Comments on the Government of Canada Draft Screening Assessment Report for Talc (December, 2018)

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<th>Definition</th>
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<tr>
<td>ADI</td>
<td>Acceptable Daily Intake</td>
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<tr>
<td>AT</td>
<td>Averaging Time</td>
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<tr>
<td>CA</td>
<td>Concentration in Air</td>
</tr>
<tr>
<td>CEPA</td>
<td>Canadian Environmental Protection Act, 1999</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CIR</td>
<td>Cosmetic Ingredient Review</td>
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<tr>
<td>CMP</td>
<td>Chemicals Management Plan</td>
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<tr>
<td>Danish EPA</td>
<td>Danish Environmental Protection Agency</td>
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<tr>
<td>DSAR</td>
<td>Draft Screening Assessment Report</td>
</tr>
<tr>
<td>EC</td>
<td>Exposure Concentration</td>
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<tr>
<td>ECCC</td>
<td>Environment and Climate Change Canada</td>
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<tr>
<td>ED</td>
<td>Exposure Duration</td>
</tr>
<tr>
<td>EF</td>
<td>Exposure Frequency</td>
</tr>
<tr>
<td>ERC-I</td>
<td>Ecological Risk Classification for Inorganic Substances</td>
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<tr>
<td>ET</td>
<td>Exposure Time</td>
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<tr>
<td>FAO</td>
<td>Food and Agriculture Organization of the United Nations</td>
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<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>JECFA</td>
<td>Joint FAO/WHO Expert Committee on Food Additives</td>
</tr>
<tr>
<td>LOAEC</td>
<td>Lowest Observed Adverse Effect Concentration</td>
</tr>
<tr>
<td>MAK-Commission</td>
<td>Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area</td>
</tr>
<tr>
<td>MMAD</td>
<td>Mass Median Aerodynamic Diameter</td>
</tr>
<tr>
<td>MOE</td>
<td>Margin of Exposure</td>
</tr>
<tr>
<td>mppcf</td>
<td>Million Particles Per Cubic Foot</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NLR</td>
<td>Neutrophil-to-Lymphocyte Ratio</td>
</tr>
<tr>
<td>NOAEC</td>
<td>No Observed Adverse Effect Concentration</td>
</tr>
<tr>
<td>NTP</td>
<td>National Toxicology Program</td>
</tr>
<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PEC</td>
<td>Predicted Environmental Concentration</td>
</tr>
<tr>
<td>PM₄₀</td>
<td>Particulate Matter with a Diameter of 4 μm or Less</td>
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<tr>
<td>PNEC</td>
<td>Predicted No Effect Concentration</td>
</tr>
<tr>
<td>POD</td>
<td>Point of Departure</td>
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<tr>
<td>PSP</td>
<td>Poorly Soluble Particle</td>
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<tr>
<td>PVC</td>
<td>Polyvinyl Chloride</td>
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<tr>
<td>RR</td>
<td>Relative Risk</td>
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<tr>
<td>TiO₂</td>
<td>Titanium Dioxide</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>--------------------------------------------</td>
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<tr>
<td>US EPA</td>
<td>United States Environmental Protection Agency</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WoE</td>
<td>Weight of Evidence</td>
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I. Executive Summary

The Draft Screening Assessment Report (DSAR) for talc (CAS# 14807-96-6) (ECCC and Health Canada, 2018) considers the potential for talc to cause ecological harm and harm to human health.

The potential for talc to cause ecological harm was addressed in the 2018 Environment and Climate Change Canada (ECCC) Ecological Risk Classification for Inorganic Substances (ERC-I; ECCC, 2018), which was conducted using consistent, thorough, and transparent methods, making it suitable for regulatory decision-making. Based on this assessment, the DSAR identified talc as being of low ecological concern.

With regard to the evaluation of talc's potential to cause harm to human health, the DSAR does not follow Canada's own guidance for risk evaluations and deviates from best scientific practices. Specifically, the DSAR lacks transparent documentation of both the methods and data used in the assessment, and important information that can and should inform the assessment has not been considered. Consequently, the evaluation of talc’s potential to cause harm to human health presented in the DSAR is incomplete and unclear, and, in many instances, the DSAR’s conclusions are not supported by scientific evidence.

The DSAR should:

- Include improved transparency with detailed documentation regarding the methods and data used in the evaluation;
- Consider and incorporate all available relevant data; and
- Utilize a comprehensive weight-of-evidence (WoE) approach following Health Canada guidance and best scientific practices to assess the collective information used in the determination of the potential human health risks associated with talc use.

In addition, the following observations regarding the DSAR are provided herein.

Health Effects Assessment

Oral and Dermal Exposure

The DSAR appropriately concludes that the potential health effects from oral and dermal exposure to talc are of low concern.
Inhalation Exposure

The assessment of human health effects from inhalation exposure to talc does not consider all the available evidence or follow standard practices for risk assessment, and lacks transparency regarding the decision-making process. Specifically:

- The DSAR does not fully consider talc particle size, particle overload, or the steady-state toxicokinetics of poorly soluble particles (PSPs) of low inherent toxicity after inhalation exposure to talc when evaluating the toxicokinetics of talc after inhalation exposure.
- The DSAR does not consider all available human and experimental animal evidence regarding health effects from inhalation exposure to talc or provide any rationale for omitting this evidence.
- Collectively, the available human and experimental animal data regarding inhalation toxicity of talc support a health-protective margin of exposure (MOE) lower than the value that appears to have been used in the DSAR (approximately 100).

Perineal Exposure

The DSAR does not consider all the available evidence regarding health effects from perineal exposure to talc and does not properly conduct a WoE assessment of a potential causal association with ovarian cancer.

- The DSAR does not consider all the relevant evidence on the perineal toxicokinetics of talc, which collectively indicates a lack of retrograde transport to the ovaries.
- There is little evidence from animal studies regarding perineal exposure to talc, and the evidence that is available does not support a human hazard for perineal talc exposure.
- The epidemiology evidence does not support a causal relationship between perineal exposure to talc and ovarian cancer.
- The available scientific evidence does not provide sufficient support for the hypothesized modes of action of chronic irritation or immune-mediated response leading to ovarian cancer after talc exposure.
- The DSAR does not correctly apply the Bradford Hill considerations when evaluating the WoE. As concluded by other recent reviews, the overall evidence does not support a causal relationship between perineal talc use and ovarian cancer.

Exposure Assessment

The DSAR conducts a quantitative exposure assessment only for inhalation exposures to talc. However, there were numerous inconsistencies and discrepancies in this assessment, and a general lack of transparency regarding methods, exposure scenarios, and decisions regarding data selection.
The DSAR should include justification as to why the United States Environmental Protection Agency (US EPA) guidance for inhalation exposure to contaminants at hazardous waste sites was used rather than the typical approaches for estimating human exposures to chemicals in consumer products for other chemicals assessed under the Chemicals Management Plan (CMP).

The DSAR should include justification for the exposure scenarios selected for evaluation.

The DSAR should include justification for the use of PM₄ (particulate matter with a diameter of 4 μm or less) to represent adult exposures to respirable particles of talc.

The DSAR should include justification for the selection of data regarding talc concentration in air (CA), exposure frequency (EF), exposure time (ET), and exposure duration (ED) in the determination of the adjusted exposure concentration (EC) associated with certain scenarios for the use of talc-containing products.

Characterization of Risk

While the DSAR appears to consider an MOE of 100 or higher to be adequately health-protective for inhalation exposure to talc, the collective evidence in human and experimental animals supports that an MOE of 25 should be used instead because the critical effect (i.e., lung overload) is a local effect. There are also various errors, inconsistencies, and overly conservative assumptions in the DSAR regarding inhalation exposures associated with the use of talc-containing products. When the appropriate MOE of 25 and more reasonable exposure parameters are used in the risk assessment, talc inhalation exposures from the use of talc-containing consumer products do not pose any appreciable risk to human health.

DSAR References

The DSAR does not include many relevant references that provide critical information on the WoE. The DSAR also does not adequately critically review the original research studies or reviews of those studies that are included. The DSAR should be updated to include all relevant references and a critical evaluation of each one.

Conclusions

The DSAR does not consider all of the available data or follow standard risk assessment methodology, including Health Canada’s own guidance regarding WoE and the agency’s typical practice for evaluating exposure to consumer products. The available information regarding talc’s potential to cause harm to human health does not support a conclusion that talc meets the criteria under Section 64(c) of the Canadian Environmental Protection Act, 1999 (CEPA) that it is entering or may enter the environment in a quantity or concentration under conditions that constitute or may constitute a danger to human life or health in Canada. Consequently, it is
premature for the Government to consider risk management for talc, and the Risk Management Scope for Talc (Health Canada, 2018a) should be withdrawn.

II. **DSAR Overall Approach**

The Draft Screening Assessment Report (DSAR) (ECCC and Health Canada, 2018) lacks transparent documentation of both the methods and data used in the assessment, and important information that can and should inform the assessment has not been considered. Consequently, the evaluation of talc’s potential to cause harm to human health presented in the DSAR is incomplete and unclear, and, in many instances, the DSAR’s conclusions are not supported by scientific evidence.

The Government of Canada, under the auspices of the Minister of the Environment and the Minister of Health, conducted a screening assessment of talc pursuant to Section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA). Notice of the publication of the DSAR was made in the *Canada Gazette*, Part 1: Vol. 152, No. 49, on December 8, 2018.

In 2006, the Government of Canada implemented the Chemicals Management Plan (CMP) under CEPA as an initiative aimed at assessing roughly 4,300 of the 23,000 chemical substances on the domestic substances list categorized as meeting the criteria for further attention and reducing the risks posed by chemicals to Canadians and the environment when necessary. The risk assessment process is a scientific evaluation of the risk posed by a substance, considering both the hazardous properties of the substance and the nature of the exposure of Canadians or the environment to the substance.

The Government of Canada developed the Risk Assessment Toolbox to formally identify approaches that have been used to address substances under the CMP (Health Canada, 2016). The Toolbox notes, among its Type 3 approaches, three levels of fit-for-purpose assessment that apply an appropriate level of effort using standard risk assessment methods considering both hazard and exposure, for either the ecological assessment and/or health assessment, in increasing levels of detail. The Government’s work plans and spreadsheets indicate that a Type 3 approach for human health assessments should be used for talc (Government of Canada, 2018). In addition, the Government notes, with respect to risk assessment of chemical substances: "In conducting a risk assessment, a weight of evidence approach and precaution are applied" (Health Canada, 2017). Recent guidance regarding the Government’s approach to the application of weight of evidence (WoE) is available (Health Canada, 2017, 2018b).

The Government has considered the potential for talc to cause ecological harm and harm to human health. The ecological risk of talc was characterized previously as part of the 2018 Environment and Climate Change Canada (ECCC) Ecological Risk Classification for Inorganic Substances (ERC-I; ECCC, 2018), so the DSAR’s focus is on the evaluation of talc’s potential to cause harm to human health. Per the work plans noted above, the Government’s intent was to conduct a level 3 exposure and hazard characterization associated with consumer use of
products containing talc, and it would appear this was intended as a level 3-2 de novo assessment based on the Toolbox descriptors. However, the DSAR provides few details regarding the intent and processes used by the Government in its preparation of the report.

Specifically, the DSAR lacks transparent and detailed documentation of the methods and evidence on which the conclusions it presents are based. The DSAR does not provide any detailed information on evidence identification (e.g., literature search strategies, study inclusion/exclusion criteria) or synthesis processes (e.g., WoE evaluation framework). Important evidence has been omitted from the health effects assessment and the DSAR does not provide any rationale for omitting this evidence. As a result, some of the conclusions in the DSAR are not supported by all the available evidence.

To ensure that the regulatory decision-making process is scientifically sound, additional details regarding the risk assessment approach, the evidence identified and assessed, and the evaluation of the WoE in the DSAR should be provided.

Reviews of and comments on the significant sections of the DSAR are provided below.

III. Sources and Uses of Talc

The DSAR has included sufficient information regarding the sources and uses of talc.

Based on information submitted as part of a CEPA Section 71 survey and from the Canadian International Merchandise Trade database, the DSAR reports that talc is manufactured and imported into Canada at quantities ranging from 50 million to 100 million kg per year (ECCC and Health Canada, 2018). This information is consistent with industry information that was submitted to the Government of Canada in recent years but was not cited in the DSAR (CCTFA and IMA-NA, 2015; CA Canada and IMA-NA, 2018).

The DSAR identifies talc as being used in major technical applications related to the manufacture of paper, plastics, and paints, among other products. In addition, there are important minor uses of talc in consumer products such as cosmetics. Approximately 3-4% of the talc produced in North America is reported to be used in cosmetics. Likewise, this information regarding talc uses is consistent with recent industry submissions (CCTFA and IMA-NA, 2015; Cosmetics Alliance Canada and IMA-NA, 2018).

The DSAR’s summary of the sources and uses of talc is appropriate.

IV. Characterization of Ecological Risk

The ecological risk of talc is low.
The ecological risk of talc was characterized as part of the ERC-I (ECCC, 2018). This involved read-across of ecotoxicological hazard endpoint data from an Organisation for Economic Co-operation and Development (OECD) screening information dataset for synthetic amorphous silicates (OECD, 2004). Using the lowest acceptable ecotoxicity endpoint and an assessment factor, a predicted no effect concentration (PNEC) for aquatic species of 40 mg/L was derived, which reflects the low ecotoxicological hazard potential of talc.

Using data from the Domestic Substances List-Inventory Update and import data from the Canada Border Services Agency, predicted environmental concentrations (PECs) for talc were modeled and compared to the PNEC to provide the prospective ecological risk characterization for talc. The ERC-I identified talc as being of low ecological concern.

The ERC-I approach used to assess the ecological risks of talc and other inorganic substances is consistent with science-based methodologies utilized by ECCC under the CMP. This approach is also consistent with industry information that was submitted to the Government of Canada in recent years but was not cited in the DSAR (CCTFA and IMA-NA, 2015; CA Canada and IMA-NA, 2018). The ERC-I evaluation included peer review by qualified external experts and stakeholder consultation as part of its development and finalization. Consequently, the ERC-I evaluation’s results and conclusions regarding talc can be considered appropriate to use for regulatory decision-making for talc under CEPA.

*The DSAR’s conclusion regarding the ecological risks of talc is appropriate.*

V. Human Health Effects Assessment Methodology

The human health effects assessment does not consider all the available evidence, does not follow standard practice for weight-of-evidence analyses, and lacks transparency regarding the decision-making process.

A WoE analysis involves a review of all relevant studies, considering the strengths and weaknesses of each, and weighing their points of agreement and contradiction. There are a number of methods for evaluating scientific evidence using a WoE approach (e.g., Rhomberg et al., 2011; Adami et al., 2011), all of which emphasize a systematic and transparent approach to the analysis. Perhaps the most widely used approach (either as proposed or with slight modifications), including by many regulatory agencies (including Health Canada), is that outlined by Sir Austin Bradford Hill in his address to the British Royal Academy of Medicine in 1965. Details about the WoE approach used by Health Canada (2018b) and the Bradford Hill considerations are provided in Appendix A.

As described in the sections that follow, the DSAR does not include a WoE analysis or provide transparent documentation for its decision-making process. It does not discuss all the relevant literature; it does not critically assess the quality or reliability of individual studies or pieces of information, or the sources of summarized information; and it does not critically assess each
line of evidence based on the overall strength or confidence in the information and its relevance to the assessment outcome. For example, the DSAR does not critically evaluate the primary epidemiology studies of perineal talc exposure and ovarian cancer, but relies heavily on the results of a systematic review and meta-analysis by Taher et al. (2018), which is not yet publicly available and does not appear to have been peer reviewed. The DSAR does not provide sufficient details on the methods of the Taher et al. (2018) review and does not critically assess whether the results and conclusions of Taher et al. (2018) were robust. Also, while the DSAR describes some of the scientific evidence regarding ovarian cancer and perineal talc exposure in the context of the Bradford Hill considerations, it does not consider them in an appropriate, scientific manner (see Appendix B). In addition, the DSAR does not discuss evidence regarding respiratory effects and talc inhalation exposure in the context of the Bradford Hill considerations at all.

Although the comments below do not constitute a full WoE analysis, they demonstrate the importance of considering how the larger body of scientific literature and the quality of individual studies impact the interpretation of the evidence regarding talc’s potential to cause harm to human health.

The DSAR should include transparent and appropriate WoE analyses for evaluating the health effects of talc exposures.

VI. Toxicokinetics

1. Oral and Dermal Exposures

The DSAR appropriately concludes that the potential health effects from oral and dermal exposure to talc are of low concern.

The DSAR briefly describes the toxicokinetics of talc after oral and dermal exposures. As indicated in the DSAR, oral and dermal exposures are of low concern regarding the potential human health hazards of talc, and thus, the short summaries of oral and dermal talc toxicokinetics provided in the DSAR are appropriate.

The DSAR has included sufficient information regarding the toxicokinetics of talc after oral and dermal exposures.

2. Inhalation Exposure

The DSAR does not fully consider talc particle size, particle overload, or the steady-state toxicokinetics of poorly soluble particles (PSPs) of low inherent toxicity when evaluating the inhalation toxicokinetics of talc.
The DSAR provides a brief, one-paragraph overview of talc inhalation toxicokinetics. In particular, the DSAR provides a summary of Wehner et al. (1977a), in which radioactive talc in the form of baby powder was administered to hamsters via a single 2-hour nose-only exposure. The DSAR notes the deposition of a portion of the administered talc in the alveoli, the biological half-life of 7-10 days, the completion of alveolar clearance after 4 months, and the lack of translocation of talc from the respiratory tract to other parts of the body. The DSAR also briefly introduces the issue of impaired clearance of talc particles with increasing exposures, citing original work by Pickrell et al. (1989) and reviews by Oberdorster (1995a), the Danish Environmental Protection Agency (Danish EPA, 2016), and Germany’s Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK-Commission, 2012).

The inhalation toxicokinetics of talc (and other PSPs of low inherent toxicity\(^1\)) impacts the interpretation of animal inhalation studies, and thus warrants a more robust analysis in the DSAR. This should include a consideration of particle toxicokinetics, particle overload, and the steady-state toxicokinetics of PSPs of low inherent toxicity.

Inhaled particles can be deposited in various compartments of the respiratory system, including the nasopharyngeal region (i.e., including the nose, mouth, pharynx, and larynx), the bronchial region (i.e., the trachea, bronchi, and bronchioles), and the alveolar-interstitial region (i.e., alveoli, respiratory bronchioles) (NIOSH, 2011). Generally, respirable particles (<~2.5 μm in aerodynamic diameter) deposit in the middle and lower airways, and larger inhalable particles (<~10 μm) deposit in the upper airways. Deposited particles can be removed from the respiratory tract over time by a variety of clearance mechanisms. Insoluble particles that deposit in the bronchial region can be cleared by mucociliary clearance, while smaller insoluble particles that deposit in the alveolar-interstitial region are subject to longer retention times because this region lacks mucociliary clearance capability. Most particles that deposit in the alveoli are engulfed (i.e., phagocytosed) by alveolar macrophages, which may digest or migrate the particles to facilitate removal (NIOSH, 2011). The ability of a particle to be retained and remain intact in the lung is considered an important factor in the process of an adverse biological response. Generally, the deeper in the lung the deposition, the longer the retention time.

In its safety assessment of cosmetic talc, the Cosmetic Ingredient Review (CIR) Expert Panel indicated that the average particle size of typical cosmetic talc ranges from 4-15 μm, with only minor fractions in the respirable range (Fiume et al., 2015). Recently, Cosmetics Alliance Canada conducted a (confidential) voluntary membership survey to collect information on the particle size distribution of talc in cosmetic talc formulations (Cosmetics Alliance Canada, 2017). For body powders, the average raw-material particle size specifications were reported in the

\(^1\) Other PSPs of low inherent toxicity include titanium dioxide (TiO\(_2\)), carbon black, toner particles, polyvinyl chloride (PVC) particles, diesel soot, coal dust, petroleum coke, oil shale, and volcanic fly ash (Warheit et al., 2016; Oberdorster, 1995b); these are differentiated from other particles that are cytotoxic, such as quartz.
range of 10.5-25 μm, without the expectation of a reduction in size in finished cosmetic talc formulations (Cosmetics Alliance Canada, 2017). In contrast, the DSAR reported the particle size distribution of three products (one baby powder and two adult body powder products) containing high concentrations of talc (>90%) available in Canada from an unpublished study (Rasmussen, 2017). The particle size distribution for the three products ranged from <0.5-8 μm, with median particle sizes ranging from 1.7-2 μm.

In the study from which the DSAR derives the no observed adverse effect concentration (NOAEC) it uses for evaluating talc inhalation exposures, the National Toxicology Program (NTP, 1993) used micronized talc to reduce the particle size of the talc powder to mass median aerodynamic diameters (MMADs) of 2.7 -3.2 μm. Compared to typical talc particle sizes in cosmetic products, the particle sizes used by NTP (1993) likely deposited deeper in the lung and had a longer retention time and greater potential to elicit adverse pulmonary effects than cosmetic talc would. It appears that the justification for deriving the NOAEC using the NTP (1993) study may be from the personal communications by Rasmussen (2017), in which Rasmussen states that there are consumer products sold in Canada in which all of the talc particles are within the inhalable range (<10 μm) and the median particle size is within the respirable range (<4 μm).

Talc is one of several PSPs of low inherent toxicity that are subject to lung overload, a condition in which alveolar macrophage-mediated clearance of particles in the lung is impaired following prolonged high-dose exposures (Warheit et al., 2016). When alveolar macrophage-mediated lung clearance is impaired, the eventual outcome with continued exposure to PSPs is the accumulation of excessive lung burdens (Oberdorster, 1995b). There are toxicological implications of the excessive dust load that can occur with particle overload, including non-cancer respiratory toxicity (e.g., pulmonary inflammation, fibrosis, epithelial hyperplasia) and, in rats, cancer (Warheit et al., 2016). Thus, even rather benign particles can induce adverse pulmonary effects when inhaled chronically at sufficient concentrations (Oberdorster, 1995b, 2002).

In essence, when inhalation exposures to PSPs of low inherent toxicity are high enough to overwhelm and impair the capacity of alveolar macrophages to clear the deposited particles, the retained lung burden increases more than would be predicted with normal clearance kinetics. Conversely, if the deposition rate in the alveolar region is less than or equal to the clearance rate, lung clearance mechanisms function properly and no excessive accumulation of particles is expected (Oberdorster, 1995b). Importantly, the risk of lung overload is non-linear, i.e., there is likely a threshold of exposure to PSPs of low inherent toxicity below which lung overload, and the adverse respiratory effects secondary to it, would not occur. This threshold can be used to identify a NOAEC for pulmonary effects tied to the prevention of impaired alveolar macrophage-mediated clearance (Oberdorster, 2002). However, because lung overload is clearly a high-dose effect, this increases the uncertainty when extrapolating the study results of lung overload in experimental animals to humans exposed to much lower concentrations (Oberdorster, 2002).
Another concept that is important for talc toxicokinetics is that of a steady-state lung burden during continuous exposure (ILSI, 2000; Oberdorster, 2002). With normal alveolar clearance (i.e., deposition rate ≤ clearance rate), it has been predicted that lung burden will reach an equilibrium after approximately five retention half-times have elapsed (for example, the alveolar retention half-time for rats is 70 days) (Oberdorster, 1995b). The DSAR states that "lung burdens were proportional to respired concentrations" (ECCC and Health Canada, 2018), presumably in reference to the 2-hour exposure study by Wehner et al. (1977a). The DSAR also states that "[e]pisodic exposures from product use are expected to increase lung load due to the long alveolar clearance of talc" (ECCC and Health Canada, 2018). These statements do not acknowledge that lung burdens would not be expected to increase indefinitely with continued exposure to talc as long as normal alveolar clearance is operational.

The DSAR should discuss the evidence indicating that the average particle sizes of talc in personal care products generally prevent the retention of talc in the human lung, should rely on experimental studies using talc with relevant particle sizes, and should consider the toxicokinetics of PSPs in general to inform lung burden and lung overload following inhalation exposure to talc.

3. Perineal Exposure

The DSAR does not consider all the relevant evidence on the perineal toxicokinetics of talc, which collectively indicates a lack of retrograde transport to the ovaries.

The DSAR indicates that talc particles have been observed in human ovaries and that perineal exposure has been associated with talc in the lymph nodes and ovaries of women diagnosed with ovarian cancer. It also suggests that talc can migrate from the vagina to the ovaries by retrograde transport and that inert particles that are the same size as talc placed in the vagina can be transported to the upper genital tract. However, the DSAR does not consider all the relevant literature regarding perineal toxicokinetics and does not consider the methodological limitations of the studies it cites. These limitations are discussed further below.

a Talc in Ovarian Tissues

The DSAR does not discuss how several case studies and small-scale studies do not provide definitive evidence that perineal talc use is associated with the presence of talc in ovarian tissues.

With regard to the presence of talc in the ovaries, the DSAR only cites studies by Heller et al. (1996a,b). However, the scientific literature includes a number of individual case studies and small-scale studies that explored the presence of talc particles in ovarian tissues. These studies examined tissue samples from surgical patients, including patients with ovarian cancer and others judged to have healthy ovarian tissues.
Based on results from an extraction-replication technique that their laboratory developed to study the presence of foreign particles in tissue samples, Henderson et al. (1971) reported that talc was observed in tissue samples from 10 of 13 ovarian tumors, 12 of 21 cervical tumors, and 5 of 12 samples judged to reflect normal ovarian tissues (from patients with breast cancer). In a subsequent investigation, these researchers reported observing talc in additional samples: three samples from normal ovaries, three from cystic ovaries, and three from adenocarcinomas (Henderson et al., 1979). Using several microscopic methods, a more recent case study report indicated the presence of talc particles in samples collected from the pelvic lymph nodes of one woman with ovarian cancer (Cramer et al., 2007). These researchers stated that the use of polarized light microscopy identified "diffuse areas of birefringence compatible with talc," and that examination of the samples using scanning electron microscopy and X-ray spectroscopy confirmed the presence of talc (Cramer et al., 2007).

In a study of ovarian samples from 100 women with "grossly normal" ovaries undergoing surgery for pelvic disease, Mostafa et al. (1985) observed "crystalline foreign particles" in histological evaluations of the samples from 9% of the subjects. They then analyzed four samples containing the foreign particles using a scanning electron microscope and computer-assisted microscopic X-ray analysis to evaluate the elemental composition of the particles. Based on these analyses, these researchers concluded that the particles were composed largely of magnesium and silicon. They did not definitively confirm the observed particles as talc but identified talc and asbestos as the "most common compounds containing magnesium silicates" (Mostafa et al., 1985). Heller et al. (1996b) examined the presence of talc particles in normal ovarian tissue samples collected from 24 women undergoing incidental oophorectomy (i.e., surgical removal of one or both ovaries) to address benign ovarian neoplasms. They identified talc particles in samples from all 24 women by either polarized light microscopy or analytic electron microscopy. As discussed further below, these researchers also collected information regarding the study subjects' perineal talc use and found no relationship between talc particle counts in the ovary samples and the participants' reported talc use.

Several aspects of these studies must be considered when evaluating their significance for assessing the plausibility of perineal talc use as an exposure that could substantially contribute to the development of ovarian cancer. First, some methods used in these studies did not definitively identify talc as the particle type observed in the samples. For example, Mostafa et al. (1985) characterized the particles as "crystalline foreign particles" containing magnesium and silicon based on histological evaluation and scanning electron microscopy. As they noted, asbestos is another magnesium silicate that is relatively common. Other methodological issues include that the particles detected in the samples could have been due to sample contamination, e.g., from particles on the gloves of individuals obtaining or analyzing the samples. For example, because such questions had been raised regarding their earlier study (Henderson et al., 1971), Henderson et al. (1979) noted that they were particularly careful to avoid contamination sources in their 1979 study.
More importantly, the evidence does not provide any clear pattern of exposure that is suggestive of a dose-response relationship, especially in the context of perineal talc use. There is no evidence of a difference in ovarian particle content between healthy study subjects and those with ovarian cancer. For example, in Henderson et al. (1979), the highest measure of talc presence was observed in a sample from normal ovaries.

With respect to Heller et al. (1996b), these authors found no patterns suggesting any association between talc particle counts in ovarian tissue samples and perineal talc use. These researchers approximated talc exposure levels by estimating the subjects’ "lifetime talc applications." Using light microscopy, they observed talc particles in ovarian samples from all but one of the study subjects. Using electron microscopy, they observed talc particles in approximately one-half of the study subjects, including subjects with ("exposed") and without ("unexposed") perineal talc use. Light and electron microscopy reportedly measure different size particles. The reported talc particle counts from both types of microscopy showed no quantitative relationship with the estimated level of talc use Heller et al. (1996b). For example, in unexposed women, particle counts observed using light microscopy ranged from 0-2,200 per gram, while counts in exposed women ranged from 26-464 per gram. The lowest particle count in the exposed group was reported for the woman with the highest estimated lifetime talc applications. In the electron microscopy results, talc particle counts in the exposed and unexposed groups spanned ranges similar to each other. The counts for approximately one-half of the women in each group were zero, and there was no indication of increasing particle counts with increasing exposure. These results provide no evidence of an association between perineal talc use and the presence of talc particles in ovarian samples.

In addition to the studies by Heller et al. (1996a,b), the DSAR should cite the individual case studies and small-scale studies that explored the presence of talc particles in ovarian tissues and acknowledge that they do not provide definitive evidence that perineal talc use is associated with the presence of talc in ovarian tissues.

### Retrograde Transport

The DSAR does not discuss human and animal mechanistic transport studies that do not support retrograde transport of talc from perineal application of talc powder.

A number of investigations have examined particle transport in the female reproductive tract. Almost all of the identified human studies involved hospitalized populations and particles other than talc. It has not been demonstrated that the mobility of these other particle types is representative of talc mobility. Animal studies investigated talc as well as other particle types. No identified studies of humans or animals specifically examined particle transport following external application to the perineal area. Instead, the studied particles were typically in a solution and were placed within the reproductive tract (e.g., intravaginally). In one case, starch particles from surgical gloves were introduced into the reproductive tract during gynecological examinations.
In one study of hospitalized patients, Egli and Newton (1961) deposited inert carbon particles in solution in the vaginas of women patients undergoing elective abdominal hysterectomy. In two of the three patients, they observed particles in the patients’ fallopian tubes within approximately 30 minutes. Wehner et al. (1986) noted that this study was not quantitative and did not include any blanks or negative controls. De Boer (1972) placed India ink (a suspension of carbon particles) at various locations within the reproductive tracts of 178 women undergoing abdominal surgery. They concluded that the placement location was associated with the frequency of observing particles in the fallopian tubes. In particular, noting the role of the cervix as a barrier to transport, these researchers observed that particles placed in the vagina were seen in the fallopian tubes in only 1 of 37 patients. Venter and Iturralde (1979) placed a solution of albumin microspheres labeled with radionuclides intravaginally in 24 patients undergoing gynecological surgeries. In 9 out of 14 cases in which radioactivity measurements in the uterus were counted separately from those in the ovaries and fallopian tubes, radioactivity levels were detected in either the ovaries or fallopian tubes. The five negative results were all from patients with tubal damage from previous infections. Venter and Iturralde (1979) concluded that these findings indicated that particle transport from the vagina to the fallopian tubes is possible. Kunz et al. (1996) also investigated particle transport in the female reproductive tract using radioactively labeled albumen microspheres. In this study of 64 women, a solution containing the particles was placed in the vagina just outside the entrance to the cervix. Some microspheres entered the uterus and reached the fallopian tubes within minutes.

In a more recent study of approximately 60 surgical patients, Sjosten et al. (2004) investigated retrograde migration of starch particles from powdered gloves. Either 1 or 4 days prior to elective hysterectomies, study subjects had an intravaginal gynecological examination where powdered gloves (exposed group) or powder-free gloves (control group) were used. For individuals undergoing the exam 1 day prior to the surgery, there were statistically significant differences in the numbers of particles between the exposed and control groups in the cervix, uterus, and fallopian tubes. Ovaries were not examined. For individuals undergoing the exam 4 days prior to the surgery, statistically significant differences were observed for small and large particles in the cervix and uterus.

Conditions in these studies raise questions regarding whether their findings can be generalized to healthy women. In particular, questions exist regarding whether the health status of the women might have affected clearance function (IARC, 2010). Study conditions in which women were under anesthesia and had restricted movements during surgical procedures could also have impacted typical transport functions. In some instances, the researchers deliberately instituted measures to encourage mobility of the instilled particles. For example, Egli and Newton (1961) scheduled women for observation/surgery at or near ovulation (when they expected transport to be optimal), had the women lying down during the observation period, and administered oxytocin as a potential agent to facilitate particle transport. A concern specific to the Venter and Iturralde (1979) study using radionuclides is whether the
radioactivity counts reflected actual particle transport or leaching of the radioactivity from the particles (e.g., as discussed in Wehner et al., 1986). A final concern is that several studies directly applied talc in a liquid medium, which is not comparable to external perineal exposure of a dry powder.

Furthermore, even if talc particles are observed to be present in ovarian cancer tissue samples, their presence does not prove that they played any causal role in the development of the cancer, an observation recognized by several of the researchers in this area. For example, Henderson et al. (1979) noted that their 1971 study merely observed the presence of talc in the tissue samples and "did not suggest that it was the cause of malignancy." Similarly, Mostafa et al. (1985) acknowledged that their study did not "demonstrate that [particulate] matter is capable of producing proliferations under some circumstances." Instead, the focus of their study was on the presence of particulate matter in the female pelvis. More recently, Cramer et al. (2007) also noted that "case reports cannot establish causality."

Based on its review of the available literature, the International Agency for Research on Cancer (IARC, 2010) characterized the evidence for retrograde transport of talc to the ovaries in normal women as "weak." This conclusion is consistent with the observation of an earlier review at a workshop sponsored by the International Society of Regulatory Toxicology and Pharmacology and the United States Food and Drug Administration (FDA) that, while results for other types of particles were mixed, "available histological and physiologic studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region" (Carr, 1995).

Potential talc transport in the reproductive tract has also been studied in rodents, rabbits, and primates. Several of these studies involved intrauterine or intravaginal installation of talc in a liquid medium, which does not mimic perineal use. Seventy-two hours following a single intravaginal administration of a radiolabeled talc suspension in three rabbits, radioactivity was observed only at the site of administration (Phillips et al., 1978). Similar readings taken 72 hours after six daily intravaginal doses found no migration of talc to the animals' ovaries; a small amount of radioactivity was reported to be associated with the cervix and fallopian tubes. In a study using 26 rabbits, Edelstam et al. (1997) reported finding starch particles in peritoneal cavity rinsate collected on multiple days following intravaginal administration of a single dose. The authors stated that this finding indicates "the possibility of retrograde migration" but also noted that they did not see overall statistically significant differences in the numbers of particles in the rinsates between the control and exposed groups (Edelstam et al., 1997). A study in eight rats reported some evidence of talc transport to the ovaries following intrauterine administration of a single dose of a talc-containing solution (Henderson et al., 1986). Evidence of talc transport to the ovaries was reported for two out of six rats administered a single intravaginal dose and examined 4 days later, but not in those examined 24 or 48 hours post-dosing.

Studies in monkeys, the species with a reproductive tract most closely resembling that of humans (Wehner et al., 1985), provided no evidence of retrograde talc transport. In one study,
six cynomolgus monkeys received 30 intravaginal applications of a radioactive talc suspension over a 45-day period (Wehner et al., 1986). Despite the extensive dosing, radioactivity readings provided no evidence of talc transport to the uterus or beyond. A pilot study for this investigation had similar findings (Wehner et al., 1985). A similar study by these researchers using bone black also found no evidence of particle transport to the uterus or beyond (Wehner et al., 1985). In this investigation, five cynomolgus monkeys were administered a single intravaginal dose of the test solution, and evidence of translocation was collected 1 hour (three monkeys) or 72 hours (two monkeys) after administration. These animals also received an injection of oxytocin to mimic certain experimental procedures used in previous human studies.

No animal studies directly examined potential talc transport following external perineal administration of talc. However, potential transport of talc particles to the ovaries was explored as one element of a lifetime whole body exposure toxicity study in rats undertaken by NTP (Boorman and Seely, 1995). In this study, rats were exposed to a talc aerosol at very high concentrations that were sufficient to cover their fur and the cage bars, providing “ample opportunity for perineal as well as oral and respiratory exposure” (Boorman and Seely, 1995). Examination of the ovaries and ovarian bursa found no evidence of material consistent with talc.

Taken together, the human and animal mechanistic transport studies do not support retrograde transport of talc from perineal application of talc powder.

While the DSAR mentions a few studies that assessed mechanistic transport of talc in the reproductive tract, it does not critically review any of these studies and excludes several other relevant studies (discussed above). Collectively, all the available studies do not support retrograde transport of talc to the ovaries from perineal application of talc powder.

VII. **Health Effects Assessment**

1. **Oral and Dermal Exposures**

The available data do not demonstrate health effects from oral or dermal exposure to talc.

The DSAR briefly discusses the lack of adverse effects from oral exposure to talc in laboratory studies and cites several safety assessments by various scientific and regulatory bodies that indicate a lack of human health hazard from oral exposure to talc. The DSAR’s conclusion that oral talc exposure is of low concern regarding human health is appropriate.

As discussed in the DSAR, while the body of evidence on dermal exposure to talc is limited, the available research, combined with the water-insoluble nature of talc powder, indicates a lack of dermal absorption, irritation, or sensitization from dermal exposure to talc.
The DSAR’s conclusions regarding the health effects from oral and dermal exposures to talc are appropriate.

2. Inhalation Exposure

The DSAR does not consider all the available data regarding health effects from inhalation exposure to talc. The available human and experimental animal data justify a health-protective margin of exposure (MOE) substantially lower than the value that appears to have been used in the DSAR (approximately 100).²

The DSAR considers a number of studies that evaluated toxicity from inhalation exposure to talc in humans and laboratory animals, concludes that chronic inhalation exposure to talc causes talcosis in humans, and identifies a NOAEC of 2 mg/m³ from an NTP study of rodents. However, the DSAR evaluation of health effects from talc inhalation exposures is undermined by several critical issues, which are discussed in detail below.

a Human Studies

NOAEC values derived directly from human studies of long-term talc exposure considerably reduce the uncertainty associated with the use of a point of departure (POD) from an animal toxicity study.

The DSAR briefly summarizes a comprehensive safety assessment of talc by the Danish EPA (2016) and a recent meta-analysis (Chang et al., 2017), discusses the uncertainties regarding workplace co-exposures and smoking in occupational epidemiology evidence for talc, and appropriately dismisses lung cancer as a critical effect from talc inhalation exposure.

With regard to non-cancer respiratory effects, the DSAR focuses on pure talc-induced pneumoconiosis (i.e., talcosis) and summarizes findings from a number of human studies. However, all but one study cited by the DSAR are case reports or case series. A case series is a group or series of case reports of individuals who had a similar health outcome or were given a similar treatment (Hennekens and Buring, 1987). Case reports usually contain information about individual patients, but they can vary in terms of the level of detail provided about patients’ clinical histories. Also, because there are no individuals without the outcome to consider for comparison, it is not possible to determine whether a particular exposure or treatment was a causal factor for the health effects of concern (Grimes and Schulz, 2002). Thus, the primary utility of case series is for hypothesis generation. Only results from comparative studies (e.g., clinical trials and analytical epidemiology studies) can be used to evaluate possible causal associations. While the case reports/series described pneumoconiosis patients with past

² When extrapolating from a POD in experimental animals to humans, an MOE of 100 is typically used as the cutoff for being adequately health-protective. This default MOE value of 100 is the product of the interspecies uncertainty factor (default value = 10) and the intraspecies uncertainty factor (default value = 10).
inhalation exposure to talc, because of the study design, these studies cannot establish talc exposure as a causal factor for the observed pneumoconiosis.

The only comparative study cited by the DSAR is a longitudinal cohort study conducted by Wild et al. (2008) in French and Austrian talc workers with an average exposure duration (ED) of 14.5 years and a mean exposure concentration (EC) of 1.46 mg/m³ between 1988 and 2003. The study evaluated the prevalence of small radiological opacities (as a marker for talcosis) and other respiratory outcomes, and reported that cumulative exposure to talc was significantly associated with an increased prevalence of small radiological opacities. However, the DSAR does not consider that the observed association with talcosis was limited to cumulative talc exposure at study initiation (reflecting higher exposures from earlier periods), and cumulative talc exposure within the study period was not associated with talcosis. The DSAR also does not discuss any limitations or uncertainties of the study, such as the potential for exposure misclassification, or acknowledge the conclusion by Wild et al. (2008) that "there was no evidence of detrimental effects of talc exposure, as assessed within the study period, on lung function and small radiological opacities."

There are several additional epidemiology studies that evaluated radiological manifestations of pneumoconiosis in workers exposed to pure talc, all of which have been discussed in the talc assessment performed by Germany’s MAK-Commission (2012). Despite citing the MAK-Commission assessment, the DSAR does not include these epidemiology studies in its assessment of talc inhalation exposure, nor does it provide any rationale for omitting these studies.

Fine et al. (1976) administered pulmonary function tests, chest X-rays, and respiratory questionnaires to 80 rubber workers exposed to industrial-grade talc and 189 non-exposed workers from 1972-1974. The maximum cumulative exposure to talc was estimated to be below 60 million particles per cubic foot (mppcf)-years (i.e., 8 mg/m³-years) among the exposed workers, and none of the talc-exposed workers had radiological findings consistent with talcosis.

Rubino et al. (1979) conducted a survey in 43 talc millers who did not have other exposures to inorganic or organic dust to assess the exposure level at which talcosis may occur. The cumulative talc exposure in these workers ranged from <80 to ≥320 mppcf-years. Radiographic opacities with profusion ≥1/0 did not appear until cumulative exposure exceeded 160 mppcf-years (i.e., 21.3 mg/m³-years).

A cross-sectional survey conducted among 202 workers exposed to industrial-grade talc dust and 101 unexposed controls in India evaluated a number of respiratory health outcomes, including radiological changes indicating pneumoconiosis (Damodar et al., 1983; Bachani and Agarwal, 1985). While the study reported that the talc dust had a very low free-silica content, no quantitative exposure estimates were provided. Out of 79 workers with more than 5 years of
exposure, 2 workers had radiological changes consistent with pneumoconiosis, compared to none of the 123 workers with less than 5 years of exposure or the 101 unexposed controls.

Wild et al. (1995) evaluated respiratory effects among 166 French talc millers, many of whom were also included in the longitudinal study by Wild et al. (2008). The estimated talc ECs ranged from 0.5-50 mg/m³, with a geometric mean of 1.87 mg/m³, and the cumulative exposures spanned from 0-20 to >500 mg/m³-years. The results clearly suggest a threshold effect: the prevalence of small radiological opacities (profusion ≥1/0) did not increase until the cumulative talc exposure exceeded 50 mg/m³-years.

While the occupational exposures assessed in these epidemiology studies were not to cosmetic-grade talc, the talc had very few and low concentrations of impurities. Given that there are no comparative human studies conducted in consumers with exposure to cosmetic talc, these occupational studies provide valuable insights into the potential respiratory effects resulting from high levels of talc exposure. In addition, some of these studies provide NOAECs for talcosis in humans (Table 1). Because of the observational nature of the epidemiology studies and the inherent uncertainties in the exposure estimates, these observed NOAECs cannot be readily used in a quantitative exposure/risk assessment. However, because they are long-term exposure values obtained directly from human populations, these NOAECs considerably reduce the uncertainty associated with the use of a POD identified from an animal toxicity study.

Table 1. Observed NOAECs for Pneumoconiosis in Occupational Epidemiology Studies of Talc

<table>
<thead>
<tr>
<th>Study</th>
<th>Observed NOAEC (mg/m³-years)</th>
<th>Mean Duration of Exposure (years)</th>
<th>NOAECoccupational (mg/m³)</th>
<th>Adjusted NOAECb (mg/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine et al. (1976)</td>
<td>8</td>
<td>8.9</td>
<td>0.90</td>
<td>0.32</td>
</tr>
<tr>
<td>Rubino et al. (1979)</td>
<td>21.3</td>
<td>15.5</td>
<td>1.37</td>
<td>0.45</td>
</tr>
<tr>
<td>Wild et al. (1995)</td>
<td>50</td>
<td>12.0</td>
<td>4.17</td>
<td>1.49</td>
</tr>
</tbody>
</table>

Notes:
NOAEC = No Observed Adverse Effect Concentration.
(a) NOAECoccupational = Observed NOAEC / Mean Duration of Exposure.
(b) Adjusted NOAEC = (NOAECoccupational × 5 days/week × Ventilation Rateoccupational [10 m³/day]) / (7 days/week × Ventilation Ratenn-occupational [20 m³/day]) (TCEQ, 2012).

The DSAR should cite and discuss additional epidemiology studies that reduce uncertainty regarding the inhalation toxicity of talc.

b Animal Studies

The DSAR does not include all the available animal toxicity studies that are relevant to inhalation exposure to talc, including studies of other PSPs.
The DSAR describes the results of a chronic inhalation study of talc in rats and mice conducted by NTP (1993). The DSAR concludes that cancer effects observed in rats in this study are not relevant to humans because such a response has been demonstrated to be specific to the rat; this is consistent with a number of reviews of the NTP (1993) study (e.g., Warheit et al., 2016; Wehner, 2002; ILSI, 2000; Goodman, 1995; Oberdorster, 1995a). With regard to non-cancer effects, the DSAR identifies the lowest concentration administered to both rats and mice of 6 mg/m\(^3\) as the lowest observed adverse effect concentration (LOAEC) for lung effects, acknowledging that lung overload occurred at this and the higher administered concentration (18 mg/m\(^3\)) in both rats and mice. Thus, the DSAR relies on the NTP (1993) 4-week inhalation range-finding study for selection of a NOAEC, which was the lowest EC of 2 mg/m\(^3\). The NOAEC was adjusted to a continuous EC of 0.36 mg/m\(^3\).

The DSAR ultimately compares the adjusted NOAEC to the average air concentration of talc following the use of loose-powder personal care products, similarly adjusted to continuous exposure. It then calculates MOEs to describe the ratio of the adjusted NOAEC to the adjusted air concentrations associated with personal care product use. Consistent with the customary calculation of MOEs, no factors are included for differences in human or animal susceptibility. In general, MOEs of less than 100 have been used by regulatory agencies as a cutoff for further evaluation (Faustman and Omenn, 2013). MOEs calculated in the DSAR are 50-106 for powders and 327 for dry hair shampoo. The DSAR considers the MOEs for the talc powders to be "inadequate to account for uncertainties in the health effects (including a lack of a NOAEC from chronic studies) and exposure databases" (ECCC and Health Canada, 2018). Despite these uncertainties, the DSAR uses this NOAEC for its risk assessment.

Wehner (1994) noted that, compared to doses in the NTP (1993) study, talc aerosol doses received by users of cosmetic talc are several orders of magnitude lower and would not cause lung overload. In addition, the NTP investigators used micronized talc to reduce the particle size of the talc powder (Wehner, 2002). Thus, compared to MMADs of 6.0-6.9 μm talc used in other inhalation studies (e.g., Wehner et al., 1977a,b), the powder used in the NTP (1993) study had an MMAD of 2.7-3.2 μm, which is "distinctly finer than the cosmetic powder normally used" and is not reflective of human exposure conditions (MAK-Commission, 2012). This would have affected the location of deposition from mostly in the mid-airways, where efficient mucociliary clearance mechanisms function, to mostly in the deeper airways, where much slower alveolar macrophage clearance mechanisms are operational (Wehner, 2002).

Even setting this aside, the NOAEC from the 4-week study should not be used as the basis of a quantitative risk assessment. As noted by Oberdorster (1995a), "using an exposure duration of only 4 weeks as a range-finding study for a subchronic study makes it very difficult to get an accurate prediction of the accumulation kinetics." Wehner et al. (1977b) conducted a toxicity study in hamsters, a species capable of developing pulmonary lesions following prolonged inhalation of certain cytotoxic agents. Specifically, hamsters were administered talc aerosol for 3, 30, or 150 minutes/day, 5 days/week, for 30 days, or for 30 or 50 minutes/day, 5 days/week,
until death or a maximum of 300 days. For the lifetime/300-day exposures, the mean total aerosol fraction was 27.4 mg/m$^3$, with a respirable fraction of 8.1 mg/m$^3$ and an MMAD of 6.0 μm. Unlike the NTP (1993) study, the talc particles were not micronized, so the size of the particles evaluated in the study was comparable to that of cosmetic talc. There were no effects of talc exposure on the type, incidence, or degree of histopathological change in the exposed groups compared with sham-exposed controls, including in lung tissue. Thus, the NOAEC for the chronic portion of the study is 8.1 mg/m$^3$. Although IARC (2010) noted the high mortality rate in this study and criticized this study for its short daily exposure time (ET), the 30 or 50 minutes per day of exposure used in the chronic portion of this study is longer than that expected for cosmetic talc use durations$^3$ and closer to human use practices than the 6 hours per day used in NTP (1993). The DSAR does not cite Wehner et al. (1977b) and provides no basis for excluding this study from the assessment.

Using the same approach that the DSAR uses to adjust the NOAEC in the NTP (1993) study, the NOAEC of 8.1 mg/m$^3$ in Wehner et al. (1977b) adjusted for continuous exposure is 0.6 mg/m$^3$. This results in MOEs of 85-176 and is based on a chronic study. The use of a more reliable NOAEC increases confidence that use of cosmetic talc does not present an inhalation hazard to humans.

In addition to studies of talc, there is a broader database available for benign particles (i.e., PSPs). As discussed in Section VI.2 of these comments, the PSPs share common toxicokinetics and modes of action for lung overload. Therefore, animal studies of other PSPs can inform the NOAEC for inhaled talc powders. Oberdorster (1995b) considered the available data on benign particles to derive an occupational exposure limit for this class of particles, citing the "very good correlation between increasing retained volumetric lung burdens of very different types of particles [toner, diesel, titanium dioxide (TiO$_2$), polyvinyl chloride (PVC), and carbon black] and diminishing lung clearance rates." Oberdorster (1995b) estimated that a maximum chronic lung burden of 2 mg/g (which is not expected to cause lung overload) would be achieved by inhaling a concentration of 1.2 mg/m$^3$ during a work shift (including assumptions for human lung weight, average fractional clearance rate, percentage of deposition of inhaled particles in the alveolar region, and occupational inhalation rate). Another approach considered by Oberdorster (1995b) is to base a lung burden, not to be exceeded to prevent lung overload, on a volumetric load of 1 μL particle per gram of lung (the same for both rats and humans based on mathematical deposition models of inhaled particles). This would be accomplished with an occupational exposure limit of approximately 1 mg/m$^3$ for a particle of unit density (1 g/cm$^3$). Benign particles have, on average, a density of 3 g/m$^3$, so the respective occupational exposure limit would be 3 mg/m$^3$. Converted to a continuous exposure for non-occupational populations, the lower of Oberdorster's (1995b) estimated occupational

$^3$ The DSAR assumes exposure to cosmetic talc to be, at most (for baby powder), 1.5 applications per day, and 5 minutes per application (i.e., 7.5 minutes per day).

$^4$ 8.1 mg/m$^3$ x 2.5/24 hours x 5/7 days.
exposure limits – 1.2 mg/m³ – would be 0.43 mg/m³. This value accounts for the interspecies
differences between rodents and humans.

In addition to the study by NTP (1993), the DSAR should cite and discuss additional animal toxicity
studies of inhalation exposure to talc or other PSPs that provide information regarding the POD for the
critical effect (i.e., lung overload).

c  Interspecies Uncertainty Factor and Margin of Exposure

Available human and experimental animal data indicate that an uncertainty factor for
interspecies differences may not be warranted for the risk assessment of talc inhalation
exposure, and a lower MOE than the typical value of 100 is adequately health-protective for
inhalation exposure to talc.

The DSAR determines that chronic inhalation of talc causes pneumoconiosis and identifies a
NOAEC of 2 mg/m³ based on increased lung burden and impaired clearance in rodents.
However, the DSAR does not evaluate all of the relevant human and animal studies and does
not provide any rationale for this omission. The DSAR also does not acknowledge the lack of
comparative human studies on consumers with inhalation exposure to talc from personal care
products and the ensuing uncertainties with regard to whether any adverse respiratory effects
could occur from typical use of personal care products containing talc powder.

As summarized above, both human and animal evidence, although limited by study quality,
indicate that inhaled talc exposure can cause pneumoconiosis through lung overload, which is a
threshold effect.

With regard to the critical health effects level, several occupational epidemiology studies' observed NOAECs (adjusted to continuous exposure in non-occupational populations) ranged from 0.32-1.49 mg/m³. However, the DSAR readily dismisses these relevant data from epidemiology studies and only relies on the POD from a single animal study with considerable uncertainties.

In the two experimental studies of talc exposure in rodents, the NTP (1993) study relied on by
the DSAR and Wehner et al. (1997b), the adjusted NOAECs were 0.36 and 0.6 mg/m³, completely
overlapping with the observed NOAECs in humans. In addition, the exposure limit (adjusted
to continuous exposure from occupational exposure) derived from animal studies of other PSPs
is 0.43 mg/m³, which is also comparable to the NOAECs in human and animal studies of talc
exposures.

Moreover, Jarabek et al. (2005) used dosimetry models to extrapolate internal dose metrics from
animal species to humans and to estimate the human-equivalent concentrations for inhalation
exposures to PSPs. The study reported that the human-equivalent concentrations are 1-5 times
those of rats, *i.e.*, humans would need to be exposed to 1-5 times the concentration that rats are exposed to in order to achieve the same internal doses as in rats.

Similar NOAECs in humans and rodents, in combination with dosimetry modeling results, provide support that the interspecies uncertainty factor (typically a value of 10) is not warranted for the risk assessment of talc inhalation exposure.

*The DSAR should acknowledge that the available data in humans and experimental animals, including similar NOAECs and dosimetry modeling results, greatly reduce the uncertainty regarding interspecies differences and indicate that a much lower MOE than the typical value of 100 is adequately health-protective.*

3. Perineal Exposure

The DSAR does not consider all the available data and does not properly apply a WoE approach to evaluate a potential causal association between perineal exposure to talc and ovarian cancer.

The DSAR notes that IARC concluded that perineal use of talc-based body powder is possibly carcinogenic to humans based on "limited" evidence in humans; this means that "chance, bias or confounding could not be ruled out with reasonable confidence" (IARC, 2015). The DSAR also mentions that a minority of the IARC Working Group that evaluated talc considered the evidence inadequate (ECCC and Health Canada, 2018). Consistent with this, the DSAR references the CIR Expert Panel (2013), which determined that there is no causative relationship between cosmetic use of talc in the perineal area and ovarian cancer. This is followed by a review of animal and human studies in the DSAR; however, in both cases, the review is not conducted using a WoE methodology, is very high-level, and omits several key concepts, as described below.

a. Animal Evidence

There is little evidence from animal studies regarding perineal exposure to talc, and the evidence that is available does not support a human hazard.

The DSAR concludes that rodents are poor experimental models for perineal exposure but indicates two studies that reported foreign-body reactions and inflammation. Hamilton et al. (1984) injected 10 mg of talc per ovary directly into the surrounding bursal space in rats and evaluated the histopathology at various time points up to 18 months after the injection. The authors noted foreign-body granulomas, but this is most likely a result of the extremely high dose tested. In addition, the authors found no evidence of carcinogenicity in the treated animals after 12 months (findings at other time points were not reported). It has been argued that this study does not show ovarian tumor effects from talc exposure because of short follow-up times. However, this study lasted 18 months after a direct injection of talc onto the
ovary surfaces. This would have provided ample opportunity for tumors to develop, if talc had a carcinogenic effect.

The DSAR also cites Keskin et al. (2009), who applied 100 mg of talc in a saline solution either intravaginally or perineally to rats daily for 3 months. At the end of the 3 months, genital and reproductive tissues were evaluated for histopathological changes. This dose is an order of magnitude higher than that in the Hamilton et al. (1984) study, so foreign-body reactions and inflammation would be expected as a result of this high dose. There was no evidence of carcinogenicity in any of the tissues. As noted in the DSAR, all of the rats that received talc intravaginally or perineally developed reproductive tract infections. The DSAR did not mention that it is unclear whether the infections were talc-related, as two of seven untreated animals also developed infections (including one ovary infection) and no information was given as to sterility of the test materials. The DSAR notes that a 3-month time course may not have been sufficient for tumor formation. For these reasons, this study is not informative as to the effects of talc on reproductive tissues.

The DSAR should fully consider the limitations of the available animal studies regarding the carcinogenicity of perineal exposure to talc and acknowledge that the available evidence in experimental animals does not support a human hazard.

b. Epidemiology Evidence

The epidemiology evidence does not support a causal relationship between perineal exposure to talc and ovarian cancer.

The DSAR lists several meta-analyses that estimated risks of ovarian cancer associated with talc use. Only the results of Taher et al. (2018) are described, but this study is not publicly available and, to our knowledge, has not undergone peer review. Only the study design, sample size, and one risk estimate and 95% confidence interval (CI) are listed for individual original epidemiology studies. Importantly, the DSAR does not evaluate the methodological strengths and limitations of the Taher et al. (2018) or any other meta-analysis or original epidemiology study or the impact of these limitations on the interpretation of results. As such, the DSAR does not use WoE methodology to evaluate human evidence.

Below, the methods and conclusions of several more recent peer-reviewed meta-analyses are discussed. While meta-analyses of case-control studies collectively report small positive associations between talc and ovarian cancer, it is difficult to interpret these results without accounting for bias in the underlying studies, and the meta-analysis results from three prospective cohort studies are null. Given these critical limitations, the results of the meta-analyses of talc use and ovarian cancer showing modestly positive associations are not informative and, despite being statistically significant, they do not support a causal relationship between talc and ovarian cancer.
In 2006, IARC reviewed all published research relevant to the potential carcinogenic effects of talc, including risks associated with inhalation in occupational settings as well as perineal use (IARC, 2010). The review covered epidemiology evidence published up through 2006, and IARC concluded that the evidence for ovarian cancer risk associated with perineal talc use was "limited" in human studies. However, some IARC Working Group members maintained that the epidemiology evidence was "inadequate." The IARC Working Group indicated that recall bias "could not be ruled out" as an explanation for positive findings and that, if present, this bias would tend to inflate observed risk estimates. Since 2006, no validation studies have been conducted to assess the accuracy of the exposure assessment methods used in case-control studies, nor have any other analyses been conducted to resolve whether or not recall bias accounts for the positive association that has been observed in case-control studies. Therefore, IARC’s concerns about recall bias still apply to the current epidemiology evidence base.

More recently, Wentzensen and Wacholder (2014) reviewed the available epidemiology evidence relevant to talc exposure and ovarian cancer. The authors are two scientists from the National Cancer Institute (NCI) of the National Institutes of Health and declared no conflicts of interest. Wentzensen and Wacholder (2014) concluded that the overall evidence was inconclusive, and they echoed the IARC Working Group’s concerns that case-control studies of talc use and ovarian cancer, while generally positive, were likely affected by recall bias. Wentzensen and Wacholder (2014) recommended that new techniques in exposure assessment be employed in future epidemiology studies of talc use and ovarian cancer to help resolve the issue of recall bias. To date, no such studies have been described in the published literature.

That same year, the FDA indicated that it did not find conclusive evidence of a causal association between perineal talc use and ovarian cancer. Specifically, the FDA noted that exposure to talc is not well characterized in epidemiology studies, such that it is not known whether there was contamination by asbestos or other asbestiform minerals, or other structurally similar compounds, and that various consumer brands or lots of talc were not identified (FDA, 2014). The FDA also noted that several studies acknowledged biases in study design and that no single study considered all the factors that could potentially contribute to ovarian cancer, including selection bias and/or confounding that could result in spurious positive associations (FDA, 2014). The FDA reported that case-control studies do not demonstrate a consistent positive association across studies; lower confidence limits are often close to 1 and exposure-response is lacking. There was also mention of the lack of specificity (i.e., exposure does not account for all cases of ovarian cancer) and the lack of a cogent biological mechanism by which talc could cause ovarian cancer. Finally, the FDA (2014) referenced the IARC (2010) analysis but noted that the Nurses’ Health Study revealed no overall association between ever using talc and ovarian cancer.

As of January 2019, NCI concluded that "the evidence is inadequate to determine whether perineal talc exposure is associated with an increased risk of ovarian cancer" (NCI, 2019). NCI cited inconsistent results from case-control and cohort studies and the lack of evidence of exposure-response in a previous meta-analysis as support for this conclusion.
Seven meta-analyses of talc use and ovarian cancer have been published, each reporting similar findings. The most recent is that conducted by Berge et al. (2018), who reported a summary RR of 1.22 (95% CI: 1.13-1.30) for having ever used perineal talc and ovarian cancer. When the studies were analyzed by study type, the RR for case-control studies was 1.26 (95% CI: 1.17-1.35), while no association was found for cohort studies (RR = 1.02; 95% CI: 0.85-1.20). Weak trends were reported for duration and frequency of talc use. When stratified by cancer subtype, an association was detected for serous carcinoma, on the basis of 13 case-control studies only (RR = 1.24; 95% CI: 1.15-1.34). The authors also reported significant heterogeneity by study design (case-control vs. cohort) and noted that this result does not support a causal association between talc exposure and ovarian cancer. In addition, the authors proposed that a significant association for combined case-control, but not cohort, studies suggests that the case-control results could be explained by recall bias.

Another recent meta-analysis was conducted by Penninkilampi and Eslick (2018). These authors also reported a significant association between perineal use of talc and ovarian cancer in case-control studies (OR = 1.35; 95% CI: 1.27-1.43 for having ever used talc perineally) but not in cohort studies (OR = 1.06; 95% CI: 0.90-1.25), confirming the difference in outcomes between the two study types. Penninkilampi and Eslick (2018) also reported a significant association between talc use and invasive serous ovarian cancer in cohort studies. However, the authors did not use the most recent publications for two of the cohort studies (Houghton et al. (2014) was superseded by Urban et al. (2015) for the Women’s Health Initiative population, and Gertig et al. (2000) was superseded by Gates et al. (2010) for the Nurses’ Health Study population). The use of the older cohort studies did not affect the results for overall ovarian cancer risk, but it did affect the results by histological types. Urban et al. (2015) did not report results by histological types (Houghton et al. (2014) reported no association), but Gates et al. (2010) did, and there was a null association between talc use and serous invasive ovarian cancer (hazard ratio [HR] = 1.06; 95% CI: 0.84-1.35). Had Penninkilampi and Eslick (2018) used the most recent results from the same population as Gates et al. (2010), the association between serous invasive ovarian cancer and talc use would have been null.

Langseth et al. (2008) completed a meta-analysis in conjunction with the IARC review of epidemiology evidence. Langseth et al. (2008) calculated a statistically significant, positive meta-RR among relevant case-control studies for ever vs. never using talc and noted significant heterogeneity by whether the study was population- or hospital-based. They noted that the influence of recall bias could not be ruled out.

Important limitations inherent in meta-analysis should be considered when interpreting any meta-analysis results. Even though meta-analyses can be a powerful tool for leveraging statistical power across a number of studies, producing high precision in meta-results, a risk is that this precision can result in "over-conclusiveness." As described by Greenland and O'Rourke (2008), the CIs and p-values associated with meta-analysis results can give the impression that results are more precise and conclusive than they really are. When interpreting
meta-analysis results, it is essential to remember that CIs and \( p \)-values reflect random error only and do not reflect sources of bias; accurate CIs that account for uncertainty about bias are likely to be much wider (Greenland and O’Rourke, 2008). Bias in the underlying case-control studies, such as recall bias, would bias the meta-analysis results in a similar manner, which is a particular concern in meta-analyses of talc and ovarian cancer, given that recall bias is likely to operate in a consistent manner across all case-control studies. In other words, bias in individual studies becomes compounded, in effect, in meta-analysis. Standard meta-analysis methods do not account for biases in underlying studies in any way. Greenland and O’Rourke (2008) recommended adjusting results from individual studies to account for biases, if possible, before combining results in meta-analysis and stated that "failure to fully and properly emphasize the nonrandom sources of uncertainty in a meta-analysis may encourage and even support faulty conclusions and bad policy decisions."

In summary, recent reviews of the epidemiology evidence regarding talc and ovarian cancer have concluded that evidence is limited and may be affected by recall bias and other uncertainties. Meta-analysis results from three prospective cohort studies are null. In contrast, the meta-analyses indicate that case-control studies collectively report small positive associations between talc and ovarian cancer, but it is difficult to interpret these results without accounting for bias in underlying studies. Narrow CIs and small \( p \)-values associated with meta-analyses of case-control studies should be interpreted with caution to avoid overconfidence in the results. Given critical limitations, the results of meta-analyses of talc use and ovarian cancer showing highly precise, modestly positive associations are not informative and, despite being statistically significant, they do not support a causal relationship between talc and ovarian cancer.

The DSAR should critically evaluate primary epidemiology studies and/or available systematic reviews and meta-analyses, fully consider the study limitations and their impact on the interpretation of the results, and acknowledge that the epidemiology evidence does not support a causal relationship between talc and ovarian cancer.

c. Mode of Action

The available scientific evidence does not provide sufficient support for the hypothesized modes of action of chronic irritation or immune-mediated response leading to ovarian cancer after talc exposure.

The DSAR discusses two possible modes of action for talc and ovarian cancer: local chronic irritation leading to an inflammatory response and an immune-mediated response triggered by talc in the lower genital tract.

While the theory of inflammation having a role in ovarian tumorigenesis has been put forth, this has not been definitively established (Cramer and Finn, 2011). More importantly, the DSAR only cites one study, Keskin et al. (2009), in support of inflammation as a possible mode of
action for ovarian cancer. As discussed above, Keskin et al. (2009) applied 100 mg of talc in a saline solution either intravaginally or perineally to rats daily for 3 months. All of the rats that received talc intravaginally or perineally developed reproductive tract infections. It is unclear whether the infections were talc-related, as two of seven untreated animals also developed infections (including one ovary infection) and no information was given as to sterility of the test materials, but it is likely that the infections caused the increase in inflammatory cells. The DSAR does not mention the infections in this study.

As further support for this mode of action, the DSAR cites a single study by Henderson et al. (1986) that reported talc particles in the ovaries of rats that received intrauterine instillations of talc or that were dosed intravaginally. However, the DSAR does note that talc was not found in rabbits or monkeys after single or multiple intravaginal applications in the Henderson et al. (1986) study, or mention that installation of a liquid medium does not mimic perineal use of a dry powder. The DSAR also cites two studies that reported talc particles in human ovaries and discusses several studies that measured translocation of other inert particles. Although the DSAR does mention possible explanations for talc in human ovaries, it offers no critical review or evaluation of these studies and does not discuss other studies that bear on this topic. These and several other studies are discussed in these comments in the toxicokinetics section of these comments (Section VI.3). As described in detail above, these study results do not provide any definitive evidence that perineal talc use is associated with the presence of talc in ovarian tissues, nor do they support the hypothesis that this transport pathway plays a causal role in ovarian cancer.

The DSAR cites the Cramer et al. (2005) study regarding the possibility of an immune-mediated mode of action triggered by talc in the lower genital tract. This hypothesis involves the immune responses to mucins, which are glycoproteins found in certain tissues, including the fallopian tubes. The form of a certain mucin (MUC1) that is expressed in response to inflammation is similar to the form that is expressed in tumors. Cramer and his colleagues proposed that chronic inflammatory events might prime the immune system to become tolerant to MUC1, thus diminishing the immune response to the form expressed in ovarian tumors and increasing the chance that the tumors will continue to develop (Cramer, 2012). Cramer and his colleagues have extended this hypothesis to include talc as an agent of chronic inflammation that might act to diminish the immune response to ovarian tumors, thus causing ovaries to be more susceptible to cancer (Cramer, 2012; Williams et al., 2014). This hypothesis would negate the need for talc to physically reach the ovaries in order to exert an effect. Various lines of evidence have been put forth in support of this hypothesis, but the evidence does not stand up to scrutiny and does not support a chronic inflammatory role for talc in the causation of ovarian cancer.

First, there is no evidence in the literature that talc affects mucin proteins. Williams et al. (2014) claimed to present evidence that talc causes inflammation in women who apply talc perineally, based on the neutrophil-to-lymphocyte ratio (NLR) in peripheral blood as a general measure of
inflammation in women with ovarian cancer. The authors reported that talc use was associated with a greater NLR. In fact, there was no exposure-response relationship, and there was a statistically significant decrease in NLR among all women who used talc for less than 20 years compared to women who did not use talc. Among women who used talc for more than 20 years, the NLR was slightly, but not statistically significantly, greater than the NLR for women who did not use talc (geometric mean = 4.1, 95% CI: 3.4-4.9 for >20 years of use, compared to geometric mean = 3.7, 95% CI: 3.4-4.0 for women who did not use talc). NLRs for premenopausal women followed the same pattern, except the decrease in women with less than 20 years of talc use was not statistically significant. This does not support the claim of increased inflammation in women who use talc, and there is no other evidence in the literature to support increased inflammation in women from perineal use of talc.

The rat study by Keskin et al. (2009) has also been cited as evidence that talc causes inflammation in the reproductive tract. As discussed above, this study used methods that are not applicable to normal human use of talc and had serious study quality issues. Therefore, this study does not provide evidence in support of increased inflammation in women from perineal use of talc.

Some evidence that tubal ligation protects against ovarian cancer in talc users has also been cited as evidence that talc causes ovarian cancer, either by general inflammation or by direct action in the ovaries. Several investigators have suggested that tubal ligation could protect against talc-mediated inflammation leading to ovarian cancer by raising anti-MUC1 antibodies, thereby increasing immune protection against ovarian tumors (for example, see Cramer, 2012). However, in the most recent and largest ovarian cancer study published by Cramer et al. (2016), women who had tubal ligations were at greater risk for ovarian cancer than women who did not have tubal ligations. Thus, the evidence for tubal ligation-conferred protection against ovarian cancer is contradictory and does not support a mechanism for cancer involving increased inflammation from perineal use of talc.

The DSAR should critically review all of the available studies that investigated chronic irritation triggered by talc use in the lower genital tract, which do not provide sufficient support for an inflammatory response or immune-mediated response as possible modes of action for ovarian cancer resulting from perineal talc exposure.

\( d. \) Bradford Hill Considerations

The DSAR does not correctly apply the Bradford Hill considerations when evaluating the WoE. As concluded by other recent reviews, the overall evidence does not support a causal relationship between perineal talc use and ovarian cancer.

The DSAR concludes that the Taher et al. (2018) meta-analysis and the Bradford Hill considerations suggest a small but consistent statistically significant positive association between ovarian cancer and perineal exposure to talc and that available data are indicative of a
causal effect. As described in detail in Appendix B, an evaluation of perineal talc exposure and ovarian cancer in the context of the Bradford Hill considerations indicates that the reported associations are not likely to be causal. The small positive findings in case-control studies (and meta-analyses based on these studies) have not been confirmed in any of the three high-quality prospective cohort studies that have been published. The possibility of recall and other biases cannot be ruled out for any of the published case-control studies; in fact, some specific aspects of case-control studies strongly suggest that biases and/or confounding have affected the results, and modest and plausible amounts of recall error could have caused the positive associations.

Overall, the alternative hypothesis (bias and confounding caused positive associations in the case-control studies) best fits the evidence across all the scientific disciplines, i.e., the inconsistent epidemiology results, the consistently null results in cohort studies (which are less susceptible to bias than case-control studies), the null results in animal carcinogenicity studies, the inadequate evidence for retrograde transport of talc, and the lack of evidence for genotoxicity or any other plausible mechanism of action. Thus, the overall evidence does not support a causal relationship between perineal talc use and ovarian cancer. This is in agreement with others that conducted similar analyses, including the FDA (2014), NCI (2019), and CIR (Fiume et al., 2015).

The DSAR should appropriately apply the Bradford Hill considerations to the evaluation of the WoE.

VIII. Exposure Assessment

The DSAR is lacking in transparency regarding the approach, key experimental details, and key decisions regarding data selection in the assessment of exposure associated with the use of consumer products containing talc.

The exposure assessment focused on routes of exposure for which critical effects were identified; namely, non-cancer lung effects following inhalation of insoluble respirable particles of talc and an association with ovarian cancer following perineal exposure to talc. However, no inhalation or perineal exposures were identified with respect to the major commercial or industrial uses of talc in paper, plastics, ceramics, and putties.

1. Oral and Dermal Exposures

Oral and dermal exposures to talc from environmental media, food, and drinking water are expected to be low or non-existent.

Based on the limited operations at mines and processing facilities in Canada, the Government concluded that talc exposure from ambient air is not expected to be significant.
There is potential for oral exposure to talc as it is approved for use as a food additive including food packaging uses. However, the DSAR stated that exposure from these uses is expected to be minimal.

In addition, it was noted that talc is insoluble in water and is expected to settle out during water treatment. Therefore, the DSAR concluded that exposure of the general population to talc in drinking water is not expected.

The DSAR states that exposure from the oral route was not quantified because no critical health effects from the oral route of exposure have been identified (ECCC and Health Canada, 2018). In addition, the DSAR notes that the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) has assigned an acceptable daily intake (ADI) of "not specified" for talc on the basis of low toxicity (JECFA, 2006), and that talc is "generally recognized as safe" for use in food in the United States (FDA, 2015).

The DSAR indicates that talc is present in approximately 8,500 personal care products in Canada and there is the potential for dermal contact with talc from the use of personal care products. However, systemic exposure resulting from dermal contact with talc is expected to be negligible because insoluble solid talc particles do not penetrate the skin and cannot be absorbed into the body. In addition, a dermal health effect endpoint has not been identified for talc.

*The discussion of oral and dermal talc exposures in the DSAR is sufficient and appropriate.*

2. Inhalation Exposure

The DSAR assesses inhalation exposures to talc associated with consumer products containing talc, but there are numerous inconsistencies, unexplained decisions regarding data selection, and a general lack of transparency in this exposure assessment.

The science regarding exposure to cosmetic powders is significantly more advance than what is reflected in the DSAR. Steiling et al. (2018) describe an inhalation exposure assessment approach for cosmetic powders and associated physical phenomena that may influence the assessment. For example, the authors address such factors as dust cloud generation, aggregation/agglomeration, and the "dustiness" of a powder. In addition, the authors identify a number of models that are available for the purpose of estimating exposure to ingredients in consumer products.

In the DSAR, inhalation exposure to talc was estimated for six exposure scenarios associated with the use of consumer products formulated as loose powders. The six scenarios included:

- Use of baby powder on an infant resulting in exposure to the adult.
- Use of baby powder on an infant resulting in exposure to the infant.
- Use of body powder by an adult.
- Use of face powder by an adult.
- Use of foot powder by an adult.
- Use of dry hair shampoo by an adult.

An adjusted EC was calculated for each scenario using an exposure model from United States Environmental Protection Agency (US EPA) guidance for potential human exposure to contaminants found at hazardous waste sites in the United States (US EPA, 2009).

By this method, the adjusted EC is a function of the average concentration in air (CA), the daily ET, the annual exposure frequency (EF), and the number of years ED for the scenario divided by an averaging time (AT):

$$EC = \frac{CA \times EF \times ET \times ED}{AT}$$

where:

- **EC** = Average adjusted exposure concentration for exposure period (µg/m³)
- **CA** = Average concentration in air (µg/m³)
- **EF** = Exposure frequency (days/year)
- **ET** = Exposure time (hours/day)
- **ED** = Exposure duration for exposure period (years)
- **AT** = Averaging time (ED x 24 hours/day x 365 days/year) (hours)

**a. Average Air Concentration**

The DSAR does not provide justification for the approach used in deriving the CA following the use of consumer products containing talc.

The DSAR considers three peer-reviewed studies (Anderson et al., 2017; Aylott et al., 1979; Russell et al., 1979) and one unpublished study conducted by the Environmental Health Science and Research Bureau of Canada (Rasmussen, 2018) for the estimation of the talc CA following the use of talc-containing products. Aylott et al. (1979) reported mean respirable talc (<7 µm) concentrations of 0.48-1.9 mg/m³, while Russell et al. (1979) measured similar respirable (<10 µm) concentrations of 0.19-2.03 mg/m³ talc. These studies were not used by the ECCC and
Health Canada for the exposure assessment because of limitations such as the "use of older equipment, older sampling methods, and older talc products" (ECCC and Health Canada, 2018).

Results from Anderson et al. (2017) are used in the DSAR exposure assessment. Anderson et al. (2017) reported respirable talc concentrations ranging from 0.44-3.28 mg/m³ for older talc products manufactured during the 1960s and 1970s. Rasmussen (2018) replicated the exposure studies conducted by Anderson et al. (2017) using talc products currently available on the Canadian market and reported similar ranges of respirable particle concentrations (i.e., 0.48-1.8 mg/m³) following the use of talc body and face powders in three different exposure scenarios. Exposure simulations in the Rasmussen (2018) study included: (1) normal application of talc body powder (i.e., consumer use patterns, not necessarily in line with manufacturer instructions); (2) application of talc face powder according to manufacturer instructions; and (3) normal application of talc body powder prior to putting on a wetsuit.

The DSAR includes a derivation of the CA by averaging the five talc concentrations reported in Anderson et al. (2017) and two talc concentrations reported in Rasmussen (2018) (application of talc body powder in the wetsuit scenario was not included). However, inconsistencies with this approach are discussed below.

1. Data from two studies (Aylott et al., 1979 and Russell et al., 1979) are excluded from the DSAR assessment without appropriate justification. The stated reason for not including data from Aylott et al. (1979) and Russell et al. (1979) in the exposure assessment is that there are limitations due to the "use of older equipment, older sampling methods, and older talc products" (ECCC and Health Canada, 2018 [emphasis added]). Although Anderson et al. (2017) and Rasmussen (2018) used contemporary sampling equipment, Anderson et al. (2017) measured exposure to historical talc products from the 1960s and 1970s, while only Rasmussen (2018) estimated talc exposure from products currently available on the Canadian market. The ECCC and Health Canada’s use of exposure data from historic talc products is inconsistent, especially because respirable talc concentrations reported by Aylott et al. (1979), Russell et al. (1979), and Anderson et al. (2017) are comparable. Instead, it may be more appropriate to use only exposure data from the Rasmussen (2018) study, which is the only study that estimated respirable talc exposure from products currently on the market.

2. Data from one of the scenarios in the Rasmussen (2018) study, the scenario for use of talc body powder prior to putting on a wetsuit, are excluded without appropriate justification. As the talc CA (i.e., 1.36 mg/m³) is being used to estimate risk for a variety of exposure scenarios, including the use of foot powder and dry hair shampoo, it may be appropriate to include the exposure estimate from the wetsuit scenario to help account for varied product use. Further, the mean talc EC from the wetsuit scenario (i.e., 0.61 mg/m³) is similar to the range of mean concentrations reported in the other two scenarios (0.48-1.8 mg/m³) from Rasmussen (2018).
3. Rasmussen (2018) measured the PM45 particle CA of talc associated with the use of certain cosmetic products. The study did not discuss the selection of PM4 as the metric for respirable particles in talc-containing products. Brown et al. (2013) concluded that the average size of respirable particles was slightly less than 3 μm for adults and slightly greater than 4 μm for children. Moreover, they noted that the estimate of the respirable fraction is affected by the breathing habits of the individual.

4. If all of the data from the Rasmussen (2018) study were used in the risk characterization, all of the MOEs for the adult exposure scenarios would be greater than 100. The mean respirable talc concentration from all three exposure scenarios in Rasmussen (2018) is 0.96 mg/m3. If this EC were to be adjusted and then applied to the exposure scenarios in Table 6-3 of the DSAR (ECCC and Health Canada, 2018) then the resulting MOEs would be greater than 100 for all exposure scenarios except the baby powder scenario for adults and infants (Table 2).

Regarding estimation of the CA for the various exposure scenarios, the DSAR should include justification for:

- Selectively using CA data from only the Rasmussen (2018) and Anderson et al. (2017) studies (in particular, excluding exposure data from the wet suit scenario in Rasmussen [2018] and including the Anderson et al. [2017 data that used vintage talc products manufactured in the 1960s and 1970s);
- Selecting PM4 as the measure defining respirable particles in talc-containing products;
- Using the CA data that were collected in the breathing zone for the infant and adult exposure scenarios during diapering, because in both cases, the “dust cloud” will not occur in the breathing zone; and
- Using the CA data that were collected in the breathing zone for the foot powder exposure scenarios, because the “dust cloud” may not occur in the breathing zone.

b. Exposure Time

The DSAR does not provide justification for its data selection regarding ET in estimating exposures following the use of consumer products containing talc.

For infant and adult exposure scenarios, an ET of 5 minutes/application is used based on median time spent in the bathroom following a bath or shower. This median value is taken from the US EPA Exposure Factors Handbook, Table 16-35 (duration in bathroom immediately following a shower or bath; US EPA, 2011). The DSAR used a median ET of 5 minutes for all population groups, however, the median duration in the bathroom immediately following a shower or bath is reported as 2 minutes for infants aged 1-4 years), 5 minutes for children (aged

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5 Particulate matter with a diameter of 4 μm or less.
5-11 years and 12-17 years), and 10 minutes for adults (aged 18-64 years and >64 years) (all as noted in the Exposure Factors Handbook; US EPA, 2011). The DSAR does not explain the selection of 5 minutes for an ET from among the data reported.

In addition, the DSAR does not justify the use of "duration in the bathroom immediately following a shower or bath" as an appropriate measure of ET. Rasmussen (2018) used personal breathing zone monitors positioned beside the nose of volunteers applying talc-based products to measure exposure. The results indicated that the average cloud of respirable particles in the breathing zone lasted 57-65 seconds, which may be a more appropriate estimate of ET.

The DSAR should include justification for the use of the "median time spent in the bathroom following a shower or bath" as the talc ET rather than the duration of the "dust cloud" in the breathing zone following consumer product use, as presented in Rasmussen (2018).

c. Exposure Frequency

The DSAR does not provide justification for its data selection regarding EF in estimating exposures following the use of consumer products containing talc.

Exposure frequency (aka frequency of use) data for the use of baby powder by adults and infants and body powder by adults are stated to have been derived from the US EPA Exposure Factors Handbook (US EPA, 2011). Exposure frequency data for face powder, foot powder, and dry hair shampoo were derived from Ficheux et al. (2015).

However, there is a lack of transparency and consistency in the selection of the particular EF values for the scenarios evaluated. For example, the Ficheux et al. (2015) study was based on consumption of cosmetic products by the French population. There is no discussion or justification to demonstrate that the habits and practices of the French consumer are similar to those of Canadian consumers. Products and habits in the US and are more likely to be similar to those in Canada. Moreover, US EPA (2011) reports frequency of use data for face powder, foot powder, and shampoo, though not dry shampoo specifically.

Data from Ficheux et al. (2015) are available as mean, 50th percentile (median), and 90th percentile. Also, this study includes data for adult women (≥15 years old), adult pregnant women (≥15 years old), girls (4-14 years old), adult men (≥15 years old), and boys (4-14 years old). The EF values selected for the inhalation exposure assessment appear to have been taken from among the data for mean and median use frequency, and from the adult women and pregnant women surveys, without any explanation or justification for this choice.

Additional product-type-specific observations are provided below.

- **Baby Powder:** Average daily frequency of use and upper 90th percentile daily frequency of use data are provided in US EPA (2011) for three survey sources. However, it is not
clear why the 1.0 use per day frequency is chosen from among those data for adults and infants.

- **Body Powder**: An EF of 1.0 time per day or 365 times per year is chosen for body powder based on survey data reported by US EPA (2011). However, no data for the product type "body powder" is listed in the Exposure Factors Handbook. If a different product type was used as a surrogate for body powder, this should be explicitly stated to ensure reproducibility and transparency.

- **Face Powder**: The DSAR states in Table A-1 that the "EF is assumed to be daily" (once per day) or 365 times per year for face powder, based on survey data reported in Ficheux et al. (2015) (ECCC and Health Canada, 2018). However, no data on face powder per se are reported in Ficheux et al. (2015). The authors reported data for the use of "Loose Powder Foundation" face products, and the value the DSAR uses (once per day) corresponds to the median (50th percentile) for adult women from this study.

- **Foot Powder**: An EF of 0.75 times per day or 274 times per year is chosen based on survey data reported in Ficheux et al. (2015). Upon review of Ficheux et al. (2015), this value appears to be based on survey data from adult pregnant women (N = 251). Survey data were also available for adult women (mean = 0.60; N = 2,713) and adult men (mean = 0.67; N = 2,693). However, no justification is provided for why the survey data for the small sample of pregnant women is used over the other groups or the collective data.

- **Dry Hair Shampoo**: Frequency of use data for dry shampoo are only available for adult pregnant women in Ficheux et al. (2015). The DSAR assessment uses a mean EF of 0.23 times/day or 85 times per year for this product type.

**Regarding the EFs for the various talc exposure scenarios, the DSAR should include:**

- Justification for the use of consumer product use survey data for French consumers when survey data for North American consumers are available;

- Clarification and justification for the data utilized regarding the frequency of baby powder use;

- Justification for the apparent use of survey data for pregnant women only (Ficheux et al., 2015), and not adult women, adult men, or a weighted average of all three populations, for the foot powder exposure scenario;

- Clarification on whether mean or median (or another) frequency of use values were utilized for the various exposure scenarios and justification for the selection of those values; and

- Clarification regarding the source of the frequency of use data for the adult body powder exposure scenario.


d. Exposure Duration

The DSAR does not provide justification for its data selection regarding ED in estimating exposures following the use of consumer products containing talc.

The DSAR states "adult exposure for body powder, and foot powder (80 years lifetime, 12 years child)" (ECCC and Health Canada, 2018, Appendix A, Table A-1, Footnote e). However, the ED for adults listed in Table A-1 is 58 years. It is unclear how the value of 58 years was arrived at, and there appears to be a discrepancy between the value cited as a lifetime ED and the value used.

Also, the DSAR states "assume 2 children per family (Statistics Canada 2016)" (ECCC and Health Canada, 2018, Appendix A, Table A-1, Footnote e). According to the cited census data, the average number of children per family in Canada is 1.8 (Statistics Canada, 2016). The use of a value of 2.0 children per family in the DSAR to calculate the ED appears to be arbitrary.

Regarding the ED for the various talc exposure scenarios, the DSAR should include:

- Clarification and justification for the ED for adults, because the value utilized did not match the cited information.
- Justification for the use of a value for the number of children per family in Canada that is greater than that reported by Statistics Canada (2016).

e. Exposure Concentration

There are a number of inconsistencies regarding the derivation of the adjusted talc EC.

A number of inconsistencies were identified regarding the derivation of the adjusted talc EC in the DSAR, making it challenging to independently reproduce the values derived. A number of recommendations are provided above to better provide transparency and consistency to the estimation of inhalation exposure to talc following the use of consumer products.

Regarding the approach for estimating inhalation exposure to talc following the use of consumer products, the DSAR should include justification for why they used US EPA guidance for inhalation exposure to contaminants at hazardous waste sites in the US, rather than the typical approaches for estimating human exposures to chemicals in consumer products that are used for assessing other chemicals under the CMP.

3. Perineal Exposure

A POD cannot be derived from the available studies of perineal talc exposure.
The DSAR provides a very high-level overview of perineal uses of talc. It does not provide any quantitative information regarding exposure. The DSAR indicates that perineal exposure from the use of personal care products was not quantified because a POD could not be derived from the available literature. However, as discussed above, the available scientific evidence does not support a causal relationship between perineal exposure to talc and ovarian cancer. The lack of critical effects associated with perineal exposure to talc in humans does not warrant a quantitative exposure assessment.

*The DSAR should acknowledge that the evidence does not support ovarian cancer as a critical effect in humans following perineal talc exposure, and thus, the quantification of perineal exposure to talc is not warranted.*

IX. **Characterization of Risk to Human Health**

The available data do not support the DSAR’s conclusions regarding the characterization of risk to human health following inhalation and perineal exposure to talc in consumer products.

1. **Oral and Dermal Exposures**

Oral and dermal exposures to talc do not pose any appreciable risk to human health.

The DSAR concludes that oral or dermal exposure to talc does not pose any appreciable risk to human health, and this conclusion is consistent with those of other regulatory and scientific bodies such as the Danish EPA (2016), US EPA (1992), Germany’s MAK-Commission (2012), FDA (2015), and JECFA (2006).

*The DSAR’s conclusions regarding the lack of appreciable health risks from oral and dermal exposures to talc are appropriate.*

2. **Inhalation Exposure**

Inhalation exposure following use of consumer products containing talc is sufficiently low and does not pose any appreciable risk to human health.

To characterize human health risk as a result of inhalation exposure to talc following the use of consumer products, the adjusted EC was compared to the adjusted NOAEC to derive an MOE. While the DSAR does not specifically define what MOE it considers to be adequately health-protective for talc inhalation exposure, it appears to use a default MOE of 100. This MOE is usually the product of an uncertainty factor of 10 for interspecies differences and an uncertainty factor of 10 for intraspecies variability. Notably, the default value of 10 for the interspecies uncertainty factor can be further divided into a factor of 4 to account for interspecies difference in toxicokinetics and a factors of 2.5 to account for interspecies difference in toxicodynamics.
(IPCS, 2005). It should be noted that the default value of 4 for the interspecies toxicokinetics uncertainty factor is appropriate for critical effects that involve systemic absorption or metabolism. When there is only a local effect, such as the case with lung overload following talc inhalation exposure, application of this uncertainty factor is not warranted (ECHA, 2012). Therefore, an MOE of 25 should be adequately health-protective for talc inhalation exposure.

Furthermore, as discussed in Section VII.2 of these comments, the available data in humans and experiment animals, including similar NOAECs and dosimetry modeling results, greatly reduce the uncertainty in interspecies extrapolation. These data not only support the removal of the interspecies uncertainty factor for toxicokinetics (i.e., 4), but also suggest that the interspecies uncertainty factor for toxicodynamics may not be warranted. Therefore, an MOE of 25 should be considered conservative when assessing whether talc inhalation exposures may pose any risk to human health.

The DSAR calculates MOEs less than 100 for the use of baby, body, and face powders and MOEs greater than 100 for the use of foot powder and dry hair shampoo. Notably, the DSAR's MOE for foot powder is 106 (ECCC and Health Canada, 2018, Table 6-3, pp. 26-27), yet the DSAR states that "[t]he MOEs for baby powder, body powder, face powder, and foot powder are considered potentially inadequate to account for uncertainties in the health effects and exposure database" (ECCC and Health Canada, 2018). Moreover, all the MOEs calculated in the DSAR are higher than 25, indicating an adequate margin of safety.

Even so, as discussed above, there are several errors, inconsistencies, and overly conservative assumptions in the derived adjusted talc ECs. Table 2 (below) demonstrates how these errors, inconsistencies, and overly conservative assumptions may affect the derived MOEs and overall conclusions from the DSAR's talc inhalation risk characterization. Scenarios explored in Table 2 include: (1) the use of an EC of 0.96 mg/m³ (average exposure from Rasmussen [2018]), (2) the use of an ET of 1 minute (duration of respirable talc cloud formation in breathing zone), (3) the use of an EF of 0.64 days/year for the foot powder scenario, (4) the use of an EF of 0.74 days/year for the face powder scenario, and (5) the combined effect of changing all these parameters. This increases all the MOEs to well over 100.
Table 2. Effects of Minor Changes in Exposure Parameters on Risk Characterization (MOE)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>DSAR (ECCC and Health Canada, 2018)</th>
<th>EC = 0.96 mg/m³</th>
<th>ET = 1 Minuteb</th>
<th>EF = 0.64 (Foot Powder)c</th>
<th>Talc Concentration = 0.96 mg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adjusted EC</td>
<td>MOE</td>
<td>Adjusted EC</td>
<td>ET = 1 Minute</td>
</tr>
<tr>
<td>Baby Powder, Infants</td>
<td>0.0071 50</td>
<td>0.0050 72</td>
<td>0.0014 254</td>
<td>0.0028 127</td>
<td>0.0010 360</td>
</tr>
<tr>
<td>Baby Powder, Adults</td>
<td>0.0071 50</td>
<td>0.0050 72</td>
<td>0.0014 254</td>
<td>0.0071 51</td>
<td>0.0010 360</td>
</tr>
<tr>
<td>Body Powder, Adults</td>
<td>0.0047 76</td>
<td>0.0033 108</td>
<td>0.0009 381</td>
<td>0.0047 76</td>
<td>0.0007 540</td>
</tr>
<tr>
<td>Face Powder, Adults</td>
<td>0.0047 76</td>
<td>0.0033 108</td>
<td>0.0009 381</td>
<td>0.0035 103</td>
<td>0.0005 733</td>
</tr>
<tr>
<td>Foot Powder, Adults</td>
<td>0.0034 106</td>
<td>0.0024 148</td>
<td>0.0007 523</td>
<td>0.0029 123</td>
<td>0.0004 872</td>
</tr>
<tr>
<td>Dry Hair Shampoo, Adults</td>
<td>0.0011 327</td>
<td>0.0008 469</td>
<td>0.0002 1,656</td>
<td>0.0011 331</td>
<td>0.0002 2,346</td>
</tr>
</tbody>
</table>

Notes:
DSAR = Draft Screening Assessment Report; EC = Exposure Concentration; EF = Exposure Frequency; ET = Exposure Time; MOE = Margin of Exposure
(a) Effect of changing the EC to 0.96 mg/m³, based on data from Rasmussen (2018).
(b) Effect of changing ET from 5 minutes to 1 minute, based on the duration of the respirable talc cloud in the breathing zone (Rasmussen, 2018).
(c) Effect of changing the EF from 0.75 to 0.64 times/day, based on the average value reported for men, women, and pregnant women (weighted by sample size; Ficheux et al., 2015).
(d) Effect of changing the EF from 1.0 to 0.74 times/day, based on the average value reported for women and pregnant women (weighted by sample size; Ficheux et al., 2015).
The DSAR should consider an MOE of 25 or higher to be adequately protective of human health, explore the use of more reasonable exposure parameters for the talc risk characterization, and acknowledge that talc inhalation exposures from the use of consumer products do not pose any appreciable risk to human health.

3. Perineal Exposure

The overall evidence does not support a causal relationship between perineal talc exposure and ovarian cancer.

The DSAR concludes that there is a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer, quoting Narod (2016), who stated: "It is unlikely that the association between talc and ovarian cancer is due to confounding and so it is fair to say that if there is a statistically robust relationship between talc use and ovarian cancer it is likely to be causal." The DSAR also quotes Penninkilampi and Eslick (2018), who noted that cohort studies evaluating serous invasive ovarian cancer are "suggestive of a causal association." Finally, the assessment relies on Taher et al. (2018), who suggested that perineal exposure to talc powder is a "possible" cause of ovarian cancer.

Narod (2016) wrote an editorial and does not have any references to support the claims regarding confounding. Penninkilampi and Eslick (2018) did not use the most recent study of the Nurses’ Health Study population (Gates et al., 2010), in which there was no association with serous invasive ovarian cancer. Finally, as stated multiple times throughout these comments, the Taher et al. (2018) study is unpublished, to our knowledge has not been peer reviewed, and has several methodological limitations, particularly regarding the interpretation of results.

A proper WoE evaluation clearly shows that bias and confounding are the most likely explanations for the positive associations in the case-control studies of talc exposure and ovarian cancer. This best fits the evidence across all the relevant scientific disciplines, i.e., the inconsistent epidemiology results, the consistently null results in cohort studies (which are less susceptible to bias than case-control studies), the null results in animal carcinogenicity studies, the inadequate evidence for retrograde transport of talc, and the lack of evidence for talc genotoxicity or any other plausible mechanism of action.

The DSAR should acknowledge that the overall evidence does not support a causal relationship between perineal talc use and ovarian cancer.
X. **Uncertainties**

The DSAR does not sufficiently consider biases in epidemiology studies and inappropriately dismisses the impact of these biases on the interpretation of study results.

Regarding the epidemiology evidence on perineal talc exposure and ovarian cancer, the DSAR argues that the fact that the positive association is strongest for the serous histological cancer type detracts from the hypothesis of reporting bias, because this type of bias would likely operate for all histological cancer types. As discussed throughout these comments, the presence of bias and confounding is the most likely explanation for positive associations in the case-control epidemiology studies of talc and ovarian cancer. This is true regardless of how exposure is designated (e.g., ever vs. never); modest and plausible amounts of recall error could have caused the positive associations. Also, serous tumors are the most common tumor subtype, so the positive association may be due solely to this fact (i.e., there are more women with this tumor subtype, so it is easier to study). Also, results for this subtype are not consistent. Other uncertainties regarding talc and ovarian cancer include that the epidemiology evidence for an association is contradictory between the cohort and case-control studies, and there is no evidence of an effect in animal studies. The evidence for retrograde transport of talc from perineal applications to the ovaries is insufficient in both animals and humans, and there is no relationship between particles found in ovaries and talc use or tumor incidence. There is no evidence that perineally applied talc causes inflammation in the reproductive tracts of women.

*The DSAR should acknowledge that, taken together, the evidence is not consistent with the hypothesis that talc causes ovarian cancer.*

XI. **DSAR Conclusion**

The available data and best practices in risk assessment do not support the conclusion that talc is entering or may enter the environment in a quantity or concentration under conditions that constitute or may constitute a danger to human life or health in Canada.

The DSAR concludes that talc "is entering or may enter the environment in a quantity or concentration under conditions that constitute or may constitute a danger in Canada to human life or health" (ECCC and Health Canada, 2018). Based on the arguments presented throughout these comments, this is not supported by the science.

*The DSAR should be updated to reflect that talc does not constitute a danger to human life or health in Canada.*
XII. DSAR References

Many relevant references are not included in the DSAR, and others are not critically reviewed.

Although a complete WoE analysis has not been presented herein, this document includes over 40 references (indicated by asterisks in the reference list) that are not cited in the DSAR, most of which provide critical information that impacts the WoE for talc risk to human health. In addition, as discussed in great detail in these comments, the DSAR does not adequately critically review either the available individual original research studies of talc exposure or reviews of these studies. Had this been done, it would be clear that the MOEs for talc inhalation exposure are more conservative than necessary to be considered precautionary and that the evidence does not support talc as a cause of ovarian cancer.

The DSAR should be updated to include all relevant references and a critical evaluation of each one.

XIII. Risk Management Scope for Talc

It is premature for the Government to consider risk management for talc.

The Risk Management Scope for Talc indicates that the government will consider measures to prohibit or restrict talc and will communicate with the public to help individuals avoid inhalation or perineal exposure to talc if the proposed conclusion for talc is confirmed in the final screening assessment (Health Canada, 2018a). As discussed throughout these comments, the available evidence indicates that talc does not pose a risk to Canadians or the environment, and thus should not be added to the List of Toxic Substances in Schedule 1 of CEPA. As such, risk management for talc is not necessary.

It is premature for the Government to consider risk management for talc, as talc does not constitute a danger to human life or health. Consequently, the Risk Management Scope for Talc should be withdrawn.

XIV. Conclusions

The DSAR does not consider all of the available data or follow standard risk assessment methodology, including Health Canada’s own guidance regarding WoE and its typical practice for evaluating exposure to consumer products. The available information regarding the potential for talc to cause harm to human health does not support a conclusion that talc meets the criteria under Section 64(c) of CEPA that it is entering or may enter the environment in a quantity or concentration under conditions that constitute or may constitute a danger to human life or health in Canada. Consequently, it is premature for the Government to consider risk management for talc, and the Risk Management Scope for Talc should be withdrawn.
XV. References

* Signifies an information source that was not considered in the DSAR.

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Appendix A

Weight-of-evidence Methodology

To assess whether talc exposure is likely to be causally associated with health outcomes, one should conduct a weight-of-evidence (WoE) analysis of epidemiology, toxicity, exposure and transport, and mechanistic studies. As described by Health Canada (2017):

A WoE may be applied at various stages of the assessment. It can be used to evaluate the quality of a single study, to assess similar studies for a particular parameter or endpoint, or to integrate information across multiple lines of evidence to support the risk assessment conclusion. Using a WoE involves a number of common steps. In the context of risk assessments conducted under CEPA 1999 [the Canadian Environmental Protection Act, 1999], the assessment approach undertaken will determine the details of each step, but generally they include:

1. gathering available and relevant information from multiple sources, including stakeholder submissions of information through voluntary or mandatory surveys, or information requirements for new substances notifications
2. critically assessing the quality or reliability of individual studies or pieces of information, or the sources of summarized information (for example, international assessments)
3. assembling similar information for a parameter or endpoint to develop individual lines of evidence
4. critically assessing each line of evidence based on overall strength or confidence in the information and its relevance to the assessment outcome
5. combining the lines of evidence to characterize risk and reach an assessment conclusion, in consideration of their relative strengths, consistency and coherency.

Additionally, Health Canada (2018) provided a checklist for transparent documentation of the WoE approach for the risk assessment process. It includes:

- evidence gathered: all available to date, individual sources and types
- evidence included for further consideration, and why (i.e., inclusion criteria)
- evidence excluded from further consideration, and why (i.e., exclusion criteria)
- lines of evidence assembled (list individual studies under each line)
- assessment criteria applied to lines of evidence, and scoring tools used (if any)
- values/weighting assigned to each line of evidence (e.g., descriptions, alphanumeric)
- integration scheme (e.g., best professional judgment, mathematical formula, criteria framework)
- overall conclusion/recommendation(s)
This document stresses, "documentation on how the risk assessment is conducted and the rationale for either including or excluding certain sources of evidence is a critical component of the decision making process."

Health Canada (2018) also states, "[t]he WoE approach is routinely applied by most scientific risk assessment agencies internationally and while several definitions for WoE exist, there is no single, universal standardized/commonly agreed upon definition or specific guidance on how to implement a WoE approach."

With regard to the role of WoE in applying precaution, Health Canada (2017) states:

Applying precaution in risk assessment means using conservative but realistic assumptions to account for the uncertainty identified at various stages of an assessment. The application of precaution is considered depending on the WoE and uncertainties for the particular data set being evaluated...

Precaution is applied at various stages of an assessment, when necessary, to avoid the potential underestimation of risk due to a lack of information, thus erring on the side of being protective of human health and the environment. However, if multiple assumptions are made throughout the assessment, there also needs to be consideration of whether the end result would be a conclusion that is unrealistic. In this case, further refinement of assumptions may be needed, if this is possible. If conservative assumptions have been made but there is no indication of potential risk to either human health or the environment, then further refinement is not needed.

Both WoE and precaution are influenced by uncertainty, thus all three concepts must be considered together in decision-making. A limited low quality data set will increase assessment uncertainty, reduce the strength and likely consistency of the WoE, thereby increasing the need to consider precaution. Conversely, a more robust data set will decrease uncertainty resulting in application of less precaution.

A WoE analysis involves a review of all relevant studies, considering the strengths and weaknesses of each, and weighing their points of agreement and contradiction. There are a number of methods for evaluating scientific evidence using a WoE approach (e.g., Rhomberg et al., 2011; Adami et al., 2011), all of which emphasize a systematic and transparent approach to the analysis. Perhaps the most widely used approach (either as proposed or with slight modifications), including by many regulatory agencies (including Health Canada), is that outlined by Sir Austin Bradford Hill in his address to the British Royal Academy of Medicine in 1965. Hill put forth several considerations to help determine whether an exposure is likely to be causally associated with disease in humans (Hill, 1965). These considerations are described below:
1. **Strength of Association.** Although a modest risk does not preclude a causal association, an observed risk is less likely to be due to chance, bias, or other factors if it is large and precise.

2. **Consistency.** Consistency refers to the reproducibility of findings within and across studies. Discordant results indicate that findings of effect in certain studies are likely due to chance, bias, or confounding factors. If results are consistent among studies with similar designs, this evidence of association is not as strong as consistent results among studies of different designs, or of different people, places, circumstances, and times. Also, the same bias (e.g., recall bias) and/or confounder could be present in a number of studies, leading to similar observed risk estimates that are all attributable to that bias and/or confounder, rather than causality. In this case, consistent results would be indicative of a consistent methodological limitation across studies.

3. **Specificity.** There are two ways that one can examine specificity: by determining whether (1) one disease is specific to an exposure; or (2) one exposure is specific to a disease. The second criterion is often difficult to meet because many diseases have multiple causes (some of which may be unknown).

4. **Temporalia.** A causal interpretation is strengthened when an exposure is known to precede the occurrence of a disease. For carcinogens, this exposure must occur long enough in the past for an effect to be observed. Temporality is the least definitive (but 100% necessary) of the Hill considerations because many events occur prior to the appearance of the disease that may have nothing to do with its cause.

5. **Dose-response.** To determine whether a dose-response relationship exists, one must compare risks across exposure groups and relate exposure to dose. This is typically done when using risk estimates based on internal comparisons (e.g., relative risks [RRs] or odds ratios [ORs]) or risk estimates based on populations with similar age distributions.

6. **Biological Plausibility.** If available evidence on the biological mechanism of an effect is sufficient to allow a scientifically defensible determination for causation, it can add weight to an association reported in epidemiology studies. Conversely, if evidence indicates that a biological mechanism is not plausible, that places doubt on epidemiology findings.

7. **Coherence.** To address coherence, one must determine whether all of the known facts related to the case fit together in a consistent manner.

8. **Experiment.** If a substance is a causal factor in a disease process, then the association between exposure and effect should be altered by an experiment of preventative action. It is often not possible or practical to conduct such experiments, however.

9. **Analogy.** The final consideration is often difficult to meet. If there is evidence for a similar effect with a different agent, this also adds support for a causal association.

Bradford Hill’s considerations are not intended as a checklist from which causality can be concluded; rather, they allow for informed conclusions based on available evidence. Overall,
these considerations can help one determine whether an association between an exposure (or exposures) and human disease is likely to be causal or whether other explanations are more likely (Ward, 2009). As stated by Dr. Hill:

None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as sine qua non. What they can do, with greater or less strength, is to help us make up our minds on the fundamental question – is there any other way of explaining the facts before us, is there any other answer equally, or more, likely than cause and effect? (Hill, 1965, p. 299)

Based on this statement, one should also evaluate alternative hypotheses to determine whether there is a more likely explanation for observed epidemiology associations than causation.

Dr. Hill's postulates were mainly intended for evaluating epidemiology evidence, although he stated that if available data on the biological mechanism of an effect are sufficient to allow a scientifically defensible determination for causation, this adds weight to an association reported in epidemiology studies.
Appendix B

Inappropriate Use of the Bradford Hill Considerations in the DSAR

The Draft Screening Assessment Report (DSAR) discusses the scientific evidence regarding perineal application of talc and ovarian cancer in the context of the Bradford Hill considerations (described in detail above) as reported by Taher et al. (2018). As demonstrated below, it did not consider the evidence in an appropriate manner. Had it done so, it would be clear that the database is sufficiently robust to eliminate the need for additional precaution (as described in Appendix A).

Strength

Bradford Hill stated that, while a modest risk does not preclude a causal association, an observed risk is less likely to be due to chance, bias, or other factors if it is large and precise. The DSAR does not actually address the magnitude of associations overall. Rather, it tallies the number of case-control studies with a statistically significant odds ratio (OR) of 1.5 or greater. An OR of 1.5 should not be considered large, and results of a few individual studies are not meaningful. All relevant studies need to be considered to determine whether, as a whole, the association is large and precise.

The DSAR acknowledges the lack of association in cohort studies but points to a statically significant association (OR = 1.25) with serous-type ovarian cancer in the study by Penninkilampi and Eslick (2018). The DSAR then indicates that follow-up periods in the cohort studies may not have been sufficient, that individual studies "may not be sufficiently powered to detect a low OR," and that "[w]ith larger sample sizes, more individual studies may have demonstrated stronger associations." Penninkilampi and Eslick (2018) did not use the most recent publication using the Nurses’ Health Study population (Gates et al., 2010), which would nullify the association with serous invasive cancer. Also, as indicated by Berge et al. (2018), "[i]t should be noted that the cohort studies included in the meta-analysis comprised a total of 429 cases of ovarian cases exposed to genital talc and 943 unexposed cases: the statistical power of the meta-analysis of these cohort studies to detect a RR [relative risk] of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as explanation of the heterogeneity of results." Also, whether individual cohort studies had the power to detect a "low OR" is a moot point when assessing the strength of association; a low OR does not indicate a strong association.

Overall, cohort studies consistently reported that perineal talc use was not associated with increased ovarian cancer risk. No hospital-based case-control study reported a statistically significant overall association. While population-based case-control studies reported modest associations with risk, this is most likely a result of bias and/or confounding. The small positive association observed in case-control studies can be explained by a plausible amount of recall
bias, as each one used the same method (i.e., subjects’ self-reports about past talc use) to
determine exposure. While meta-analyses showed small and statistically significant increased
risks of ovarian cancer in women who used talc, it is important to note that limitations of
meta-analyses can lead to over-conclusiveness (i.e., artificially small confidence intervals [CIs]
and p-values). In addition, meta-analysis results are subject to the same biases as the individual
studies on which they are based.

Consistency

Consistency refers to the reproducibility of findings within and across individual studies. The
DSAR indicates that results of meta-analyses are consistent and that epidemiology studies were
conducted over different time periods, among different ethnicities, and spanned many
geographical areas worldwide.

Consistency does not refer to the results of meta-analyses, but to individual studies. It would be
surprising if meta-analyses were not consistent since they all assess mostly the same individual
studies. Also, while there are differences among the case control-studies, the fact remains that
they all use the same study design. As stated above, if results are consistent among studies
with similar designs, this evidence of association is not as strong as consistent results among
studies of different designs, or of different people, places, circumstances, and times. Also, the
same bias (e.g., recall bias) and/or confounder could be present in a number of studies, leading
to similar observed risk estimates that are all attributable to that bias and/or confounder rather
than causality. In this case, consistent results would be indicative of a consistent
methodological limitation across studies.

The results of epidemiology studies are not consistent across study designs. Cohort studies,
which are less subject to bias, are consistently null. None of the hospital-based case-control
studies reported a statistically significant overall association. Population-based case-control
studies reported modest increases in ovarian cancer risk, which are most likely due to bias
and/or confounding. Meta-analyses based primarily or only on case-control studies also
reported a modest increase in ovarian cancer risk, but meta-analyses, like individual case-
control studies, have critical issues that limit the interpretation of their findings. Also, a number
of epidemiology studies assessed different modes of talc powder use that contribute to women’s
overall exposures and found that observed risks of ovarian cancer with regard to these specific
uses are not consistent or what would be expected if the association between perineal talc
exposure and ovarian cancer were causal.

The small positive findings reported in case-control studies are likely due to similar sources of
biases (e.g., recall bias) and confounding, and thus do not strengthen the collective evidence for
a causal relationship. The consistency in null findings among cohort studies, which are not
vulnerable to recall bias, strengthens the evidence for a lack of causal association.
Specificity

The DSAR states that "perineal talc exposure is specifically associated with cancer of the ovary and not other organs." However, this inappropriately assumes that the association is causal. Ovarian cancer is not specific to one particular cause. There are many known risk factors and several hypotheses regarding causation. The reported association between talc and ovarian cancer in some studies is likely due to bias and confounding rather than any carcinogenic action of talc. Thus, talc and ovarian cancer are not specifically associated with each other, so the conditions of specificity are not met.

Temporality

The DSAR states: "In all case-control studies reporting positive outcomes, the participants recalled that exposure to talc preceded the reported outcome. However, in the cohort studies (reporting a lack of positive association), it is not known whether the follow-up period was adequate to detect a potential association between perineal talc exposure and ovarian cancer (Taher et al. 2018)." While it is true that talc use (if recalled correctly) occurred before the cancer diagnosis in case-control studies, it is not likely that cohort studies did not have enough follow-up time, as it is likely that participants in these studies used talc before the studies were initiated.

Biological Gradient

The DSAR correctly indicates a lack of evidence for exposure-response. There is no consistent exposure-response relationship in the epidemiology studies of talc and ovarian cancer. Case-control studies that evaluated exposure-response and took into account frequency of application, duration of talc use, or both had mixed results. There was no exposure-response relationship found in any of the cohort studies. There was also no increased cancer risk with the use of diaphragms stored in talc, which would be expected to yield greater talc transport to the ovaries (if it occurs) versus external use. Importantly, none of the studies had any quantitative information on the level of talc exposure per use or any quantitative estimates of the amounts of talc that are claimed to be transported to various locations in the reproductive tract. Biomonitoring studies do not provide evidence that perineal talc use is correlated with the presence of talc particles in ovarian tissues, and there is no relationship between the number of particles found in ovarian tissue and incidence of tumors.

Taken together, the talc-ovarian cancer epidemiology studies, including cohort studies and several case-control studies, have not consistently reported exposure-response relationships. In addition, exposure misclassification from both random and systematic error has not been ruled out in the studies that reported exposure-response relationships. For these reasons, the condition of a dose-response relationship for talc and ovarian cancer is not met.
**Biological Plausibility**

The DSAR states: "Particles of talc are hypothesized to migrate into the pelvis and ovarian tissue, causing irritation and inflammation. The presence of talc in the ovaries has been documented (Heller et al. 1996b). This evidence of retrograde transport supports the biologic plausibility of the association between perineal talc application and ovarian exposure."

Although not discussed in the DSAR, the evidence regarding the direct genotoxicity of talc and neoplasticity in talc-exposed cultured cells is mostly negative and does not indicate that talc is genotoxic (Endo-Capron et al., 1993 Litton Bionetics, Inc., 1974, as cited in Fiume et al., 2015).

Evidence regarding the retrograde transport of talc applied perineally to the ovaries in humans and animals does not support the hypothesis that perineal use of talc plays a causal role in ovarian cancer. Almost all of the identified human studies exploring particle transport in the female reproductive tract involved hospitalized populations and may not be generalizable. Studies that evaluated the interaction between talc use and tubal ligation/hysterectomy reported mixed results (Wong et al., 1999; Cramer and Xu, 1995; Cramer et al., 2016), and thus do not consistently support the retrograde transport hypothesis. Further, the degree to which the mobility of the non-talc particles used in many of the human and animal studies is representative of talc mobility, even in unhealthy patients, has not been established. The exposure setting of primary interest – i.e., talc transport following external application of talc powder on or near the perineum – has not been directly studied in humans or animals.

In addition, there is no dose-response relationship between talc use and the number of talc particles found in ovarian tissue. Likewise, there is no relationship between the number of particles found in ovarian tissue and incidence of tumors. The presence of talc particles in ovarian cancer tissue does not prove that they played any causal role in development of the cancer.

The proposed mechanism of carcinogenicity involving talc effects on the immune system, including inflammation and immune system suppression, has not been demonstrated and is speculative. In addition, there is no evidence in humans that talc applied perineally causes general inflammation or inflammation of the reproductive tract. The single study that has been cited as evidence for this did not actually demonstrate that perineally applied talc causes inflammation. Also, there is no solid evidence in animal studies of talc-induced inflammation of the reproductive tract to support this mechanism for perineally applied talc. Thus, there is insufficient evidence for any proposed mechanism by which talc could plausibly cause ovarian cancer.
Coherence

The DSAR cites studies that indicate that tubal ligation reduces ovarian cancer risks associated with talc as supportive of coherence. First, this does not actually address coherence; to address coherence, one must determine whether all of the known facts related to the case fit together in a consistent manner. Second, in the most recent and largest ovarian cancer study published by Cramer et al. (2016), women who had tubal ligations were at greater risk for ovarian cancer than women who did not have tubal ligations. Thus, the evidence for tubal ligation-conferring protection against ovarian cancer is contradictory and does not support a mechanism for cancer involving increased inflammation from perineal use of talc. There was also no increased cancer risk with the use of diaphragms stored in talc, which would be expected to yield greater talc transport to the ovaries (if it occurs) versus external use.

The epidemiology evidence for an association between talc and ovarian cancer is contradictory, and there is no evidence of an association in animal studies. The evidence for retrograde transport of talc from perineal applications to the ovaries is insufficient in both animals and humans, and there is no relationship between particles found in ovaries and talc use or tumor incidence. There is no evidence that perineally applied talc causes inflammation in the reproductive tracts of women. Taken together, the evidence is not consistent with the hypothesis that talc causes ovarian cancer.

Experiment

The DSAR does not mention this Bradford Hill consideration. There is no relevant experimental evidence on talc and ovarian cancer in humans.

Analogy

The DSAR does not address the analogy consideration. There is no evidence for a similar effect (ovarian cancer) with a substance analogous to talc. There is no evidence that any other substance applied perineally could enter the reproductive tract and either reach the ovaries and cause cancer or cause an inflammatory effect that results in ovarian cancer.

Conclusion

In conclusion, when the Bradford Hill considerations have been appropriately applied to the evaluation of available evidence, it is apparent that the weight of the evidence does not support a causal relationship between perineal talc exposure and ovarian cancer.