Musser, SM. Department of Health and Human Services, Food & Drug Administration, RE Docket numbers: 94P-0420 and FDA -2008-P-0309-0001/CP. March 18, 2014.

Comparison of Talc Use in other Countries and Ovarian Cancer Rates

Talc powder use was developed in the United States in the 1870s and was adopted more widely in the UK from the early 1900's. However as personal habit, talc use was not widely adopted in other Western countries. It is therefore useful to compare talc use in the UK, with talc use in Sweden where little talc is used.

A study was made to compare the amount of talc powder use in these two markets. Using sales data supplied by an Independent company (IRI), total talc use (including Johnsons) was measured in UK and Sweden over the 3 years, 2009, 2010, 2011. Taking accepted population figures of 9,380,000 for Sweden and 62,219,000 for UK, it is possible to calculate annual average talc use per person. In Sweden the average annual talc use was 34,920 kg for the whole country; equivalent to use of only 3.72 grams of talc per person. In UK the average annual talc use was 2,300,118 kg for the whole country; equivalent to a use of 36.96 grams of talc per person. (1)

In summary the amount of talc use per person in UK is almost 10x more than in Sweden.

For Sweden, the most recent epidemiology study of ovarian cancer incidence was published in November 2008. It reported an age-standardised rate of 15.3 per 100,000 women (2). Comparable data for the UK reported a similar figure of 16.2 per 100,000 women (3). The incidence rates per 100,000 women do vary considerably with rates of 19.2 and 18.7 in Latvia and Lithuania respectively to 10.8 and 7.2 in Spain and Portugal respectively (3). Thus in regards to the above range from 7.7 to 19.2 per 100,000 women, the incidences in UK and Sweden are considered as essentially similar.

It is apparent from the above data that the rates of ovarian cancer in Sweden and United Kingdom bear no relation to the amount of talc usage. Despite the per capita talc use in UK being 10X that used in Sweden, the rates of ovarian cancer are essentially similar between the two countries. It would be expected that if talc use were a factor in ovarian cancer, the rates in UK would be much higher than in Sweden.

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1. Market Research Data, Personal Communication from Marketing Dept of Johnson & Johnson Consumer UK and Johnson & Johnson Consumer Sweden.
2. Cancer incidence in Sweden 2007, The National Board of Health & Welfare ISBN 978-91-85999-73-7, pub 25 Nov. 2008.

3. Ovarian Cancer. UK incidence statistics, pub by Cancer Research UK. www.cancerresearchuk.org.
4. Granstrom C et al. Population attributable fractions for ovarian cancer in Swedish women by morphological type. Br J Cancer. 88:199-205, 2008.

Dr. Cramer's Hypotheses

Dr. Cramer has published several publications that have attempted to construct a relationship between talc use and ovarian cancer. The basis of much of Dr. Cramer's work on this relationship has been to consider meta-analyses of several studies. However, these analyses have indicated an odds ratio (OR) / Risk Ratio (RR) marginally over 1.0. Typically, several studies quote OR of 0.7, 0.84, 1.13, 1.3, 1.27, 1.39, 1.33.

The topic of statistical epidemiology is a complex one. It is often stated that several weak links do not make a strong chain. Certainly it is generally accepted by experts in this field that because of confounding factors, there cannot be a "cause-and-effect" relationship with OR numbers as reported above. Instead, it is generally accepted that an OR of 2.0 or higher is required to make a cause for a valid association. OR numbers less than this are generally regarded as co-incidental and the result of bias or confounding factors.

Confounding factors are represented by habits data that may not always be accurately recollected in a hindsight questionnaire. For instance, the subject may not recollect body powder habits accurately after many years; there may not be accurate recollection of dietary and other habits such as dairy intake, alcohol use, etc.

Factors that are known to contribute towards ovarian cancer include body mass index, familial history, and dietary intake. Factors known to protect from ovarian cancer include numbers of children, number of years on an oral contraceptive pill, and breastfeeding. A higher number of children, higher number of years on the oral contraceptive, and breastfeeding offer protection from ovarian cancer, as do tubal ligation and hysterectomy.

An important Swedish study (1) used the Swedish database of 1,030,806 women followed from 1993 through 2004, and identified 3,306 and 822 women with invasive and borderline ovarian cancer, respectively. The Swedish data base follows residents after 1931, along with their biological parents. Factors increasing the Odds Ratio in invasive epithelial ovarian cancer were identified as a family history through a mother proband, which increased the risk of invasive ovarian cancer to 2.54, and through a sister to 2.76 relative to women with no family history. Nulliparity showed a Risk Ratio (RR) of 2.12 relative to those who had at least 3 children.

An earlier Swedish study reported the strong relationship with dairy consumption (2) and risk of serous ovarian cancer. It was reported that after adjustment for potential confounders, women who consumed 4 or more servings of total dairy products per day had a risk of serous ovarian cancer twice that of women who consumed less than 2 servings per day (Risk Ratio: 2.0; 95% CI: 1.1, 3.7; P for trend = 0.06). No significant association was found for other subtypes of ovarian cancer. Milk was the dairy product with the strongest positive association with serous ovarian cancer (rate ratio comparing consuming 2 glasses or more of milk per day with

consuming milk never or seldom (2.0; 95% CI: 1.1, 3.7; P for trend = 0.04). The data indicated that high intakes of lactose and dairy products, particularly milk, are associated with an increased risk of serous ovarian cancer but not of other subtypes of ovarian cancer.

Dr. Cramer claims to have derived an ovarian cancer OR of 3.53 in talc users for a sub-group of patients in his recent re-analysis of data from the New England Case Control Study. However, there is no indication that other factors that have been associated with an increased risk of ovarian cancer, such as dairy intake and psychotropic drug use (both of which Dr. Cramer have published on previously), were controlled for in this analysis. Nor is it clear whether protective factors, such as breastfeeding, were taken into account. Of note, use of less than 360 applications was shown to have a *protective* effect (OR 0.34) compared to never users. This evaluation was done for litigation purposes and it is a questionable scientific approach to select a data point relevant to a specific person and to work backwards rather than to consider overall data. Thus, the usefulness of this analysis is questionable and certainly cannot be taken to prove that talc use causes ovarian cancer.

In summary, the Cramer hypothesis has not shown a truly statistical cause and effect relationship between talc use and ovarian cancer.

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2. Larsson SC, Bergkvist L, Wolk A. Milk and lactose intakes and ovarian cancer risk in the Swedish mammography cohort. *Am J Clin Nutr*, 80(5):1353-7, 2004.

Suggested Mechanisms of Cancer Causation

Plaintiffs' experts have suggested that the contamination of talc with metals such as chromium, arsenic, iron, nickel and lead may lead to immune toxicity. However, the plausibility of this mechanism in the context of cosmetic talc products which, at best, may contain trace amounts of some metals, has never been described in the published literature.

Dr. Rosenthal also suggested several other hypotheses as to how cosmetic talc use may cause ovarian cancer. For instance, Dr. Rosenthal's report discusses the possibility that talc particles maybe engulfed by macrophage cells resulting in an immune response and possible macrophage injury. It is hypothesized that macrophages may transport talc particles to distant sites. It is also postulated that talc particles may be taken up by macrophages, and that the macrophages may be activated, releasing cytokines, oxidants, growth factors and transport talc particles to lymph nodes. It was also postulated by Dr Rosenthal that epithelial cells at the mucosal surface could take up a mineral particle landing on a mucosal surface. Dr Rosenthal reports that talc used in the therapeutic procedure of pleurodesis may disseminate beyond the pleura after its use. But none of these hypotheses have been tested with regard to cosmetic talc and there is no scientific literature supporting any of these hypotheses.

Moreover, there has been no evidence presented of any of these biological activities in relation to Ms. Blaes' tissue samples. For example, Dr Rosenthal hypothesized that talc may cause the

deposition of ferruginous bodies in tissues, which may result in tissue injury. However it is clear from the pathologist report (1) in this case that ferruginous bodies associated with talc particles are not reported by the pathologist. Even if ferruginous bodies were present there is no evidence to show a causal relationship to ovarian cancer.

Whilst a hypothesis is a valuable means to further investigate a scientific topic, it is important to realize that only by extensive research can a hypothesis be validated. This has simply not occurred in this case.

REFERENCES

1. Godleski JJ. Report on pathology slides re Ms S Blaes, April 3rd 2015.

Evidence of Talc In the Ovary in This Case

Dr. Godleski's report presents his findings of a review of pathology slides for tissues from Ms. Blaes (1). Specifically, 368 particles were found and analyzed. 226 particles were composed of elements including carbon, sodium, calcium and phosphorus, alone or in combination. These elements can occur endogenously. Further, 140 had elemental composition composed of foreign material; 101 had a variety of materials but did not have the concentrations of both magnesium and silicon; and 33 were identified as having magnesium and silicon in the concentrations required for talc, but also had other minerals such as calcium.

However, just 6 particles were identified as having only the elements magnesium, silicon and oxygen in the proportions expected of talc.

Finally, Dr. Godleski has stated in his opinion that "talc found in this case is evidence for a causal link between the presence of talc and the development of this patients ovarian cancer". But he has given no basis for this conclusion other than the claim of the presence of talc. The mere presence of a particle does not indicate a cause and effect relationship. This was recognized as far back as 1971 when Henderson and colleagues merely drew attention to the presence of talc in tissues and did not suggest it was a cause of malignancy. Such a claim is certainly not valid from a medical or scientific view. Notably, of the 368 particles analyzed, only 6 are reported as pure talc. Dr. Godleski failed to answer the obvious question and that is what role, if indeed any, is played by the other 362 particles analyzed. To suggest a causal relationship between talc and ovarian cancer in this case is evidence of poor scientific judgment.

REFERENCES

1. Godleski JJ. Report on pathology slides re Ms. Blaes, April 3rd 2015.
2. Henderson WJ et al. Talc and carcinoma of the ovary and cervix. J Obstet Gynaecol, Br Commonwealth, 78:266-72, 1971.

CORNSTARCH-BASED BABY POWDER

~~Cornstarch-based dusting powders have been in use since the early 1900s.~~ Johnson & Johnson Baby Products, Inc. began developing a cornstarch-based baby powder in the early 1970s to

provide a slightly different product that would appeal to a different consumer base, but that would provide similar benefits. Johnson's Baby Powder with Cornstarch was launched in 1980. Cornstarch, which is derived from corn, is readily available in the United States. Talc, on the other hand, must be mined from the ground, often from remote and sometimes politically unstable, geographical locations. Also, as described above, the talc used in Johnson's Baby Powder, and other Johnson's personal care products, must meet rigorous standards to qualify for use in these products.

Research showed cornstarch to be, like talc, non-toxic to humans. However, cornstarch-based baby powder is not the exact equivalent of talc-based baby powder. For example, talc appears to decrease friction between skin and diapers, which can decrease chafing, better than cornstarch. On the other hand, cornstarch has superior absorptive abilities to talc. Also, blinded consumer comparison tests showed that users tended to prefer talc-based baby powder because of its fragrance and silkier texture. Another complication is that raw cornstarch is more prone to bacterial and fungal contamination and must be stored under more stringent conditions than talc.

Cornstarch-based personal care products presently represent approximately one half of the Johnson & Johnson powder market. Notably, the Shower to Shower Ms. Blaes claimed to have used contains both cornstarch and talc, with cornstarch being the more prominent constituent.

SUMMARY

In summary, Johnson's Baby Powder and Shower to Shower, both of which contain talc, are non-toxic and safe to use as intended. Johnson & Johnson Consumer Companies, Inc.'s purity standards are stringent and the talc utilized in these products is of the highest quality and is not contaminated with asbestos or any other contaminant. Nor has it ever been. Johnson & Johnson Consumer Companies, Inc. has closely tracked talc safety and, based on all the data available to date, there is simply no evidence that talc used perineally causes ovarian cancer.

In preparation for this opinion, I was provided with Plaintiff's expert reports as well as Ms. Blaes' medical records. Any opinions set out herein are to a reasonable degree of scientific certainty.

Dated: July 17, 2015